

Psychosocial outcomes in women at increased familial breast cancer risk

MD THESIS

VOLUME 1

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Declaration

I, Emma MacInnes (née Surgey), confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. Copyright transfers have been obtained for all previously published work arising from this thesis, including permission from co-authors to reproduce the work within this thesis.

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Publications and presentations arising from this work

Oral Presentations:

The European Society for Surgical Oncology, Bordeaux, September 2010 – oral presentation entitled: MRI screening for women at increased risk of familial breast cancer: referral patterns, efficacy and outcomes in Sheffield, UK. **Emma Surgey**, Ashley Genever, Rachel Lott and Lynda Wyld.

The British Association of Surgical Oncology ~ The Association for Cancer Surgery Scientific Conference, November 2011 – oral presentation entitled: Dual MRI and mammographic screening for women at increased familial breast cancer risk: A tertiary centre experience. **Emma Surgey**, Jenna Morgan and Lynda Wyld.

North Trent Breast Education Meeting, Rotherham, 2013 – oral presentation entitled: Risk reducing mastectomy for increased familial breast cancer risk. **Emma MacInnes**.

The European Society for Surgical Oncology, Valencia, September 2012 – oral presentation entitled: Factors influencing risk management choices (risk reducing surgery or screening) in women at high familial breast cancer risk. **Emma Surgey**, Sally Erskine, Karen Collins, Jane Hughes, Jane Wilkinson, Rebecca Haines, Jackie Cook and Lynda Wyld.

University of Sheffield Medical School 11th Annual Research Meeting, Sheffield, 2015 – oral presentation entitled: MRI and mammographic screening in young women at increased risk of familial breast cancer. **Emma MacInnes**.

University of Sheffield Medical School 12th Annual Research Meeting, Sheffield, 2016 – oral presentation entitled: Risk Management Decision Making in women at increased familial breast cancer risk. **Emma MacInnes**.

Poster presentation:

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Published Abstracts:

MacInnes E, Erskine, S, Hughes J, Morgan J, Collins K, Wyld L. Factors influencing management choices (risk reducing surgery or screening) in women at high familial risk. EJSO, 2012, 38, 9, 778-779.

Surgey E, Morgan J, Wyld L. Dual MRI and mammographic screening for women at increased familial breast cancer risk: A tertiary centre experience. EJSO 2011, 37(11), 1014.

Surgey, E, Genever A, Lott R, Wyld L. MRI Screening in women at increased familial risk. EJSO, 2010, 36, 836.

Erskine S, **Surgey E**, Collins K, Hughes J, Wilkinson J, Haines R, Cooke J and Wyld L. Psychosocial and physical outcomes in women at increased familial breast cancer risk. EJSO, 2010, 36, (11), 1107.

Publications

Genever A, **Surgey E**, Jolly I, Ingram C. Breast MRI screening for high risk family history: the Sheffield experience. *Cancer imaging* (2010) 10, S203. DOI 10.1102/1470-7330.2010.9081

MacInnes E, Erskine S, Collins K, Hughes J, Wilkinson J, Wyld L. Risk management decision making in women at increased familial breast cancer risk. Submitted to *Psycho-oncology*.

Abbreviations

ADM – acellular dermal matrix

AI – aromatase inhibitor

ATM – gene conferring an increased risk of breast cancer

BC – breast cancer

BRCA1 – gene conferring increased risk of breast and ovarian cancer

BRCA2 – gene conferring increased risk of breast and ovarian cancer

BRIP – gene conferring an increased risk of breast cancer

BRRM – bilateral risk reducing mastectomy

BSE – breast self examination

BSO – bilateral salpingoophorectomy

CBE – clinical breast examination

CHEK2 – gene conferring an increased risk of breast cancer

CI – confidence interval (generally 95% unless otherwise stated)

CLM – contralateral mastectomy

COX II – cyclo-oxygenase two

CRRM – contralateral risk reducing mastectomy

CT – computed tomography

DBR – delayed breast reconstruction

DNA – deoxyribonucleic acid

ERG – expert reference group

EQ5D – questionnaire tool for measuring health status

ER – oestrogen receptor

FBC – familial breast cancer

HADS – hospital anxiety and depression scale

HER2 – human epidermal growth factor receptor

HRT – hormone replacement therapy

IBIS – breast research group with a risk calculator for familial risk estimation

IBR – immediate breast reconstruction

IES – impact of events scale

IVF – *in vitro* fertilisation

LD – latissimus dorsi (muscle used as a pedicled flap in breast reconstruction)

MM – mixed methods

MMG – mammogram / mammography

MRI – magnetic resonance imaging

NAC – nipple areola complex

NHSBSP – national health service breast screening programme

NICE – national institute for health and care excellence

NSAID – non-steroidal anti-inflammatory drug

NVIVO – computer software used for qualitative data analysis

OR – odds ratio

PALB2 – gene conferring an increased risk of breast cancer

PARP – poly ADP ribose polymerase (used as a target by PARP inhibitors such as olaparib)

PGD – preimplantation genetic diagnosis

PND – prenatal diagnosis

PR – progesterone receptor

PRISMA – preferred reporting items for systematic reviews and meta-analyses

QN - questionnaire

QoL – quality of life

RAD50, RAD51C, RAD51D – all genes conferring an increased risk of breast cancer

RMD – risk management decision

RMDM – risk management decision making

RMS – risk management strategy

RRM – risk reducing mastectomy

RRS – risk reducing surgery

RRSO – risk reducing salpingoophorectomy

SERM – selective oestrogen receptor modulator

SF36 – questionnaire tool to measure health status

SNPs – single nucleotide polymorphisms

TNBC – triple negative breast cancer

TP53 – gene conferring increased risk of multiple cancers

TV – transvaginal (ultrasound scan)

USS – ultrasound

Abstract

Introduction

There are a number of strategies that women with a vastly increased risk of familial breast cancer, particularly those with *BRCA* 1 and 2 gene mutations, may choose to protect themselves. The main risk management strategies have very different risk and benefit profiles and include enhanced imaging surveillance, use of chemoprevention (SERMs or AIs) and risk reducing surgery. Knowledge of hereditary breast cancer risk and cancer anxiety can impact on quality of life. Options for managing this elevated risk, whilst effective, may have long-term psychosocial consequences. This study aimed to explore the impact of living at risk, to identify the psychosocial outcomes for this group of women and for their partners and to assess factors that impact on risk management decisions and their ultimate decision satisfaction.

Methodology

A sequential exploratory mixed methods study was used, including a systematic review, a qualitative phase of study, using in-depth, semi-structured interviews with women and partners of women at high risk who had faced these choices, questionnaire development including focus group review and finally a quantitative phase of study using the questionnaire to explore associations and to assess the generalisability of the strength of these findings. (See figure 0.1).

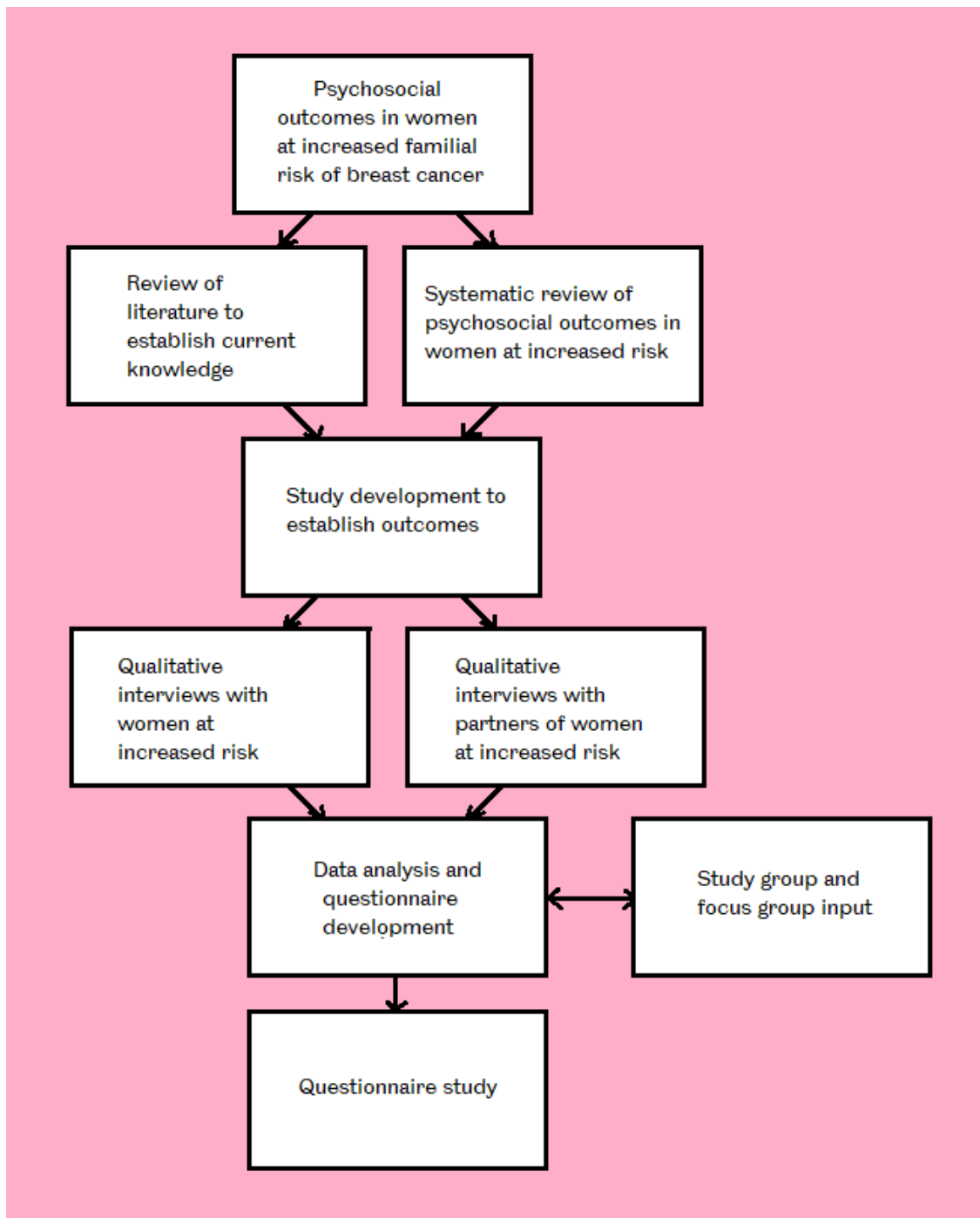
Results

Generally psychosocial outcomes are acceptable to women with high levels of decision satisfaction, but for a minority, risk reducing measures result in long-term psychosocial morbidity. The more common causes of distress include adverse body image changes, generalised and cancer-specific anxiety and distress. Good support, particularly that of a partner, can reduce this negative impact. Partners struggle to balance existing commitments with the time demands of providing this support.

Conclusion

Recognising women at increased risk of adverse effects related to their choice of risk management strategy may allow targeted support to enable women to better understand *and* manage their risk with a reduction in associated psychosocial distress.

Figure 0-1 Schema of work



Timeline of project

I registered for an MD in October 2010, as a part-time staff candidate with a time allowance of 6 years at 50% WTE, giving an initial submission deadline of October 2016. During this time, I have also been working variable time splits between my clinical training and research. I have also had two 1-year leaves of absence for maternity leave which means the deadline has been pushed back to 2018. Due to the rapid expansion in related research in the field over this time period it has been necessary to update the literature review over the course of the project to ensure that it remains current. The underpinning research question, which was novel when the project started, has to some degree been overtaken by progress in the field over this time period but this still represents a new addition to knowledge to the field exploring the choice between surgery and surveillance in high risk women. At the time I began this work, I registered as Emma Surgey, I have since married and changed my name to MacInnes.

1. Chapter one – Introduction

The field of familial breast cancer research is one that has seen massive changes in the past 2 decades. General awareness of familial risk has increased in both the professional and the public domains, with an impact on numbers of women presenting for risk assessment and of risk reducing surgery interest and uptake. Previous work on this topic has been largely focussed on the outcomes of risk reducing breast surgery in women with *BRCA* gene mutations. This study aimed to look more holistically at women who are at increased risk, both with and without gene mutations, looking at the overall psychosocial effects of living with increased risk. This introduction reflects the broad aims of this study, identifying and exploring relevant previous literature in three areas:

- Women living at increased risk
 - Genetics of hereditary breast cancer
 - Risk assessment and gene testing
 - Perception of risk
 - Effects of living with an increased risk of breast cancer
- Risk management options
- Risk management decision making

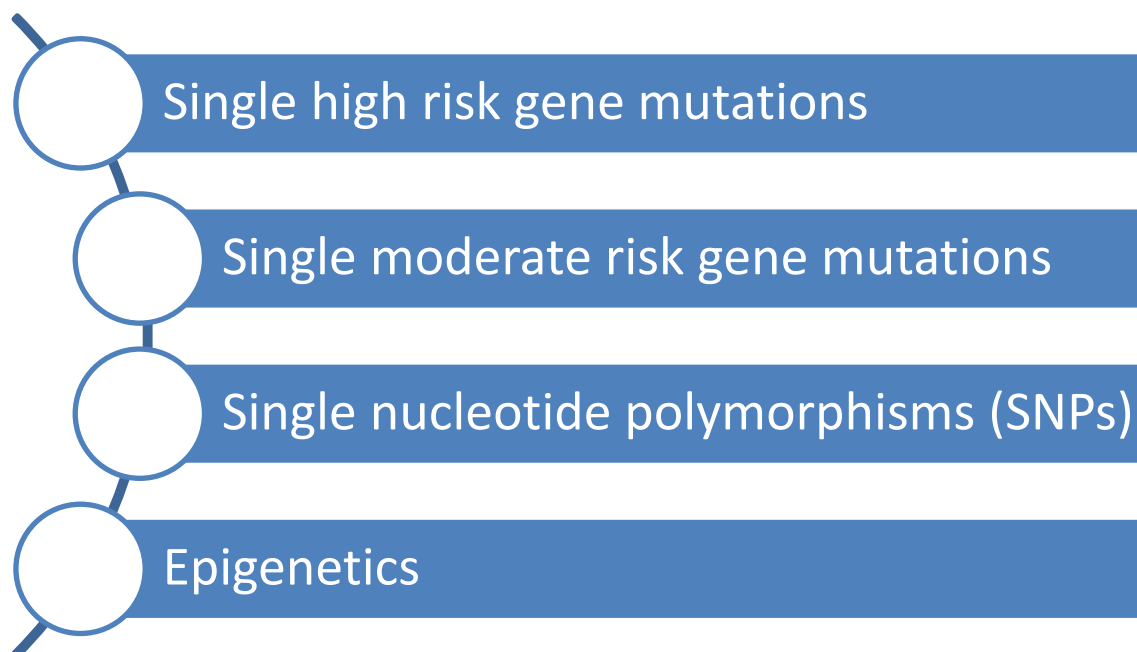
A broad introduction is provided to give as full a context as possible to better understand the aims of the study of psychosocial outcomes presented here. It does not provide a comprehensive description or review of every aspect of familial breast cancer as this is beyond the scope of this thesis.

1.1 Genetics of increased familial breast cancer risk

Breast cancer is the most common cancer to affect females and incidence rates are rising across the developed world due to rising life expectancy, screening programmes and lifestyle changes (Ferlay J 2013) (Cancer Research 2016). In addition to these factors, a large percentage of women affected by the disease carry hereditary risk factors for breast cancer. It has been recognised since Roman times that breast cancer might run in certain families and many decades ago, genetic linkage studies predicted that potent autosomally inherited genes would be identified in some families (Easton DF 1993). In the mid 1990s, scientists finally identified these genes as *BRCA1* and 2 (Miki, Swensen et al. 1994, Wooster, Bignell et al.

1995). Since then there has been a rapid expansion in our understanding of the heredity of breast cancer. It is now known that there are numerous pathogenic (function changing) mutations in *BRCA1* and *2*, as well as non-pathogenic variants and their diagnostic testing has become routinely affordable and available across most of the western world, these genes are summarised in table 1.2. It has also become apparent, however, that there are other potent and moderate risk genes at play. Some acting via the *BRCA* pathways (BRIP, PALB), and others independently (tp53, AT, CDH1 etc) (Apostolou and Fostira 2013) – see table 1.3. Whilst some of these more recently discovered genes are only of moderate potency, others are associated with a very high risk and testing for them in the diagnostic and predictive settings is increasingly offered. There are also huge global consortia (Breast Cancer Association 2006) collecting samples for analysis of weaker hereditary factors such as single nucleotide polymorphisms (SNPs) with weak clinical impact and whose interactions may make their clinical management highly complex (Colhoun, McKeigue et al. 2003). Lastly, as scientists begin to delve into the world of epigenetics, a whole new range of hereditary risk factors may become apparent (Falahi, van Kruchten et al. 2014). Table 1.1 summarises the types of hereditary risk.

Table 1-1 Types of genetic risk



Women at increased risk fall into two categories: those with and those without a demonstrable genetic causation. In reality there is a grey area, including those in whom an identified mutation is of uncertain pathogenicity (known as a variant of uncertain significance VUS) or those for whom testing is not available. Next generation sequencing is much cheaper and quicker than traditional methods and allows simultaneous testing of a panel of genes of interest. Since this technology has become available, the number of women in whom pathogenic mutation is thought likely but remains unproven has reduced (Cheon, Mozersky et al. 2014). The age at which risk becomes apparent to women can vary widely, although with increasing breast cancer family history awareness this is likely to become an issue being faced, predominantly by younger women. Advances in gene mapping have allowed an appreciation of a greater number of genes associated with familial breast cancer risk and identification of carriers. The psychological impact of being at increased risk should not be underestimated and accordingly it is important that the far-reaching effects of this be recognised by professionals to allow women to be supported during their assessment and thereafter.

1.1.1 Genes associated with increased risk

High risk gene mutations

There are a number of genes that interact and are associated with the regulation of DNA repair. The most widely known are *BRCA 1* and *2* (the former located on the long (q) arm of chromosome 17, *BRCA2* on the long (q) arm of chromosome 13), which were discovered in 1994 and 1995 (Miki, Swensen et al. 1994, Wooster, Bignell et al. 1995). They both function as tumour suppressor genes with multiple cellular actions including DNA repair and transcription regulation due to DNA damage. *BRCA* proteins may also be involved in regulation of other genes involved in DNA repair, the cell cycle and apoptosis (Yoshida and Miki 2004). Other defined high risk gene mutations are less common and include the TP53 mutation in *Li Fraumeni* syndrome, *STK-11* mutations in Peutz-Jeghers syndrome and the PTEN mutations in Cowden's disease. In addition, there are more frequently found but less penetrant gene mutations including CHEK2, ATM, PALB2, and BRIP1 alongside an expanding array of other single nucleotide polymorphisms (SNPs) associated with increased risk (Apostolou and Fostira 2013, Fergus J. Couch 2017).

The role of *BRCA* genes in facilitating DNA repair is complex. RAD51, a recombinase associated with DNA repair, is localised to any breaks in the DNA strands by a complex of *BRCA1*, PALB2 (partner and localiser of *BRCA2*) and *BRCA2* proteins (Xia B 2006). Mutation in any of these genes can allow unregulated propagation of damaged DNA, ultimately resulting in tumour development. Mutation, does not however, always result in cancer development. Some mutations may be harmless, resulting in no change to the function of the protein, whereas others may increase risk, making interpretation of gene test results challenging. A study of a single frameshift mutation responsible for the majority of *BRCA2* mutations in Iceland found that 28% of families with the mutation did not have a corresponding higher rate of breast cancer as might be expected, suggesting other genes may further modify the expression of *BRCA2* (Thorlacius S 1996), yet further complicating the appreciation of an individual's risk.

Detection of a new mutation in an at-risk family (diagnostic testing) could previously require full DNA sequencing which could take months to complete and could initially miss mutations or have inconclusive results. The advent of next generation sequencing (which permits massive parallel sequencing) has made these delays and inconclusive analyses less common. Samples are frequently stored and re-tested as new mutations are identified. The presence of an identified mutation in a family allows at-risk family members to be tested to allow risk prediction (predictive testing). For the first member of a family to be tested this is not the case and results may be inconclusive and need clinical correlation with family history to make decisions about management (Rubinstein 2004). The risk associated with a gene mutation depends upon the actual mutation, but a prospective study of *BRCA 1 and 2* gene mutations carriers in the UK showed 60% (95% CI 44 – 75%) of women born with a deleterious mutation in *BRCA1* would develop breast cancer by age 70, and 59% (95% CI 43-76%) would develop ovarian cancer by age 70. Similarly, approximately 55% (95% CI 41-70%) of women with a deleterious mutation in *BRCA2* developed breast cancer by age 70, and 16.5% (95% CI 7.5-34%) developed ovarian cancer by age 70 (Mavaddat, Peock et al. 2013). There is considerable variability within *BRCA* mutation carriers with some having higher and some lower levels of risk (Loman and Borg 2010). Breast *and* ovarian cancer families are largely *BRCA1* mutation carriers (81%) whereas those with female *and* male breast cancer

are usually *BRCA2* (76%) (Ford, Easton et al. 1998). These findings are summarised in table 1.2.

Whilst the breast cancer penetrance rates of *BRCA1* and 2 are relatively similar, phenotypically the cancers differ substantially, and the age profiles also differ. *BRCA1* tumours are more likely to be high grade with medullary subtype features including increased mitotic count, lymphocytic infiltration, pushing margins and trabecular growth pattern and necrosis (Southey, Ramus et al. 2011). They are also usually ER, PR and HER2 negative (i.e. “triple negative” or “basal type”), with just 10-24% being ER positive, in contrast to 65-80% of *BRCA2* tumours. Recent work looking at triple negative phenotype breast cancers has identified molecular subtypes that are associated with differing prognoses and responses to systemic treatment agents (Lehmann, Bauer et al. 2011, Masuda, Baggerly et al. 2013, Prat, Adamo et al. 2013, Bose 2015, Severson, Peeters et al. 2015) with an aim of introducing tailored, targeted treatment for these aggressive tumours. Triple negative cancers have been classified by Lehmann *et al* to seven groups: two basal-like, an immunomodulatory, a mesenchymal, a mesenchymal stem-like and a luminal androgen receptor subtype (Lehmann, Bauer et al. 2011). Different expression of, for example, DNA damage response genes, vary across these subtypes and this understanding allows systemic therapies to be targeted to the specific tumour.

The effect on survival of carrying a mutated *BRCA* gene is significant. At the age of 25 years, an average woman has an 84% likelihood of living to 70. With a *BRCA1* mutation, that reduces to 59%, and 75% for *BRCA2* mutation carriers. The effects on life expectancy are reduced by risk reducing mastectomy and oophorectomy, with recent data showing a survival advantage to women who have risk reducing mastectomies (Ingham, Sperrin et al. 2013). Cause of death in the *BRCA1* cohort was ovarian cancer in 46% and breast cancer in 26% (Kurian 2010).

Table 1-2 *BRCA1* and 2 characteristics (Chappuis, Nethercot et al. 2000, Kurian 2010) (Eerola, Heikkila et al. 2005, Bane, Beck et al. 2007, van der Groep, van der Wall et al. 2011)

	<i>BRCA1</i>	<i>BRCA2</i>
Lifetime risk of breast cancer	50-80%	40-70%
Average age at diagnosis	44yrs (56yrs population based risk average age of diagnosis)	47yrs (56yrs population based risk average age of diagnosis)
Hormone receptors	18-24% ER positive Low expression of PR and HER2 receptors compared to controls	62-83% ER positive More likely luminal phenotype than matched (non- <i>BRCA</i>) controls, more likely HER2 negative than controls.
Grade	29% grades 1 and 2 71% grade 3	57% grades 1 and 2 43% grade 3
Associated <i>in situ</i> disease	Less common than in controls (41% vs 56%)	Same incidence as in controls
Ovarian risk	24-40%	11-18%
Life expectancy without intervention	53%	71%

Moderate risk gene mutations

These include mutations in ATM, CHEK2, PALB2, RAD50, RAD51C, RAD51D, BRIP, ABARXAS, BARD1, MRE11, NBS1 and XRCC2. Most of these genes are tumour suppressors and have a function in DNA repair.

- CHEK2 is a gene that codes for a protein activated in response to DNA damage. Some mutations within this gene result in increased breast cancer risk, with increased male and bilateral breast cancers of note. It is common in some areas in Europe (up to 3%). Other cancers related to mutations in CHEK2 include colon, prostate, kidney and thyroid (Wu, Webster et al. 2001) (Apostolou and Fostira 2013).
- PALB2 (also known as FANCN) codes for a protein that interacts with *BRCA2* during DNA repair. Increased rates of pancreatic and breast and ovarian cancers are seen

with mutations in PALB2, with an autosomal dominant pattern of inheritance.

Penetrance is less than in *BRCA2* mutations (Rahman, Seal et al. 2007).

- ATM proteins have multiple functions, including DNA repair. The gene has a 15% penetrance in terms of breast cancer, with a two to five fold increase in risk in carriers (Renwick, Thompson et al. 2006).
- BRIP1 codes for a protein that associates with *BRCA1* and results in breast and ovarian cancer increased risk (Seal, Thompson et al. 2006).

There are now commercially available gene test panels, for example *Breast Next®(Genetics)*, which are generally offered to women who have already tested negative for *BRCA 1* and *2*, and which test against most of these moderate risk genes. The results of these panel tests can be challenging to interpret, including potentially non-pathogenic mutations and a requirement for a difficult to establish, detailed family history, including cancer phenotypes, in order that the results can be put into context and the patient advised accordingly (Narod 2012).

Single nucleotide polymorphisms (SNPs)

There are certain positions within genes where single nucleotide variations occur that have been identified as part of normal population variation. These polymorphisms can be completely benign or they can confer a slightly increased risk of many diseases including breast cancer. They may either reduce the risk of breast cancer, or can be associated with a high risk of breast cancer, when they are known as 'causal' SNPs (Breast Cancer Association 2006, Eccles and Tapper 2010, Michailidou, Hall et al. 2013). The non-causal SNPs recognised as increasing breast cancer risk are uninformative when tested individually, but a panel test of known breast cancer risk SNPs can be performed and a score created by tallying up the number of risk SNPs the person carries. In addition to identifying women at increased risk of developing cancer, some SNPs have been shown to affect responses to chemotherapy agents or simply worsen the prognosis of breast cancer in an individual (SNPedia 2016).

Epigenetics

In addition to cancer-predisposing coding changes in DNA, there are also inheritable changes to gene expression that do not change the DNA sequence. DNA methylation and histone

modifications can lead to gene dysregulation. These processes are under the control of enzymes, which, when the change induced increases the risk of cancer, are obvious targets to reduce this risk (Byler, Goldgar et al. 2014, Falahi, van Kruchten et al. 2014). One such epigenetic regulatory therapy currently being studied are histone deacetylases (HDACs), which are novel drugs that target DNA methylation and which are undergoing trials in cancers and neurological diseases (Falkenberg and Johnstone 2014). At present there is no clinical role for these in the breast cancer risk reduction setting.

Summary table of genetic risks for familial breast cancer:

Table 1-3 Genetic basis of risk (data modified from: (Chen 2007, Apostolou and Fostira 2013)

Genetic risk and mutation	Cancers associated with deleterious gene	Risk of cancer developing (lifetime risk up to 70y %)
BRCA 1 mutation	Breast	50-65%
	Ovarian	34-45%
BRCA 2 mutation	Breast	40-57%
	Ovarian	13-23%
	Prostate, pancreas, malignant melanoma	
TP53 (Li Fraumeni)	Sarcoma, breast, brain, adrenal, leukaemia, lung	57% risk in 30 years Also quoted up to 90%
CDH1 (Hereditary gastric cancer)	Hereditary diffuse gastric, breast, colorectal	60%
STK-11 (Peutz-Jeghers)	Colon, intestinal, breast, lung, cervical, testicular, pancreatic, skin	32-54%
PTEN (Cowden's)	Glioblastoma, endometrial, prostate, breast, lung, thyroid	25-50%
ATM (Ataxia telangiectasia)	Leukaemia, lymphoma, ovary, brain, breast colon, kidney, lung	25% Radiosensitive so avoid ionising radiation or higher %
PALB2	Breast, pancreas, ovarian	20-40%
CHEK2	Breast, colorectal, ovarian, bladder	25-37%
BRIP, RAD50, RAD51, ABRAXAS	Breast, ovarian	Variable moderate penetrance

1.2 Risk assessment methods

1.2.1 Risk calculating tools

The ability of healthcare professionals to accurately determine a woman's risk of developing breast cancer related to familial risk has increased significantly over the past few years. Initially, epidemiological studies showed factors associated with an increased risk of breast cancer, focussing mainly on oestrogen exposure and pathological risk factors and these were used by Gail (National Cancer Institute; www.cancer.gov/bcrisktool) to develop an assessment tool, albeit, not one specific for familial risk. This was followed by many others, each with a specific leaning, including:

- Claus (www4.utsouthwestern.edu/breasthealth/cagene/default.asp),
- Tyrer Cuzick (IBIS 2 version 7; Professor Jack Cuzick, Centre for Cancer Prevention, London, UK),
- Manchester (Evans, Eccles et al. 2004),
- *BRCAPRO* (BayesMendel Lab, Harvard University, Boston, MA, USA; <http://bcb.dfci.harvard.edu/bayesmendel/index.php>),
- BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; Cambridge University, <http://ccge.medschl.cam.ac.uk/boadicea/>)
- Myriad (www.myriadpro.com).

These risk calculators vary in which risk factors they include and the weight they allocate to each of these risk factors, to create the composite score from the combination of risks for an individual. Factors that may be assessed include:

- Familial risk factors
 - Some risk calculators have only a limited ability to assess the family tree with simple tools such as the Gail Model limited to first degree relatives, others are much more comprehensive, including third degree relatives, paternal lineage, bilateral breast cancer and male breast cancer. Some can even factor in the immunophenotype of the cancer, giving increasing weight to TNBC cancer in the family when calculating *BRCA1* risk (BOADICEA).
 - Some limit assessment to breast cancer, others include ovarian and other cancers.
- Pathological risk factors, e.g.
 - Atypical ductal hyperplasia
 - Lobular carcinoma in situ

- Hormonal risk factors, e.g.
 - Exposure to endogenous oestrogens
 - Early menarche, late menopause, nulliparity
 - Obesity
 - Breast feeding
 - Exposure to exogenous oestrogens
 - Hormone replacement therapy
 - Combined oral contraceptive pill

A British group looking at risk prediction for use in the NHSBSP looked at the different risk assessment models and found that they were improved by adding mammographic density (a long-recognised factor increasing the risk of breast cancer four to six-fold (Boyd, Byng et al. 1995)) and by adding DNA derived information about breast cancer genes and known SNPs (Evans, Astley et al. 2016).

The differences in the various risk calculators are summarised in table 1.4.

The goal of calculating risk has changed over time. Initially clinicians needed to be able to counsel their patients on their level of risk to allow decisions about risk management. Following the increase in the accessibility and affordability of genetic testing, risk calculators have gained a role in stratifying risk into groups requiring gene testing and those in whom it was thought unnecessary. In the UK, current guidelines permit gene testing if the level of risk of *BRCA* carriage is 10% or more making use of such tools mandatory in eligibility screening. More recently, risk calculators are also being used to assess risk to offer patients appropriate breast screening from an appropriate age. They are not used in isolation to determine eligibility for risk reducing surgery, where gene testing would be a required next step. The commonly used risk calculators are summarised in table 1.4.

Table 1-4 Characteristics of risk calculators (Gail, Brinton et al. 1989, Antoniou, Pharoah et al. 2004, Evans, Lalloo et al. 2005, Pennsylvania 2016)

	Pedigree complexity	Atypia	Weight, menarche,	Tumour subtype	Breast density	Estimates <i>BRCA</i> carriage risk	Br cancer risk prediction	Age adjusted risk
BOADICCEA	FDR and SDR with and without cancer	N/A	N/A	N/A	N/A	Yes	Yes	Yes
Penstate	Single lineage only, limited to number of affected relatives	N/A	N/A	N/A	N/A	Yes	No	No
IBIS	FDR and SDR with and without cancer	Yes	Yes	No	Yes	Yes	Yes (10 year risk)	Yes
Gail	Basic – number of affected FDRs	Yes	Yes	Yes	No	No	Yes	Yes
Manchester	Basic – number of relatives at given age ranges	N/A	N/A	N/A	N/A	Yes	No	No
Claus tables	Basic – number of affected relatives	N/A	N/A	N/A	N/A	No	Yes	No

1.2.2 Gene testing

Indications for testing for genes associated with an increased risk of familial breast cancer have increased over time. Women with a strong family history of breast and-or ovarian cancer or those with a known mutation in the family are usually referred to discuss genetic testing. Those with triple negative breast cancer younger than 50 years, and those with any breast cancer younger than 30 years of any subtype are also now referred to discuss testing, with implications especially for the latter who are already having to deal with the distress associated with the cancer diagnosis at such a young age (CG164 2013).

The process of testing has changed with the discovery of a greater number of breast cancer susceptibility genes and technological changes (for example next generation sequencing) allowing quicker, cheaper access to relevant results. Testing for a genetic mutation was initially restricted to identifying a mutation within *BRCA 1 or 2* in an affected woman and then looking to see if her kindred also carried this mutation. Now a panel of tests (including ATM, CDH1, CHEK2, PALB2, PTEN, STK11, TP53, NBN, RAD51C, RAD51D, BRIP1 and BARD1) can be performed on a single blood sample for the first family member to be tested in a “mutation search / screening test”. Previously, these tests were almost always performed in an affected (i.e. has had cancer) individual. In the last few years UK guidelines have expanded to permit testing of unaffected individuals and indeed old, uninformative results from samples tested with the previous Sanger sequencing technique can now be retested using recent technology. Thereafter where a positive result is found, unaffected or affected relatives are tested for this single gene identified as mutated within their family.

Gene test results are recorded in large electronic databases, with known pathogenic mutations and variants of uncertain clinical significance (VUS) noted and updated as and when clinical information provides greater understanding of their clinical significance (CG164 2013). The sensitivity of individual gene testing is high (approaching 100%) but the clinical significance of the results is less so, in particular for mutations not recognised as pathogenic (VUS), where the patient’s risk may remain unclear for a long time. Data for *BRCA 1 and 2* are now comprehensive and VUSs in these genes account for only about 3% of all results (Egginton JM 2012). In wider gene mutation search panels, VUSs may account for up to 40% of results (LaDuca, Stuenkel et al. 2014), raising real problems in counselling and advising women on risk management. There are also now known mutations within breast cancer risk genes that do not confer an elevated risk of breast cancer (Rebbeck, Mitra et al. 2015). This is a clinically worrying issue where commercial gene panels are concerned, as there may be inadequate support for women diagnosed with VUS or moderate risk genes without expert oversight of their care and counselling.

The broader range of genes being tested in mutation search panels raises a potential additional issue of a positive result that is unexpected or not in keeping with the family history. Examples include mutations being found in genes that confer risk of other cancers more than breast, but with no history of these cancers in the family (Clifford, Hughes et al.

2016). Managing these families requires multidisciplinary input, careful counselling and care to address the ongoing risk of breast cancer, albeit, perhaps not substantiated by the gene test panel. Use of risk calculators may guide risk management choices.

In the UK the NHS has recently launched the 100,000 Genome Project which has started collecting samples (blood and tumour) from breast cancer patients, allowing whole genome sequencing. This ambitious project allows gene panel testing of thousands of women and correlation with cancer diagnosis and will hopefully result in diagnostic improvements and better targeting of cancer treatment (England 2017).

1.2.3 Increased familial breast cancer risk with no demonstrated mutation

There remains a group of women with a very strong family history of breast cancer in whom a gene mutation is not identified. Their management largely mirrors that of women with confirmed *BRCA* mutations with respect to breast cancer risk reduction strategies but without the published data on *BRCA* risk management to further support their decisions. The risk of ovarian cancer is less clear and the role of oophorectomy must be carefully assessed on an individual basis (Berek, Chalas et al. 2010). Assessing risk is complex, relying upon use of risk stratification tools that have been created with a heterogeneous group of families, resulting in estimates that may not be as accurate as for those with a recognised mutation. Women with two relatives with breast cancer under 50 years old or three relatives affected at any age were estimated by a Canadian group to have a four-fold increase in risk (Metcalfe, Finch et al. 2009). A prospective study of women at high risk without an identified gene mutation is ongoing, looking at risk reduction strategies used and long term follow up to gain a better understanding of this group (Kotsopoulos, Metcalfe et al. 2014). It is likely that this group of women will get smaller as extended panel testing becomes more widespread and the role of SNPs and epigenetic changes become better understood.

1.2.4 The psychological impact of gene testing

A retrospective study found that women requested genetic testing for three common reasons, to learn about, in order: (Metcalfe, Liede et al. 2000)

- Personal risk of cancer

- Children's risk of cancer
- Family's risk of cancer

Altruistic tendencies were noted in women being tested, both towards their family and to women generally (Tessaro, Borstelmann et al. 1997). Also highlighted by many studies was the lack of information available to women necessary for them to translate risk into real, personal terms. This is an important fact for healthcare professionals to understand, as risk appreciation will clearly guide women's decision in how to manage risk. To allow this decision to be truly informed, it is imperative that the risk be understood as fully as possible and not exaggerated or underestimated.

Authors of a paper looking at the impact of familial risk on life assurance summarised that before testing, women needed to understand three key implications of a positive or negative result:

- Options (and the effects of these options) for managing risk
- The risk of compromising future insurance policies for both the individual being tested and for their immediate family members who may, in the future, also be required to disclose positive gene test results in first degree relatives (Lynch, Doherty et al. 2003). There is a current Concordat and Moratorium in place until 2019 meaning that insurers will not ask for results of genetic tests, although they can still ask about family history directly and increase premiums on this basis (Cancer Research 2016)
- The extent to which it may affect other members of the family (Hunter and Humphries 2005).

They looked at 21 insurance companies and asked them to provide a quote for a 35 year old woman whose mother had been diagnosed with breast cancer at the age of 35 years of age in three scenarios: first, no risk modifying strategy being followed; second, mammographic screening and third, after risk reducing bilateral mastectomies. They found the different companies (that responded) changed the mortality rating in the different scenarios in an inconsistent manner (see figure 1.1).

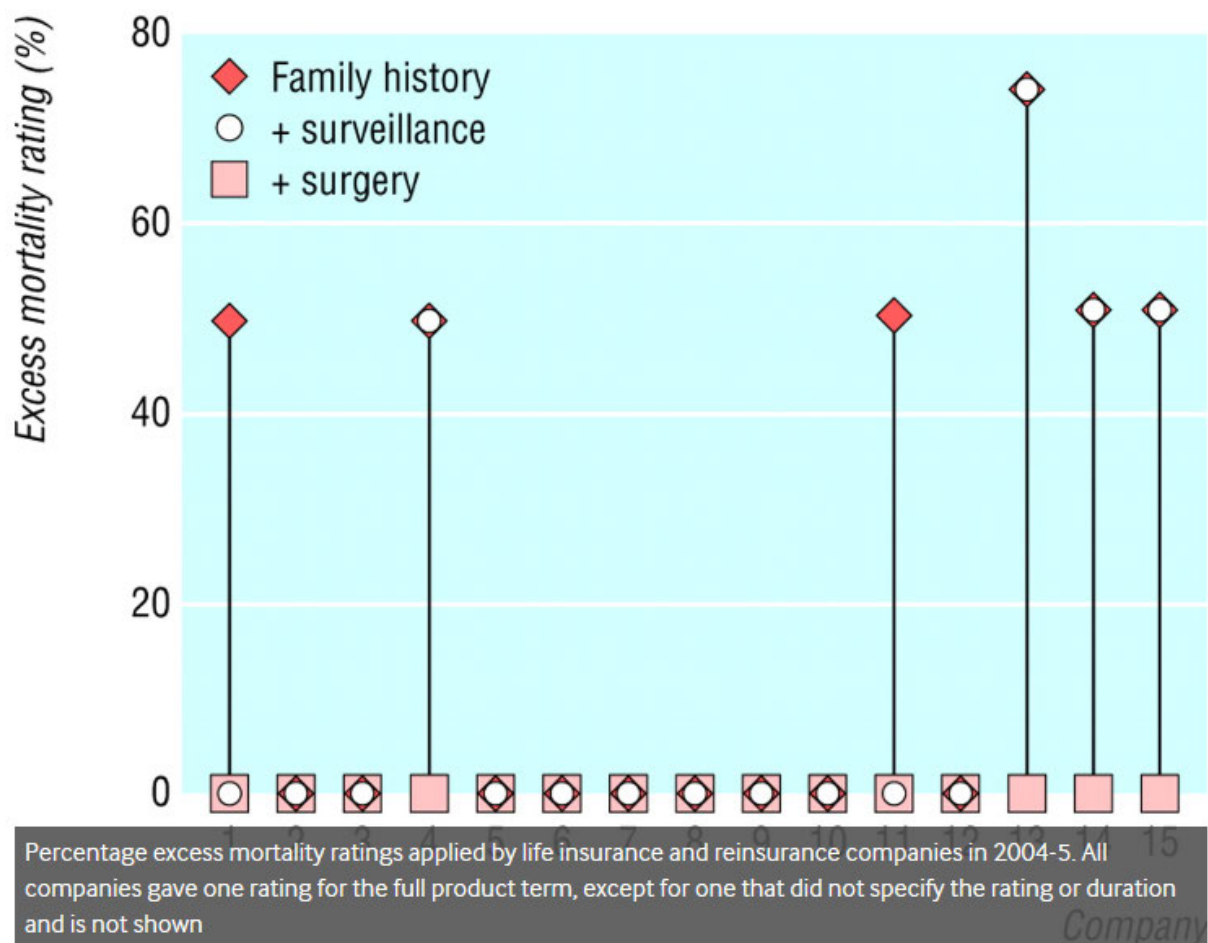


Figure 1-1 Life insurance penalties (Hunter 2005, reproduced with permission) (Hunter and Humphries 2005)

In addition, women undergoing testing should be fully aware of the complexity of interpreting gene test results and the fact that a positive result does not mean that cancer will inevitably develop. The impact on other family members is often focussed on children born to *BRCA* positive parents, although it will have implications for siblings and even parents.

The decision to undergo gene testing should not be taken without care to consider the implications highlighted by Hunter in 2005 (Hunter and Humphries 2005). Distress associated with undergoing genetic testing has been clearly described for both carriers and non-carriers (Hamilton J. 2009). Geller and colleagues found that 82% of women wanted their healthcare practitioner to make a recommendation about whether to undergo a gene test (Geller, Bernhardt et al. 1998), a possible reflection of the complexity of the decision.

1.2.5 Partners' role at the time of diagnosis

The role of partners in deciding whether to undergo testing has been examined. Husbands were more involved and influential in the decision than female relatives, even in distressed marriages. Negativity from close relationships was more influential on well-being than was positivity (Coyne 1999). The role of partners should be acknowledged in pre-test counselling. "Husbands want to understand and better support their wives", additionally, parents (with increased risk) have concerns about how and what to tell children regarding a hereditary risk (Norris, Spelic et al. 2009). A review noted that women experienced higher distress levels if their partners were not supportive during the testing process (Sherman, Kasparian et al. 2010).

1.2.6 Impact of gene test

Genetic testing has significant implications, particularly when the result is positive, but not exclusively so. Most women regard risk awareness as enabling but some describe feeling neither well nor unwell, but 'in limbo' (d'Agincourt-Canning 2006). A common test-related reaction is guilt regarding children's potential risk. Family circumstances often provided the context in which positive gene results were interpreted, with women also using their experience with cancer (limited as it may be) to interpret their results and guide subsequent decisions. The way diagnosis affects adolescent offspring was poorly understood and a cause of distress for some women. Testing may affect relationships within a family, for example partners becoming more distant (Metcalf, Liede et al. 2000). Women with a recent cancer diagnosis are at increased risk of negative effects related to testing (Vadaparampil, Miree et al. 2006).

Non-carriers' (in *BRCA* families) depression scores significantly increased in the first few weeks after testing, in comparison to those of mutation carriers, which were essentially unchanged, possibly explained by the concept of 'survivor guilt' (Wagner, Moslinger et al. 2000). Women with a confirmed mutation but with no personal history of cancer had greater test-related distress than those who had had cancer prior to diagnosis (Croyle, Smith et al. 1997).

Gene testing at the time of a new breast cancer diagnosis affects management plans (Evans, Laloo et al. 2005) with up to 50% opting for bilateral mastectomy initially (Schwartz, Lerman et al. 2004), instead of possible breast conserving techniques. Of 231 women tested, 21% underwent cancer management before gene test results were available. Performing a gene test with significant implications is an additional burden at a time when a cancer diagnosis is the over-riding concern. Contralateral risk reducing mastectomy at the time of therapeutic mastectomy was not associated with reduced quality of life or of increased distress (Tercyak, Peshkin et al. 2007). Factors associated with deleterious effects on quality of life were chemotherapy, a strong family history of cancer and receiving positive gene test results, effects noted in both the contralateral mastectomy group and those undergoing ipsilateral procedures alone. The advent of next generation sequencing means that tests results will be available for more women at an early stage in their cancer journey and can be factored into management decisions. However, the impact of this is still unclear and requires further research.

A commonly cited cause of dissatisfaction relating to gene testing concerned the length of time spent waiting for results, with unanimous dissatisfaction noted in one focus group (Di Prospero, Seminsky et al. 2001). Lodder and colleagues studied high risk women who declined genetic testing, finding similar distress levels in tested and untested women. Those declining tended to be childless, have higher levels of education, were younger when relatives had cancer and tended to be reluctant to consider surgery. There was no evidence of avoidance or anxiety beyond that seen in the tested group. Negative effects of a positive test result, for example insurance difficulties were quoted as a reason to decline (Lodder, Frets et al. 2003).

As awareness of *BRCA* gene mutations has increased, so have the numbers of women being referred for assessment and risk management. These women fall broadly into two groups: those with a recognised genetic mutation and those without, with overlapping but different care requirements (Lodder, Frets et al. 2002, van Oostrom, Meijers-Heijboer et al. 2003, Geirdal and Dahl 2008). Tools can be used to stratify risk according to family history (Gail, Brinton et al. 1989, Claus, Risch et al. 1994, Amir, Evans et al. 2003, Antoniou, Pharoah et al. 2004, Evans, Eccles et al. 2004). The possibility of emotional distress, family dynamic changes and future insurance difficulties should be raised as (or ideally before) high risk

status is confirmed. If, on assessment, a woman's risk perception is felt to be significantly inaccurate, counselling can better inform women prior to progressing in their management (Goodwin 2000).

The level of patient and societal awareness of hereditary breast cancer was significantly impacted on by the media coverage of the risk reducing surgery of Angelina Jolie which increased risk assessment referrals significantly and also interest in double mastectomy (Evans, Barwell et al. 2014).

Short-term deleterious psychological effects are common when a positive gene mutation is discovered (Watson, Foster et al. 2004) but also in those diagnosed at increased risk without a proven genetic abnormality (Geirdal and Dahl 2008). The age at which women present adds context to the situation they face. Risk reducing strategies such as bilateral oophorectomy or chemoprophylaxis will impact on women's ability to have a family and result in premature menopause, with a greater long-term impact in younger women. Occupation can also influence their view about how to manage risk. For women pursuing risk reduction mastectomy, breast feeding will not be possible. The impact of a pre-existing stable relationship can be significant in terms of support or lack thereof. For those not in a relationship there may be concern about the impact their risk may have on developing future relationships.

Women at increased risk of familial breast cancer have a need for concrete information about risk and risk management strategies (Werner-Lin 2008). One group found that women wanted to discuss possible surgical options and that so doing was not associated with increased anxiety (Lobb and Meiser 2004). Werner-Lin found that women who had solid genetic counselling "faired the best in the long term; [with] a substantial knowledge base about their risk in addition to familiarity with clinical trials and screening protocols to maximise surveillance". Small numbers limit this study somewhat. Another key finding was the isolation described by many women, with many wanting but struggling to make contact with other women in a similar situation.

Themes that should be addressed in counselling include (Lobb and Meiser 2004):

- Effectiveness of risk reduction measures and residual risk
- Surgical considerations, including timing
- Motivating factors
- Body-image and sexuality
- Psychological impact
- Hormonal impact of oophorectomy

One study noted that the more aspects of genetic testing were discussed, the greater the decrease in anxiety and cancer worry (Lobb, Butow et al. 2004, Cabrera, Blanco et al. 2010). Women whose doctors facilitated understanding had a greater decrease in depression. Interestingly, where more supportive communication was used, women were significantly more anxious at four weeks (OR=1.66, 95% CI=1.25–2.19, p=0.000), and these women were not more anxious at the baseline assessment. Sending a summary letter after assessment also seems to reduce anxiety and improve risk awareness (Lobb, Butow et al. 2004). Another study noted that one year after initial assessment, non-mutation carriers who chose breast screening had reduced adherence with mammography from baseline levels, demonstrating a possible need for improved risk communication and guidance in medical decision making (Lerman, Hughes et al. 2000).

Support around gene testing needs to be established with robust counselling on the implications of the gene test with comprehensive and ideally personalised information provision. Women may use internet chat-rooms as an additional source of support (Kenen, Shapiro et al. 2007) and 38% of one focus group felt they would have benefitted from a dedicated support group (Di Prospero, Seminsky et al. 2001). Women using chat-rooms in a dedicated website for women at risk of breast cancer sought three specific areas of support:

- emotional support
- specific experiential knowledge
- information from each other (Kenen, Shapiro et al. 2007).

1.3 Risk management strategies for increased familial breast cancer risk

Options for managing increased risk of breast cancer are relatively limited. The most effective strategy to reduce risk is bilateral mastectomy with or without bilateral oophorectomy. The use of selective (o)estrogen reuptake modulators (SERMs) and aromatase inhibitors as chemoprophylaxis is effective at reducing the risk of ER positive breast cancer only and despite numerous trials with long term follow-up, none has so far demonstrated any survival advantage (Fisher, Costantino et al. 1998) (Martino, Cauley et al. 2004, Fisher, Costantino et al. 2005, Barrett-Connor, Mosca et al. 2006, Cuzick, Forbes et al. 2007, Powles, Ashley et al. 2007, Sestak, Singh et al. 2014). In addition, *BRCA1* carriers tend to have ER negative breast cancers and so will likely see little benefit. Breast screening with MRI and mammography is the other widely used option, aiming to identify cancers at an early stage with an associated survival benefit (Evans, Kesavan et al. 2014). It is important that women are informed of risk factors they may be able to modify, for example exposure to oestrogens and avoiding obesity (Chen, Chen et al. 2016), however, in the case of *BRCA* carriers the potency of the underlying gene mutation and the relatively small effect size of lifestyle factor modification means that these will not have much impact in these women. All of these various strategies are discussed below in more detail.

1.3.1 Modifiable risk factors

There is little evidence to support modifying breast cancer lifestyle risk factors as a form of risk reduction in women at increased familial breast cancer risk. Risk factors were initially identified in population based studies many years ago (Gail, Brinton et al. 1989), and these changes, whilst unlikely to do harm, may equally afford little or no significant benefit, although it is thought that up to 30% of breast cancers (including those in high risk groups) could be avoided by making lifestyle changes (Harvie M 2015). Factors known to affect breast cancer risk include dietary intake of saturated fats, alcohol consumption (relative risk 1.28 with 95% confidence interval, CI: 1.07, 1.52) (Jayasekara, MacInnis et al. 2016), exercise (Pizot, Boniol et al. 2016), obesity (Chen, Chen et al. 2016), age at first childbirth, total number of pregnancies and breast feeding (Goodwin 2000). *BRCA1* women with low parity (under 3) had an increased risk of breast cancer, whilst the opposite effect was true for ovarian cancer, each birth conferring a 40% increase in risk (for up to 5 births) in contrast to the trend seen in sporadic ovarian cancer (Narod, Goldgar et al. 1995). Whilst this is

technically a modifiable factor, many women would not regard it as such and the clinical application of these findings is limited.

1.3.2 Breast screening

Screening does not affect the likelihood of cancer developing and indeed may increase the risk of it being diagnosed. It aims to detect lesions at an early stage to reduce morbidity and mortality. Options that have been proposed include:

- Breast self-examination (BSE)
- Clinical breast examination (CBE)
- Mammography
- Breast magnetic resonance imaging (MRI) screening

However only the latter 2 have any significant evidence base to support their utility.

A systematic review of BSE has shown it offers no survival benefit (Elmore, Armstrong et al. 2005), however BSE can detect some cancers missed by mammography and interval cancer detection is improved by following a BSE programme (Baines and Miller 1997). This is especially true in younger women, who have increased sensitivity in self-examination compared to an older cohort (Baines and Miller 1997), although at the cost of false positive findings and the associated morbidity (Elmore, Armstrong et al. 2005). Compliance with and frequency of BSE is obviously an important factor to consider when assessing outcomes from this screening tool. One study found women with increased anxiety to be less likely to comply with BSE advice (Kash, Holland et al. 1992), whilst others have data showing increased anxiety associated with either avoidant or hypervigilant ends of the self-examination spectrum (Brain, Norman et al. 1999). Similarly CBE has limited evidence to support its use as a screening tool (Fenton, Barton et al. 2005).

Screening a high risk group aims to detect more cancers at a pre-invasive stage than are seen in an unscreened group. The screening requirements of women at increased risk include a younger starting age and a reduced screening interval compared to population breast screening programmes. In the UK, triennial mammographic breast screening is offered to all women aged between 47-73 (NHSBSP 2011). Most European countries have similar population based screening strategies based on evidence that most sporadic cancers

occur in women from a perimenopausal age onwards (Cancer Research 2010) and taking into account the risks of ionising radiation and the costs of screening balanced against its benefits. In the UK, the National Institute of Clinical Excellence (NICE) guidelines at the time of data collection recommended those at increased risk undergo additional annual mammographic screening from 40-50 with those at very high risk having annual MRI from 30-50 years, in addition some groups are offered additional screening to the age of 60 or 70 as part of a rather complex risk and age stratified algorithm (CG164 2013).

The currently approved mammographic images include two views (usually cranio-caudal and mediolateral oblique) but there is new technology using a series of images taken along an arc through the breast which are then reconstructed to provide cross sectional images through the breast, usually at 0.5cm intervals. These can be read in a similar manner to a CT scan and may improve the definition of lesions which can be otherwise hard to spot within dense breast tissue. This technique is known as tomosynthesis (Helvie 2010). Also described and still in the early stages of clinical applicability are the novel use of contrast to enhance (conventional) digital mammography, performed during the same breast compression as used for mammography, and the use of automated ultrasound scanning used to reduce recalls and improve specificity for lesions seen on mammogram that are clearly benign on subsequent ultrasound (Helvie 2010). Automated ultrasonography has been approved in the USA for screening women with a normal mammogram and dense breasts. (Shin, Kim et al. 2015) The applicability of these techniques to family history screening programmes has not yet been reported, although as experience with them grows, it is likely that their use will be expanded.

Evidence supporting (single modality) mammographic screening in young women at risk of familial breast cancer is limited, see table 1.5 below. Younger women have increased breast density reducing the sensitivity of mammography (Kerlikowske, Grady et al. 1996) and are at greater risk of radiation induced cancer development (Law, Faulkner et al. 2007) and may also have a greater risk of interval cancers due to more aggressive disease biology in this age group. All of these reduce the utility of screening in this age group

Table 1-5 Mammographic screening trials for women under 50 years of age (Moss, Wale et al. 2015)

Trial	n=	Age (yrs)	Risk	Type of trial	Length of follow up	Findings
AGE Trial	160921	40-48	Normal, population based	Randomised	17 years	Triennial mammography from 40-48 reduced breast cancer mortality (RR 0.75, 0.58–0.97)
FH01	6710	40-49	Increased familial risk	Single arm cohort study	5yrs	Annual mammography reduced breast cancer mortality, found smaller tumours, with fewer involved nodes. Relative hazard of breast cancer death 0.24 (95% CI 0.09-0.66, P=0.005)

A systematic review demonstrated improved sensitivity by combining mammography with MRI screening, but also highlighted the relatively poor sensitivity of mammography particularly in younger aged women (Warner, Messersmith et al. 2008). A more recent single centre study found limited benefit in adding mammography to MRI screening of women at increased risk, noting the poor sensitivity of mammography in this group (Riedl, Luft et al. 2015). Mammographic sensitivity is further reduced especially in *BRCA1* mutation carriers due to these cancers' lack of typical mammographic malignant characteristics (Layer, Rieker et al. 1994). A recent paper compared the radiological appearances of triple negative cancers (frequently seen in *BRCA1* carriers) to those of hormone receptor positive / HER2 negative cancers (seen more commonly in the general population) (Boisserie-Lacroix, Macgrogan et al. 2013). Table 1.6 and figure 1.2 demonstrate the key differences in the radiological features (although both can present with features not described on this list).

Table 1-6 Radiological features of cancers

	HR positive / HER2 negative cancer – common features	Triple negative cancer – common features
Shape on imaging	Irregular	Round / oval / lobulated
Echogenicity	Hypoechoic	Hypoechoic or markedly hypoechoic
Margins	Spiculated / indistinct	Circumscribed / microlobulated / indistinct
Posterior acoustic features	Posterior shadowing	Absent / positive
MRI appearance	T2 hyposignal, homogeneous, BI-RADS 4/5	T2 hypo or hypersignal, BI-RADS 5, rim enhancement

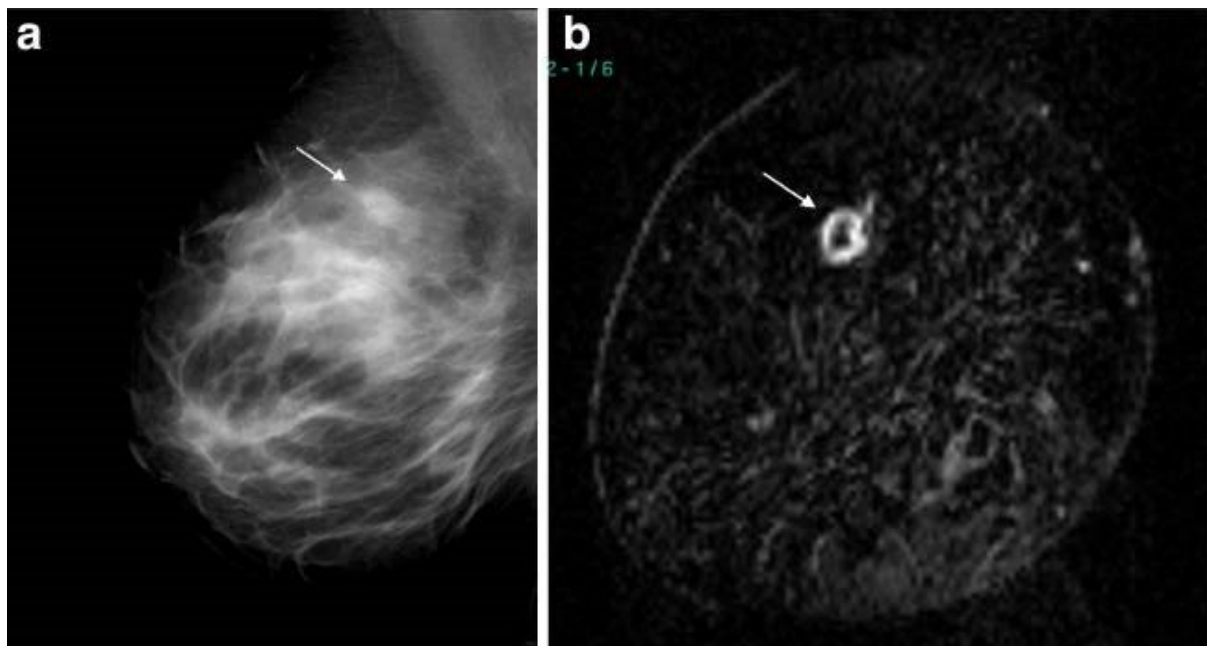


Figure 1-2 Imaging of *BRCA1* tumour: mammographic features could be considered benign but MRI rim enhancement strongly suggests malignancy. (Veltman, Mann et al. 2008) (Open access)

The risks of developing radiation-induced cancer outweigh any screening benefits of mammography in women under the age of 40 at normal levels of risk (Lieberman, Dershaw et al. 1993, Berrington de Gonzalez and Reeves 2005). Equivalent data have been derived from population figures and demonstrate a high-risk group derive a net benefit from mammographic annual screens from 40 years of age at which, where the radiation risk is less

than the benefit in terms of survival in the high risk familial group. The benefit between 30-39 years was either nil or minimal and so care must be taken to balance the increased lifetime exposure against the potential benefits of mammographic screening in women under 40 years (Berrington de Gonzalez, Berg et al. 2009).

There are two studies (including the FH01 study that included 6710 increased familial risk women undergoing screening) that demonstrate that mammographically detected cancers in women under 50 are less likely to be node positive and have improved disease specific survival than those found incidentally (Maurice, Evans et al. 2006, Duffy 2010). A recent consensus from the US advocates biennial mammography for women aged between 50 -74 but also adds that women who place higher value on the potential benefits than the potential harm may wish to start biennial screening from 40 onwards (Siu 2016). Fortunately, most women find mammography acceptable, in terms of discomfort of the procedure (Litton, Westin et al. 2009) although another study found a concerning substantial minority (15.9%) of high risk women were not adherent to mammographic screening advice (Antill, Reynolds et al. 2006).

Increasing experience with and access to breast MRI has changed the options now routinely offered to women at increased risk. Whereas previously mammography was the only option for breast screening, there is now dual modality screening with mammography and MRI scanning, which has gradually become more widely accessible. The use of MRI breast screening in high risk women has been studied over recent years and evidence and a meta-analysis of the accumulated evidence shows MRI either alone or in conjunction with mammography has improved sensitivity but reduced specificity when compared with mammography alone, i.e. it is less likely to miss cancers but is more likely to lead to false positive results with associated physical and psychological morbidity and cost (Warner, Plewes et al. 2001, Hartman, Daniel et al. 2004, Kriege, Brekelmans et al. 2004, Warner, Plewes et al. 2004, Kuhl, Schrading et al. 2005, Leach, Boggis et al. 2005, Lehman, Blume et al. 2005, Trecate, Vergnaghi et al. 2006, Hagen, Kvistad et al. 2007, Lehman, Isaacs et al. 2007, Sardanelli, Podo et al. 2007, Warner, Messersmith et al. 2008). MRI screening trials are reviewed in table 1-7.

Table 1-7 MRI breast screening studies

Study	Participants	n=	Mammogram %		MRI %		MMG and MRI %	
			Sens	Spec	Sens	Spec	Sens	Spec
Hagen 2007	Gene mutation	491	32	NR	68	NR	80	NR
Hartman 2004	High family risk	41	0	NR	100	75	100	NR
Kriege 2004	High family risk	1909	33	99	64	96	NR	NR
Kuhl 2005	High family risk	529	32	97	91	97	93	42
Leach 2005	High family risk	649	14	98	51	96	60	95
Lehman 2005	High family risk	367	25	98	100	93	100	91
Lehman 2007	High family risk	171	33	91	100	79	100	73
Sardanelli 2007	High family risk	278	59	99	94	98	100	NR
Trecate 2006	High family risk	116	33	100	100	97	100	97
Warner 2001	High family risk	196	43	99	86	91	100	NR
Warner 2004	Gene mutation	236	36	100	77	95	86	95

Most women at very high risk are offered a combination of annual MRI and mammography, meaning they are screened approximately every six months (CG164 2013). Beneficial effects are noted in women with known mutations and in those without, with detected tumours being generally small and node negative, implying a potential survival benefit (Kriege, Brekelmans et al. 2004, Warner, Plewes et al. 2004, Kuhl, Schrading et al. 2005, Leach, Boggis et al. 2005, Lehman, Blume et al. 2005) which was confirmed in 2014 by Evans *et al* (Evans, Kesavan et al. 2014) who demonstrated an improved 10 year survival for those undergoing combined MRI and mammographic screening compared to those not being screened, with

particular benefit being derived for *BRCA2* carriers having MRI screening. This may reflect the more standard subtype profile of *BRCA 2* cancers, with more time to detect them due to slow growth rates than the more typical *TNBC BRCA 1* cancers which may be more likely to develop between screening intervals.

The need for concurrent mammographic and MRI breast screening is uncertain. Mammographic screening did not improve the screening cancer yield in one high risk group undergoing concurrent MRI screening (Kuhl, Weigel et al. 2010) and interestingly, they noted no improvement in cancer yield (from that achieved with MRI screening) by adding either routine ultrasonography or clinical breast examination. A systematic review of studies adding MRI to mammography did not comment on MRI screening alone but noted several studies found mammographically detected cancers that were occult on MRI (Lord, Lei et al. 2007). A model designed to compare mammographic, MRI and combined (mammographic and MRI) screening in *BRCA1* women found that combined screening was best at detecting early stage cancer (Reis, Tavakoli et al. 2009). This model demonstrated combined screening resulted in the greatest improvement in long-term outcome. It also found that MRI screening was more cost effective as part of combined screening than when it was when used as the sole method of screening in *BRCA1* mutation carriers. A similar study of *BRCA1* and 2 mutation carriers found combined screening of *BRCA1* women to be more cost-effective than that for *BRCA2* women (Reis, Tavakoli et al. 2009). No similar data are available for women without *BRCA* mutations and as breast screening cost-effectiveness correlates to the risk of the group being screened, it is important that women's risk be accurately assessed to allow appropriate screening. The cost of treating higher stage cancers is increasing as therapeutic options develop and this is likely to impact on future screening cost-effectiveness models in favour of screening techniques proven to increase pre-invasive cancer detection.

Figures for anticipated cancer incidence in women at increased risk of familial breast cancer vary. Reis and colleagues quoted an incidence of 6 cancers per 1000 women screened (Reis, Tavakoli et al. 2009) whilst another group found a significantly higher rate of up to 13 per 1000 (Tilanus-Linthorst, Bartels et al. 2000). The Royal College of Radiologists suggest that mammographic screening outcomes for women at increased familial risk aged 40-50 should be similar to those of population screening of women aged over 50 (Radiologists 2003),

whilst a systematic review of high risk surveillance demonstrated a 2% incidence (Warner, Messersmith et al. 2008). Clearly the risk profile of the screened population will determine cancer incidence of the group and the heterogeneity of risk in a familial screening programme is likely to account for these differences.

The effects of screening are much broader than can be represented by sensitivity and specificity figures, however. The impact of cancer related anxiety may not be reduced by participation in the screening programme. The actual MRI screening process is noisy and for those with claustrophobic tendencies, lying in the tunnel can present challenges, with 4% finding it “extremely distressing” (Anderson J 2004). Most find it acceptable, but interestingly, only 89% of a cohort of 611 British women said they definitely intended to attend further MRI screening appointments (Anderson J 2004). Some women fear that screening will detect cancer too late to cure (Unic, Verhoef et al. 2000). Another study noted that 37% of women were anxious at the time of MRI, however this did not appear to affect their general health, which was better than age/sex adjusted population figures (Rijnsburger, Essink-Bot et al. 2004).

The wait for screening results can result in further anxiety, which is clearly worsened by the not infrequent need for further assessment and biopsy, with a NHS Breast screening programme recommended recall rate being below 10% and ideally less than 7% (Programmes 2012) but actual recall rates in the reported studies varied between 8-17% (Kriege, Brekelmans et al. 2004, Warner, Plewes et al. 2004, Kuhl, Schrading et al. 2005, Leach, Boggis et al. 2005, Lehman, Blume et al. 2005). It is particularly important that screening participants are aware of this fact and understand the inherent limitations of breast screening. The morbidity (physical and psychological) associated with repeated scans and biopsies should not be underestimated. One study found that a quarter of women having annual mammograms experienced at least one false positive during screening (Elmore, Barton et al. 1998). A systematic review of the psychosocial outcomes for women at increased familial risk undergoing screening further addresses this topic, see Chapter 3.2. Ultimately, combined mammographic and MRI screening has been shown to offer a survival advantage to high risk women and it remains the best alternative long-term strategy to manage risk for women who want to avoid risk reducing mastectomies.

1.3.3 Chemoprophylaxis

Increased oestrogen exposure has long been recognised as a risk factor for breast cancer. Women who experience early menarche, late menopause, the nulliparous, the obese and those taking supplemental oestrogen (hormone replacement therapy or the combined oral contraceptive) have an increased risk of breast cancer in population studies (Gail, Brinton et al. 1989). Further supporting this epidemiologically derived risk increase are the findings in trials of adjuvant tamoxifen (or similar) where contralateral breast cancer rates were reduced (see below). Research has thus focussed on whether oestrogen exposure could be modified in high familial risk women to reduce the impact of a further carcinogenic risk. There are four ways in which oestrogen exposure can be minimised for an individual:

- Oophorectomy
- Gonadotrophin releasing hormone agonist (GnRH agonist), e.g. zoladex, which suppresses oestrogen production
- Selective oestrogen reuptake modulators (SERMs), which selectively block oestrogen receptors in breast tissue
- Aromatase inhibitors (AIs), which block the synthesis of oestrogen in peripheral tissues (and are not suitable for women who have functioning ovarian oestrogen production)

Selective oEstrogen Reuptake (or Receptor) Modulator (SERM) drugs have been used for many years to treat oestrogen receptor (ER) positive breast cancers by blocking oestrogen receptors in breast cells. Tamoxifen is the most commonly prescribed SERM, with raloxifene being used less frequently. A meta-analysis of 55 trials involving 37000 women assessed the role of adjuvant tamoxifen and demonstrated a reduction in contralateral breast cancer of 47% ($p=0.00001$, $SD=9$) after five years of treatment (EBCTCG 1998). Research into the role of tamoxifen in the primary prevention of breast cancer in both normal and higher risk women has been ongoing for many decades. Early, medium term and longer-term results have demonstrated a substantial reduction in breast cancer incidence with chemoprophylaxis, but despite relatively long term follow up, they have failed to demonstrate a survival benefit, highlighting instead the significant thromboembolic and endometrial cancer risks of SERMs (Visvanathan, Chlebowski et al. 2009). Data on the use of AIs in this setting are less mature. These studies are reviewed in more detail below.

In 1992 the National Surgical Adjuvant Breast and Bowel Project (NSABP) demonstrated a 49% decrease in invasive breast cancer development in women at increased breast cancer risk treated with tamoxifen, compared to a placebo. ER positive cancer development fell by 69% but ER negative tumour development was, perhaps unsurprisingly, unaltered (Fisher, Costantino et al. 1998). The STAR trial (undertaken by the same group) compared tamoxifen with raloxifene, another SERM, finding similar efficacy in prevention of invasive breast cancer, but with different side effect profiles (Vogel, Costantino et al. 2006).

Two studies found the incidence of breast cancer dropped significantly (RR 0.65; 95% CI, 0.56-0.74) in high risk women given tamoxifen compared with matched controls (Fisher, Costantino et al. 2005, Cuzick, Forbes et al. 2007), however the incidence of endometrial and thromboembolic events rose, particularly for those on tamoxifen (Nelson, Fu et al. 2009). Consistently, the reduction in breast cancers has been limited to ER positive tumours. Evidence supporting the use of aromatase inhibitors for chemoprophylaxis (in the post-menopausal high risk group) was strengthened by the results of the IBIS II trial, demonstrating a significant risk reduction for women taking anastrozole as opposed to a placebo for five years (HR 0.47, 95% CI 0.32–68; $p < 0.0001$) (Cuzick, Sestak et al. 2014). The assumption that reducing breast cancer incidence will equate to a reduction in breast cancer death has not been demonstrated however. A summary of the evidence for chemoprophylaxis by Narod in 2015 found that the number of breast cancer related deaths in the groups taking chemoprophylaxis was actually higher than that seen in the control groups. It would appear that the cancers that do develop in the chemoprophylaxis group may be more likely to be fatal. The author notes that ER negative tumours tend to be fatal more rapidly than ER positive, meaning the benefit derived from reducing ER positive tumours may not yet be fully apparent due to the need for prolonged follow up to capture this data.

The risks of taking SERMs (endometrial cancer, thromboembolism, menopausal symptoms) need to be carefully considered, in addition to the clear explanation that breast cancer risk is reduced but in no way eliminated. Data supporting use of chemoprophylaxis agents are based on findings in women at a slightly increased risk of breast cancer. Adequate data do not yet exist to demonstrate similar efficacy in women with *BRCA* gene mutation levels of risk, nor to differentiate between *BRCA1/2*, other genetic abnormalities and women with no

detectable mutation, although one small study suggested cancer incidence may actually increase in a *BRCA1* subgroup on tamoxifen (King, Wieand et al. 2001), this has yet to be substantiated with greater numbers. This may be relevant, as different tumour characteristics are found in these different groups and some may be hypothesised to benefit less from SERM chemoprophylaxis. Lack of efficacy in a *BRCA 1* group would also be theoretically supported by the recent publication showing no protective effect of BSO on breast cancer risk in *BRCA1* carriers but strong protection in *BRCA 2* carriers (Kotsopoulos, Huzarski et al. 2017).

There is some research into other, non-oestrogen modulating agents, focussing in particular on reducing ER negative and basal type breast cancers, seen more frequently in *BRCA1* gene mutation carriers. COX II inhibition has been demonstrated to reduce breast cancer incidence with a risk reduction of 0.88 in one study (Takkouche, Regueira-Mendez et al. 2008). Women taking NSAIDs are less likely to develop cancers in the breast and bowel and this effect is more pronounced in women taking selective COX II inhibitors (Ashok, Dash et al. 2011). Unfortunately, the cardiovascular risk profile means the clinical applicability of this finding is still limited. There is also work looking at metformin (Gronich and Rennert 2013), retinoids (Veronesi, Mariani et al. 2006) and PARP inhibitors (To, Kim et al. 2014) as risk reducing agents based on data from their use in the adjuvant setting and limited data using them in the preventative setting, with likely, but unproven or unclear, benefit as chemoprophylaxis agents.

Recommendation by a doctor correlated strongly with tamoxifen use, as did cancer-worry and a previous abnormal breast biopsy (Bober, Hoke et al. 2004). Another study found that uptake of SERMs was low citing women's lack of unawareness of the benefits, off-putting risks and side effects and a perception that they are "cancer drugs" (Holmberg, Waters et al. 2015). They found a greater willingness to use a SERM for chemoprophylaxis when women felt they were "at risk", raising again the issue of risk perception and how it guides women's choices in risk management. An estimated 40% of women will not complete a full five-year course due to unacceptable side effects (Roetzheim, Lee et al. 2015). Use of tamoxifen was not associated with increased anxiety or any negative impact on psychosocial or sexual function (Thirlaway, Fallowfield et al. 1996, Fallowfield, Fleissig et al. 2001). The oral contraceptive pill offers some degree of chemoprophylaxis against ovarian cancer, whilst

theoretically increasing the risk of breast cancer (Cancer Research 2011), although evidence suggests this effect is minimal (Gaffield, Kapp et al. 2009). Whilst chemoprophylaxis continues to be offered to high risk women and may be offered to those at moderate risk, further long-term follow up data will add to our understanding of the risks and benefits and may guide practice in the future.

Chemoprophylaxis is not the focus of this MD and the section above is provided to add context and is not therefore a comprehensive review of current research into this topic.

1.3.4 Risk reducing breast surgery

Risk reducing mastectomy (RRM), also known as prophylactic mastectomy (be it bilateral or contralateral) is the most effective risk reduction strategy available to women at increased risk. Prior to the discovery of *BRCA* genes, relative indications were wide-ranging (Snyderman 1984) but improved understanding has reduced the proportion of women for whom this radical procedure is being now considered appropriate.

Bilateral RRM confers a consistent reduction in breast cancer incidence and mortality (Lostumbo, Carbine et al. 2004, Lostumbo, Carbine et al. 2010), with a risk reduction of over 90% with mastectomy in women at high and moderate risk (Hartmann, Schaid et al. 1999, Contant, Menke-Pluijmers et al. 2002, De Felice, Marchetti et al. 2015). A recent study noted that women at high family risk undergoing risk reducing mastectomy had a survival advantage over similar women who did not (Ingham, Sperrin et al. 2013). Grann and colleagues calculated a survival benefit of 2.8 to 3.4 years if RRM is done at age 30 years (*BRCA* 1/2) instead of surveillance (this study pre-dated MRI breast screening). This extended to 3.3 to 6.0 years if combined with RRSO (Grann, Panageas et al. 1998) with a reduction in breast cancer incidence of 46% and breast cancer mortality of 56% (Eisen, Lubinski et al. 2005, Rebbeck, Kauff et al. 2009). A recent update demonstrates that for a *BRCA1* woman aged 25 years, were she to die before the age of 80, the likelihood of it being due to breast cancer is 25.6%. By having risk reducing mastectomies at 25 years of age, this proportion would be entirely prevented. It also demonstrates that for a 25 year old *BRCA1* carrier, risk reducing mastectomy adds 3.3 years to her life expectancy. This drops to 0.7 years at 55 years of age (Giannakeas V 2017)

Improvement in life expectancy was much less if surgery was done beyond the age of 60, with an unsurprising survival advantage predominantly in younger women (Schrag, Kuntz et al. 1997) a finding confirmed in a more recent assessment (Ingham, Sperrin et al. 2013). There are no randomised trials for RRM nor are there ever likely to be any due to the huge variation in personal preference making randomisation impossible. Heterogeneity of risk was not fully addressed in many of these epidemiological studies, incorporating methodological biases which may be significant.

1.3.4.1 Contralateral risk reducing mastectomy

Contralateral mastectomy prevents contralateral breast cancer (risk reduction ~90%) (McDonnell, Schaid et al. 2001, van Sprundel, Schmidt et al. 2005) and improves disease free survival in women who have had previous cancer (Peralta, Ellenhorn et al. 2000, Herrinton, Barlow et al. 2005), albeit their main risk of further cancer remains associated with their primary cancer. A recent study found that contralateral risk reducing mastectomy (CRRM) (in women with cancer and mastectomy in the ipsilateral breast) resulted in improved breast satisfaction and overall psychosocial wellbeing compared to the women who had not had surgery to the contralateral breast. The improvements were small but significant. Interpreting these results is challenging as the reasons for CRRM in the group undergoing surgery, alongside the reasons for not pursuing CRRM in the non-surgical arm were not explored. Of note, CRRM was more commonly chosen in younger aged women, who more frequently opted for breast reconstruction (Hwang, Locklear et al. 2016). A review of psychosocial outcomes of CRRM found that long-term satisfaction and psychosocial wellbeing were generally high, but that women with a poor cosmetic outcome, those with body image, sexual or femininity concerns and those with long-term complications had greater risk of a poor outcome (Collins, Gee et al. 2017).

Risk of contralateral cancer is quoted as 2-3% per year in *BRCA* carriers (compared to 0.5% per year in non *BRCA* carriers) (Basu, Ingham et al. 2015) and this risk persists over 20 years. Survival after CRRM was assessed by a Dutch study that found that women with a *BRCA* mutation who have had breast cancer have improved survival with CRRM, particularly in women under 40 years and in those with grade 1-2, non triple-negative phenotype who do not require chemotherapy (Heemskerk-Gerritsen, Rookus et al. 2015). A similar survival advantage, of up to 48-63%, has been demonstrated in other studies, (Evans, Ingham et al.

2013, Metcalfe, Gershman et al. 2014). The American Society of Breast Surgeons released a consensus statement regarding CRRM finding (Boughey, Attai et al. 2016):

- CRRM is cost effective for *BRCA* carriers
- Most women are satisfied with their decision to undergo CRRM but up to a third experience post-surgical dissatisfaction with cosmesis, body image and sexuality
- Patients need to be counselled on the risks of CRRM and the risks of contralateral breast cancer
- Additional educational resources focussing on risks and benefits would potentially enhance patient's decision-making

The Manchester Breast Unit have published a protocol for managing patients who request CRRM (Basu, Ross et al. 2015), both for those with and without a gene mutation. Lifetime risk is derived from age, life expectancy and risk factors that either elevate or reduce risk (for example, oestrogen receptor positive reduces risk, family history increases it). This information, alongside a careful history to establish the reasons surgery is being requested then inform an MDT who review each case.

1.3.4.2 Breast conserving surgery

The risk of local recurrence after breast conserving surgery in *BRCA* women is unclear and somewhat controversial. It has been found by some groups to be similar to that of age-matched women with normal risk levels (Robson, Svahn et al. 2005, Kirova, Savignoni et al. 2010), but increased by others (Turner, Harrold et al. 1999, Garcia-Etienne, Barile et al. 2009, Pierce, Phillips et al. 2010). A study of 160 *BRCA* mutation carriers who had breast conserving surgery found an ipsilateral breast cancer recurrence rate of 24% at 15 years, higher than would be expected in a non-familial cohort (Pierce, Levin et al. 2006). Although locoregional recurrence rates (LRR) rates are usually quoted at half to one percent per year, it might be up to double this for an age matched *BRCA* cohort and especially in a matched cohort for biotype (TNBCs have a much higher LRR than other subtypes which would bias the data). Paired with this, is the risk of contralateral breast cancer quoted as 2-3% per year (Basu, Ingham et al. 2015) or as a lifetime risk that can exceed 60% (Metcalfe, Gershman et al. 2011) which, in addition to higher recurrence concerns (Pierce, Phillips et al. 2010), prompts many women to consider RRM, which has also been shown to offer a survival advantage over purely

ipsilateral treatment (Heemskerk-Gerritsen, Rookus et al. 2015) although has been a controversial issue due to widespread use in women at low or moderate risk in western countries. There is also the possibility that women with *BRCA* mutations have increased sensitivity to ionising radiation in the breast, increasing the risk of breast conservation yet further (Baeyens, Thierens et al. 2002, Powell and Kachnic 2003, Kirova, Savignoni et al. 2010). This conflicting evidence has prompted publication of guidelines for CRRM by the American Society of Breast Surgeons recently (Boughey, Attai et al. 2016) (discussed above). The key issue of controversy is whether this is associated with a survival benefit and this is not clear and likely to be small. The likely small increase in LLR may translate into a survival disadvantage 10 years later but there is little data on this at present

1.3.4.3 Occult malignancy

Excised breast tissue from BRRM is routinely examined and in women with *BRCA* mutations, 3% will have occult in-situ or invasive cancers (Heemskerk-Gerritsen, Brekelmans et al. 2007). Published figures for detection of occult breast cancer at 'prophylactic' surgery vary widely, in keeping with the wide range of risk groups included in different studies, and likely the quality of the pathological examination performed in different units. A cancer diagnosis has significant implications if immediate breast reconstruction has been performed and will necessitate further surgery to stage the axilla and unexpected adjuvant therapies.

1.3.4.4 Effects of RRM

A separate systematic literature review was conducted looking at the psychosocial impact of risk reducing breast surgery, see chapter three for more detail. The following paragraph summarises the findings of the systematic review.

Risk reducing breast surgery appears to be effective in reducing breast cancer anxiety. This comes at a cost to a minority of women who suffer long-term adverse effects, be that physical symptoms as a result of surgery or broad-ranging psychological effects, including body-image concerns, anxiety, depression, loss of confidence or deleterious effects on relationships, sexual function or work. Women who experience complications are at particular risk of suffering long-term adverse effects.

Breast reconstruction

Options for breast reconstruction continue to expand and techniques are touched on briefly here, but a full review is outwith the scope of this thesis. Autologous techniques include latissimus dorsi rotational flap, deep inferior epigastric free flaps and other myocutaneous free flaps. Implants and expanders can be used alone or in combination with a variety of acellular dermal matrices or non-biological meshes to add support and shape. Skin sparing and skin and nipple sparing mastectomies are now widely regarded as oncologically safe in women with cancer and are widely used in the risk reducing setting (Newman, Kuerer et al. 1998, Carlson, Styblo et al. 2003, Lanitis, Tekkis et al. 2010, Sheikh, Rebecca et al. 2011, Adam, Bygdeson et al. 2014). These techniques further enhance cosmesis. Nipple and areolar reconstruction and/or tattooing are also widely available. Reconstruction can be either immediate at the time of the mastectomy or delayed with advantages and disadvantages to both. Risk reducing surgery (unless an incidental cancer were found on histological examination) should not require radiotherapy, a major potential risk factor for adverse outcomes following immediate breast reconstruction in a cancer surgery setting. The range of options available is broad and most women will have several options to choose between.

Reconstruction is rarely completed in one operation and, especially with implant based techniques, may require late revisional surgery in up to 50% of cases in the longer term, which holds special relevance in the young age cohort having RRM. Most reconstruction results in breasts that are relatively insensate. The mastectomy part of the procedure also requires some thought. Women can choose to keep the nipple areolar complex (NAC) as part of a skin and nipple sparing technique, usually achieving a better aesthetic outcome at the cost of a theoretically increased risk of future cancer but this is not thought to be significant (Peled, Irwin et al. 2014).

A large proportion of women experience unanticipated surgical procedures following reconstruction (Lostumbo, Carbine et al. 2004), the majority of which are implant related (Frost, Slezak et al. 2005). Complications of IBR occur in 21%, of which 11% occur within the first six weeks, with 10% occurring later (Contant, Menke-Pluijmers et al. 2002). The IBR complication rate was much higher in another study, at 49.6%, with 71% resulting in further surgery, the majority of these relating to cosmesis (Heemskerk-Gerritsen, Brekelmans et al. 2007). Troublesome long-term problems described by women who have had reconstruction

include itch, firmness, numbness, temperature changes and the feeling that her breasts are not part of her (Bebbington Hatcher and Fallowfield 2003, Kenen, Shapiro et al. 2007). Rolnick and colleagues noted that most women wanted more information preoperatively in the following areas: (Rolnick, Altschuler et al. 2007)

- Longevity of reconstruction
- Look and feel of implants
- Pain, numbness and scarring
- Details about reconstructive options including images of women that have had RRM and IBR and not due to cancer.

1.3.5 Risk management options for increased familial ovarian cancer risk

1.3.5.1 Ovarian screening

Ovarian screening combines two techniques: Ca125 measurement and transvaginal ultrasonography. Ca125 is a tumour marker used to measure cancer activity. Used exclusively, Ca125 is not a reliable screening test, with normal levels in 50% of stage I cancers, and 20% of stages II-IV. Additionally false positive rates are high, with benign conditions including endometriosis and uterine fibroids all increasing Ca125 levels. In the UK serial 4 monthly measurements have recently been introduced, replacing annual measurement, which improve sensitivity and specificity but raise practicality issues when considering a wider screening programme (Bebbington Hatcher and Fallowfield 2003). Womens' adherence to ovarian screening programmes has been reported as low in many studies (Lerman, Hughes et al. 2000, Isaacs, Peshkin et al. 2002, Antill, Reynolds et al. 2006). Adherence seems to improve with increasing age and from having a relative affected by ovarian cancer (Isaacs, Peshkin et al. 2002).

The recent large, multicentre Familial Ovarian Cancer Screening Study (FOCSS) has added significantly to our understanding of what screening can achieve. This is a British multicentre comprehensive study of ovarian screening in women at increased familial risk, following women aged between 35 to 81 years of age, over several years of screening. When the study started, Ca125 was measured annually but this was changed to four monthly during the trial in response to concern that annually was inadequate and the results of this change are yet to

be reported. The initial results, based on annual transvaginal (TV) ultrasound scanning and Ca125 measurement however, showed that those women being screened annually who developed cancer were less likely to be diagnosed with stage IIIc disease or above, than those who had not been screened within the last year (26.1% vs 85.7%, $p=0.09$). They reported positive predictive values (of incident years of surveillance) of 25.5% (95% CI 14.3-40.0) and negative predictive values of 99.9% (95% CI 99.8-100) (Rosenthal 2012, Rosenthal, Fraser et al. 2013). A separate questionnaire study of the same group of women showed no significant psychological distress associated with ovarian screening (Rosenthal 2012). The authors commented that women undergoing screening had a reduced likelihood of advanced disease presentation, which may impact positively on survival, although it is too early to confirm this hypothesis. A similar multicentre British collaborative trial of ovarian cancer screening in a normal (non-high risk) population (UKCTOCS) showed that postmenopausal women at a population based risk of ovarian cancer screened with annual TV ultrasonography and Ca125 level measurement were less likely to die of ovarian cancer, once in the screening programme (i.e. when the prevalent year results were excluded). This effect was most significant in the 7-14 incident years of screening (Jacobs, Menon et al. 2016).

There is, as yet, no evidence to show ovarian screening reduces mortality in a high risk group. Trials remain underway to further assess efficacy of these techniques (Cancer Research 2011).

1.3.5.2 Risk reducing bilateral salpingoophorectomy (RRSO)

Risk reducing salpingoophorectomy (RRSO), also known as bilateral prophylactic salpingoophorectomy reduces the risk of breast and ovarian cancer, at the cost of menopausal symptoms (Rebbeck, Levin et al. 1999). Hormone replacement therapy seemed not to influence this effect greatly, if HRT was discontinued by 50 years of age (Armstrong, Schwartz et al. 2004).

A clear reduction in risk of both breast and ovarian cancer was apparent in selected women undergoing RRSO in one study, with ovarian cancer risk falls by between 75-96% (Kauff, Satagopan et al. 2002, Rebbeck 2002). Premenopausal women undergoing RRSO with *BRCA1* have a breast cancer risk reduction of 56% and *BRCA2* women of 46% (Eisen, Lubinski

et al. 2005). Extrapolation of data has shown RRSO in a 30 year old woman with *BRCA 1/2* improves survival by 0.4 to 2.6 years, more if done in conjunction with RRM, which is cost effective compared with surveillance (Grann, Panageas et al. 1998). These findings have, however, recently been called into question when other groups have looked at risk reduction afforded by oophorectomy in a *BRCA* context. One found that *BRCA1* mutation carriers did not have any reduction in breast cancer risk following oophorectomy, although *BRCA2* mutation carriers did still benefit by 35% (Kotsopoulos, Huzarski et al. 2017) and another noted that the risk reducing effect of oophorectomy in a *BRCA1* cohort was non-significant (Basu, Ingham et al. 2015).

Given the tendency for *BRCA1* tumours to be ER negative and *BRCA2* to be ER positive, research has aimed to establish whether RRSO has the same effect in both groups. A collaborative cohort study showed a hazard ratio (HR) of 0.28 for breast cancer in *BRCA2* women (95% CI 0.08-0.95) and a non-significant HR 0.61 in *BRCA1* women (95% CI 0.3-1.22) after RRSO (Kauff, Domchek et al. 2008). RRSO was profoundly protective against ER positive breast cancer, but not protective against ER negative disease, as it vastly reduces exposure to oestrogen. Other studies have failed to demonstrate statistically significant differences in breast cancer risk reduction for the two gene mutations, but these included pooled data from retrospective series, introducing the possibility of confounding factors (Rebbeck, Kauff et al. 2009).

No significant changes in general or cancer related distress were noted from before to after RRSO (Bresser, Seynaeve et al. 2007) and women did not regret their decision to have RRSO even with menopausal symptoms (Heiniger, Butow et al. 2015). There are long-term effects of this procedure, in addition to the psychosocial impact. Bone mineral density drops with a sudden and premature menopause with associated symptoms including mood swings, hot flushes and sexual dysfunction (Hallowell, Baylock et al. 2012). One group found reduced sexual pleasure, increased sexual discomfort and reduced frequency of sex after RRSO, all ameliorated to some extent by use of HRT (Johansen, Liavaag et al. 2016). Other reported changes include loss of libido, vaginal dryness, pain on coitus due to vaginal dryness and thinning and the associated relationship changes these lead to, including embarrassment and distress. Some of these symptoms can be managed with non-hormonal agents but a better result is often found with topical oestrogens, which patients must be aware will result in

some degree of systemic absorption. Current NICE guidelines support the use of oral HRT in young women after RRSO up until the age of natural menopause (CG164 2013). RRSO uptake is greater than RRM in high risk women with a shorter time to surgery, suggesting that women may find it more acceptable, at least pre-operatively (Flippo-Morton, Walsh et al. 2016).

1.3.6 Planning children

A topic dividing opinion is that of preimplantation genetic diagnosis (PGD) which has recently been approved for screening of embryos of *BRCA* positive parents (HFEA 2011, Derks-Smeets, Gietel-Habets et al. 2014). The process involves IVF, which is not appealing to some who wish to conceive naturally, and the possibility that successful implantation will not occur. This is ethically more acceptable to most people than in-utero diagnosis by chorionic-villus sampling at eleven-weeks gestation (prenatal diagnosis or PND) with the presumed plan to terminate should the embryo be found to carry the mutated gene. A disadvantage of PGD is the requirement for women to undergo hormone treatment necessary to allow harvesting of ova for IVF. If the gene carrier is the woman in the couple, this may increase her risk of breast cancer and a Dutch study is underway to investigate this further (Derks-Smeets 2017). Awareness of both PGD and PND is growing but remains limited. PGD requires couples to plan their families and to allow extra time for the process, alongside any risk reduction surgery they may choose to undergo. A qualitative study of Dutch couples with *BRCA* mutations highlighted the complexity of a couple's decision to use PGD, PND or no form of genetic selection. It found common motivating factors for all of the options and noted both doubt and guilt associated with particularly the latter but a significant emotional burden common to all (Derks-Smeets, Gietel-Habets et al. 2014). There is a paucity of data on the uptake of PGD or PND for couples carrying genes associated with familial breast cancer risk with most research focussing on the attitudes of couples to the technique. Another issue in the UK is the fact that IVF funding is variable by health region, in some not provided on the NHS at all, for others only 1 to 3 cycles are provided on the NHS and having prior children may preclude NHS treatment. Women wanting IVF for PGD are still subject to these funding restrictions.

1.4 Risk management decision making

Decisions for women at increased risk include whether to undergo risk assessment including gene testing and how to manage risk, for which many issues will be relevant. The risk management decision is made more difficult by the need to understand the concept of a risk that does not predict a definite outcome, i.e. you *may* (not will) get cancer, or with an operation you *are less likely to* (not will not) get cancer. Significant differences in management are apparent in different countries, despite having broadly similar counselling, raising the possibility that geographical factors may impact upon decisions (Evans, Anderson et al. 1999, Metcalfe, Birenbaum-Carmeli et al. 2008). The doctor-patient communication process is also likely to impact upon the decisions ultimately taken by patients (Bober, Hoke et al. 2004).

'Goal directed decision making' describes the complex process according to which goals are considered most important, which may change with time. Patients need to be aware of their options and have sufficient information to allow goal directed management. A combination of goals will be common and may introduce conflicting wishes. Common themes include: (Goodwin 2000)

- Overall survival
- Cancer prevention
- Preservation of breasts
- Maintenance of femininity (including sexual function and body-image)
- Optimisation of quality of life
- Minimisation of psychosocial distress
- Minimisation of disruption of day-to-day activities (possibly including financial cost)
- Being there for children

Previous experience affects decisions, as well as personality (Fallowfield 2008). High levels of breast cancer anxiety prior to genetic assessment correlated strongly with the intention to have mastectomy (OR=17.4; 95% CI 4.35-69.71, p=0.001). In one study, a large proportion of women considering surgery had moderate (not high) levels of risk, suggesting a role for interventions designed to reduce breast cancer-anxiety (Meiser, Butow et al. 2000). A systematic review by De Leeuw explored the factors associated with the decision to undergo risk reducing breast surgery and adherence to screening with MRI and mammography. It found that factors associated with a decision to undergo surgery included a strong family

history, increased cancer anxiety, parenthood and medical advice, however there was considerable variability noted (De Leeuw, van Vliet et al. 2008). Another study concluded that having a mother or sister die of their disease was associated with a stronger desire to undergo risk reducing surgery (Singh, Lester et al. 2013). Another group studied women undergoing family history breast surveillance to see if false-positive results correlated with a change in intention to have risk reducing breast surgery. They found no large increase in cancer related anxiety or surgery intent but clarified the existing understanding that increased cancer related anxiety is associated with risk reducing surgery intent (Portnoy, Loud et al. 2015).

The role of a psychologist's input at the time when women are deciding on risk management strategies is not universally accepted or available. A study of American women found that all felt psychological consultation would aid their decision making and preparation for surgery (Patenaude, Orozco et al. 2008). Interestingly, two-thirds of this group felt that psychological consultation post-operatively would be beneficial and the study, unsurprisingly, recommended integration of psychology into women's care.

The decision to undergo risk reducing surgery is complex. A recent single centre study showed that women with or without cancer who were found to have *BRCA* mutations more frequently decided to undergo RRSO than RRM and those who did have RRM, frequently did this some time after their RRSO (Flippo-Morton, Walsh et al. 2016). The acceptance of RRSO over RRM is perhaps unsurprising given the known possible psychological and physical adverse effects of RRM. A short paper in the *EJSO* summarised that women should not be recommended surgery but should be supported in making an informed decision, due to the key underlying Hypocratic principle to 'do no harm' in medicine (Taylor and Tischkowitz 2014).

Bellavance discussed the decision making process for women choosing between breast conserving surgery and mastectomy for breast cancer (not specifically for those at increased familial risk) and note the complexity of the decision, with the main concerns being about cancer recurrence and changes to body image and sexuality, with access to healthcare being another factor affecting decisions for some (Bellavance and Kesmodel 2016). They

commented that optimising patient education is key to allowing an informed decision but with obvious challenges, given the relative urgency of the decision and the psychological burden of a new cancer diagnosis. This is not the same for (most) women at increased risk deciding between risk management strategies, but for some, who are diagnosed with cancer at the time of their increased risk discovery, this is clearly especially relevant.

Glassey and colleagues reviewed the literature regarding decision making in high risk women for risk reducing surgery and found conflicting findings for outcomes. They recommended further research into the outcomes especially for young women contemplating risk reducing surgery to allow them to understand the likely after effects of surgery and potential impact on psychological well-being (Glassey, Ives et al. 2016).

Decision satisfaction depends upon a wide variety of factors, not least the outcome of the decision. One factor that has been frequently noted is that women for whom the decision to have surgery is based upon their doctor's advice, seem to be more likely to regret their decision (Frost, Schaid et al. 2000, Stefanek, Hartmann et al. 2001, Nekhlyudov, Bower et al. 2005). Another factor affecting decision satisfaction seems to be the degree of information (and their comprehension of this) they have before making a decision (Armstrong, Weber et al. 2005). Individualised predictions about survival and cancer incidence associated with the management options statistically improved short-term decision satisfaction, although it had no effect on anxiety. The follow up period for this study was very short and was therefore unlikely to capture the longer-term issues that are associated with these decisions, for which data are lacking. Risk perception and knowledge were significantly improved with less over-estimation of risk in women provided with tailored information (Lipkus, Samsa et al. 2001). Decision satisfaction is reduced in women with greater depressive or anxiety symptoms (Bober, Hoke et al. 2004). Women who are more satisfied with their decisions are more likely to carry them out than those who are unsatisfied or undecided (Anderson 2003). Since the majority of studies have relatively short follow up, especially those looking at psychosocial outcomes, it may be that women with greater levels of anxiety will begin to default from screening programmes over time.

Whilst evidence supports providing comprehensive and specific information, it seems it is not being translated into widespread clinical practice. In one study, most women felt there had not been enough information available to them when making decisions (Bebbington Hatcher and Fallowfield 2003), and another found that generic information was difficult to translate into their personal situation (Josephson, Wickman et al. 2000). Klitzman and colleagues conducted interviews with women deciding on whether or not to choose RRM. They comment that the role of the physician advising women is complex. Some women were disappointed by non-directiveness whereas others found their doctor too directive. They also describe the process forcing women to consider uncertainty and the stresses that go alongside this phenomenon (in deciding about risk management) (Klitzman and Chung 2010). They suggest physicians need to gauge women's desire for information depth and their feeling about paternalism vs. autonomy and to conduct discussions accordingly.

Metcalfe and colleagues developed a decision aid tool for women with *BRCA 1 or 2* who were deciding on whether to undergo risk reducing surgery. They used questionnaires to explore decision related factors before and after using the aid and found that decision conflict decreased, relevant knowledge increased with fewer women feeling uncertain at the end of the process (Metcalfe, Poll et al. 2007). This tool is specific for *BRCA* mutation carriers. Extending this early work to a greater proportion of women affected by familial risk has been undertaken by an Australian group who designed "iPrevent", a web-based decision support tool. Women or their physicians enter information pertaining to breast cancer risk and the programme selects between either BOADICEA or IBIS risk calculators to stratify the woman's risk and present data in a meaningful way (figure 1.3) (Collins, Bickerstaffe et al. 2016). Schwartz and colleagues used a CD-ROM decision aid that women viewed at home. They found that women who were initially undecided on a risk management strategy and who used the decision aid had an increased likelihood of reaching a management decision (OR = 3.09, 95% CI = 1.62, 5.90; $p < .001$), decreased decisional conflict ($B = -.46$, $z = -3.1$, $p < .002$), and increased satisfaction ($B = .27$, $z = 3.1$, $p = .002$) compared to women managed without the use of the decision aid (Schwartz, Valdimarsdottir et al. 2009). They found no benefit (or harm) in women who were already decided before using the decision aid.



Figure 1-3 - iPrevent (Collins, Bickerstaffe et al. 2016) (open access)

Decision analysis recommendations were compared with actual choices made in another group of high-risk women. Of the women who made definite choices during the study period, all (12) agreed with the recommendation based upon women's pre-ascertained time-trade off values for the possible outcomes. Of those making hypothetical choices, 78% agreed (Unic, Verhoef et al. 2000). A British focus group looked at decision aids from America, finding women wanting similar tools to be designed for women in the UK, but with variable opinion regarding format and content (Iredale, Rapport et al. 2008).

1.5 Impact upon partners and their role in Risk Management Decision Making

The impact on partners of affected women has rarely been explored. A systematic review of men's experiences of their partner's mastectomy found that men struggled to talk openly to their partners about body image after surgery. Lack of communication led to conflict and poor psychological well-being (Rowland and Metcalfe 2014). Another study using an online survey attached to cancer support boards found that partners reported changes in intimacy, attraction and communication after disclosure of familial breast cancer risk. Concern about post-surgical appearance, attraction, health and concern about sexual relationship were noted in men whose partners were awaiting surgery (Mauer 2015). Another study noted a negative effect on relationships in a context of increased familial breast cancer risk. (Metcalfe, Liede et al. 2000). There was no published work assessing the impact upon partners of women who choose enhanced breast screening.

1.6 Psychosocial impact of increased familial breast cancer risk

1.6.1 Effects of living at increased risk

The majority of published work on this topic pertains to women with *BRCA* mutations and is therefore specific to women at very high risk. The impact of a lower level of risk, albeit still above population level, is less well understood. The effects of a confirmed increased risk of breast cancer include cancer related anxiety, general anxiety and depression, fear of death, guilt, changes in body image and sexual relationships (Lodder, Frets et al. 2001, van Oostrom, Meijers-Heijboer et al. 2003). There are some documented positive effects of confirmation of increased risk including a feeling of control, enabling women to confront the disease and take preventative measures (d'Agincourt-Canning 2006).

Cancer related anxiety can be an overwhelming problem for some women, profoundly affecting their quality of life. Intrusive thoughts are often associated with anxiety and depression, similarly affecting quality of life (Bebbington Hatcher and Fallowfield 2003). The effect of cancer worry should not be under-estimated, being a dominant force driving women to consider bilateral mastectomy (Stefanek, Enger et al. 1999), with some women describing their breasts as 'time-bombs' that they cannot tolerate (d'Agincourt-Canning 2006). Younger women worry more about developing cancer, although this may vary

between individuals (Foster, Evans et al. 2002). A significant decrease in cancer worry was noted in women receiving both scientific and psychosocial information at the time of assessment, compared to those not benefitting from the additional written material (Appleton, Watson et al. 2004, Roussi, Sherman et al. 2010). Another study noted that global self-esteem and 'mastery' (an attempt to regain control over life (Taylor 1983)) correlated with reduced levels of cancer worry (Vodermaier, Esplen et al. 2010). The effect of cancer related worry on adherence to advice is a complex issue. Studies have conflicting results when an attempt is made to measure this effect, some finding over-adherence to recommendations (Antill, Reynolds et al. 2006), with others demonstrating an opposite effect (Lerman and Rimer 1993).

Development of coping strategies is associated with a reduction in anxiety. They are broadly divided into emotion focused (which aim to ameliorate negative emotions associated with the stressor) and problem focussed (which aim to practically manage the cause of the stressor) (Folkman and Moskowitz 2004). Use of problem focussed strategies is associated with a greater reduction in distress than was noted with the use of emotionally focussed strategies, perhaps unsurprisingly (Geirdal and Dahl 2008). 'Acceptance' was associated with reduced anxiety in women without a demonstrated mutation, whilst 'planning' in the *BRCA* group was associated with increased anxiety (Geirdal and Dahl 2008). A group studying psychosocial adaptation to living at risk found that challenges in one area could be overcome by facilitators in other areas, for example personal characteristics or social support networks (Heiniger, Price et al. 2015).

1.6.2 Risk perception

When discussing risk with patients, a distinction needs to be drawn between absolute risk (i.e. their 70% risk of developing cancer in a lifetime) with relative risk (i.e. the difference in risk between a 'normal' population risk level woman and a woman with a genetic susceptibility). These concepts take time to explain and to understand, with a significant proportion likely to struggle to understand (Lipkus, Samsa et al. 2001). Various factors have been shown to affect risk perception, including age, race, level of education, appreciation of family history and cancer related anxiety (Tilburt, James et al. 2011). A greater perceived risk is associated with increased intention to use and uptake of cancer detection processes such as mammographic screening (Fallowfield 2008). Cancer-related worry and anxiety have

similar associations with uptake of risk modifying behaviour, although there is considerable variability in this finding (Stefanek, Helzlsouer et al. 1995, Lostumbo, Carbine et al. 2004).

Few women attending genetic clinics were aware of population risks of breast and ovarian cancer (Foster, Evans et al. 2002). Several studies demonstrate that women who are more anxious, are more likely to over-estimate their risk (van Dooren, Rijnsburger et al. 2004), suffer more breast-cancer worry, and are more likely to opt for surgery as opposed to screening (Stefanek, Helzlsouer et al. 1995, Lostumbo, Carbine et al. 2004). This finding is to some extent contradicted by a Swedish study that found that risk estimation was accurate in women at increased risk and in a control group at normal risk levels. They concluded that interest in risk reducing breast surgery seemed not to be due to an over-estimation of risk (Brandberg, Arver et al. 2004).

1.7 Limitations and knowledge gap

The conclusions drawn from a literature review are dependent upon the quality of the papers available. Due to the radical nature of surgery and the complexities of the decision on how to manage increased risk, no randomised trials exist. To randomise women to risk reducing breast surgery (or various types, for example immediate or delayed reconstruction) or screening is likely to raise significant ethical issues. Whilst a randomised trial seems unlikely due to these potential difficulties, there are studies which have overcome similar ethical issues, for example one trial randomised men with localised prostate cancer to active monitoring, radical prostatectomy or radical radiotherapy, (Hamdy 2011).

A common weakness of many of these studies is the use of retrospective assessments of quality of life (and other related topics, for example body-image), which introduce significant recall bias and this is rarely addressed (Stefanek, Hartmann et al. 2001, Lostumbo, Carbine et al. 2004). Another common limitation is the vague definition of 'increased risk of familial breast cancer', with some older studies including women with one affected first degree relative, whilst others limit research to *BRCA* mutation carriers. This obviously impacts on the results and care needs to be taken when comparing studies. Even those quoting figures for *BRCA* carriers frequently pool *BRCA1/2* carriers, which may also impact upon results.

Biases have been introduced to many of the studies without being taken into account in the findings. Eisen and Weber comment on Hartmann's seminal paper (Hartmann, Schaid et al. 1999) regarding the risk reduction that bilateral mastectomy affords to high risk women. They note that the heterogeneity of risk was not fully addressed even in that study, which went to considerable lengths to correct for methodological biases (Eisen and Weber 1999). The Cochrane review also notes selection bias in two studies and lack of control groups in several others, including Hartmann's paper. Another example is the use of controls likely to include subjects' relatives when studying events that are likely to impact on the family as well as the subject introducing familial event bias (Lostumbo, Carbine et al. 2004).

The use of non-validated patient satisfaction tools has been shown to over-estimate satisfaction (Ware and Hays 1988). A large proportion of data available relating to outcomes from surgery especially, have been collated using questionnaires, in which a wide variety of tools are introduced, some validated and some not. Carr-Hill discusses these issues further in a review paper (Carr-Hill 1992), raising further concerns regarding the use of non-validated satisfaction tools.

The majority of research into psychosocial and physical outcomes relates to two specific events: the gene test and breast surgery. With MRI breast screening having better sensitivity in the high risk group, the options for women have changed to include a viable alternative to surgery which is now widely available. The outcomes described in previous studies pertaining to decision making and the effects of living at risk are now potentially outdated. Data exist to support MRI in the short-term, but there is a paucity of long-term data. In addition to this are the psychosocial outcomes from short and long-term breast screening, which are poorly understood. The efficacy of existing options for reducing the risk of ER negative tumours is poorly understood. The role of oophorectomy and chemoprophylaxis in *BRCA1* women needs to be clarified. Of note, increasingly, younger people at increased risk will have seen successful risk reduction management unlike previous generations who will have seen more relatives dying of cancer, affecting the degree to which existing research on the impact of gene testing can be extrapolated in the future.

1.8 Summary

In summary, women at increased risk of familial breast cancer have specific and varying problems and needs, with one size definitely not fitting all. Provision of detailed information was consistently identified as improving outcomes. Improved recognition of women who are more likely to experience psychosocial deleterious effects may allow healthcare professionals to ameliorate the impact, for example providing access to a decision aid like iPrevent (Collins, Bickerstaffe et al. 2016) providing a more accurate risk perception upon which decisions are based. The addition of MRI breast screening has offered women who do not wish to undergo surgery a better alternative to mammographic screening, potentially allowing some to delay or even avoidance of surgery with the possible addition of chemoprophylaxis and/or risk reducing oophorectomy. Management of women at increased familial breast cancer risk has changed rapidly in the last decade and a wealth of research is helping clinicians to understand this complex phenomenon better. There are still areas of uncertainty which further studies will hopefully address and on an individual level there is still significant work to be done to reduce the distress experienced by these women and their families.

Having explored the context of this study, Chapter two will describe and explore the methodology used. This is followed by the systematic reviews, the interview and questionnaire studies.

2 Chapter two – Methodology

This thesis is a mixed methods study to explore the underpinning factors determining risk management decisions in high familial risk women. As such it is a synthesis of a number of methodologies (see table 2.1) to obtain data which are then interpreted together. These are summarised below. The various methodological considerations about study design are reviewed below both in terms of general principles and specifically as used in this thesis.

Table 2-1 Mixed methods approach



Any form of research requires a rigorously applied systematic approach to allow the impact of an individual researcher to be minimised on the outcome of the research. There are many different methods described that researchers can use to gain a greater understanding of a topic, which will invariably be the underlying aim of any research study. To understand the methodological options available to conduct a research study, it is first important to understand the terminology and underpinning principles. This chapter aims to explore and define methodological options that could have been used in this study and to explain the rationale behind the decisions made in choosing techniques, including noting their strengths and weaknesses.

2.1 General methodological categorisation

Methodologies may be split broadly into several categories (Creswell 2008, Baxter 2012, Sivasubramaniyan 2012):

Deductive or inductive and iterative

Deductive studies start with knowledge and a theory and aim to gather data to prove or disprove this theory. Inductive studies are in essence, the reverse of this. They aim to use data to gain understanding of a topic and may (or may not) at the end of this process begin to form theories. Iterative studies move between the data collection process and the findings, using the findings to guide further data collection, creating theories as the studies progress.

Qualitative or quantitative

Qualitative studies are used when the research question involves understanding a phenomenon that is not quantifiable, for example decision making.

Qualitative methodology can be further subdivided into

- Narrative: explores the life of an individual
- Phenomenology: aims to understand the essence of an experience related to a particular phenomenon
- Grounded theory: aims to develop a theory from data “grounded” in the field
- Ethnography: describing and interpreting cultural groups

Quantitative studies aim to provide quantification of objective measurements. Quantitative methodology can be further subdivided into

- Experimental: Variables are manipulated to measure an effect on another variable. Examples include clinical drug trials.
- Survey research: Participants are selected from a population and a standardised questionnaire tool is used to collect data.

The nature of the research question guides the choice of methodology. For example, someone asking what is known about managing a specific condition with a particular

treatment may choose a systematic review of the literature on that topic. Researchers wanting to focus on measuring quantities or relationships between attributes usually adopt quantitative, highly structured techniques. Questions that start with ‘what’, ‘how’ and ‘why’ are often best served with a qualitative approach, although this is by no means set in stone (Bowling 2005). It is quite possible to combine methods to produce a study with the benefits of different techniques, for example, qualitative techniques are often used in conjunction with quantitative methods to add context and validity to studies (Pope 2006).

Table 2.2.2 provides a broad comparison of qualitative and quantitative techniques: (Adapted from (Baxter 2012)

Table 2-2-2 Research methodology differences

	Quantitative	Qualitative
Approach	Deductive (theory testing)	Inductive (theory generating) or iterative (developing alongside the research)
Answers	How many? When? Where?	How? Why?
Sampling	Large, random	Small, purposive
Representativeness	Generalisable	May or may not be generalisable
Instruments	Objective	Less structured e.g. interviews
Results	Numbers and statistics	Words and concepts
Researcher	Distant to subjects	Reflexive and paying attention to individuals
Approach	Follows original research plan	Flexible

2.2 Systematic literature review

The process of systematically reviewing literature has been refined by many to create an algorithmic system that allows a research question to be answered using all information that is available. Cochrane and PRISMA have published guidance on how to conduct a systematic review (Moher, Liberati et al. 2009, Cochrane 2017).

The first stage of a systematic review is to define a question. Relevant databases are then searched, references examined and a list of possible sources collated, with those that are

irrelevant being disregarded. Data are extracted and pooled, assessed against inclusion criteria and for methodological rigour and quality and then combined, analysed and synthesised to give an overall answer to the original question (Cochrane 2017).

All systematic reviews have a common aim: to systematically search, analyse and synthesis research evidence. Different types of systematic review include (Grant and Booth 2009):

- Meta-analysis, where statistical analyses are done using combined results from different (quantitative) studies. Quality assessment tools determine whether studies are included or excluded.
- Qualitative systematic review, where findings from qualitative studies are combined and synthesised. Quality review informs the discussion but rarely determines inclusion or exclusion of studies.
- Critical review, where literature is searched systematically but often not quality assessed. This type of review may be narrative and lead to hypothesis formation.

The advantage of systematic review over a simple trawl through literature is the methodological rigour that underpins the process. By systematically searching, any published material that may be relevant should be included for analysis. The process of quality assessment allows meaningful analyses and conclusions to be drawn. A systematic review provides understanding of what is known, what is unknown and what remains uncertain within a topic (Grant and Booth 2009).

2.3 Qualitative research

2.3.1 Introduction

Qualitative research aims to explore a concept or phenomenon. This is often done by obtaining the views of study participants, focussing on meanings and experiences relating to a topic with a view to understanding how and why people interact in a certain way within their social environment (Carter 2005). Qualitative methods allow 'how and why' questions to be explored, whereas quantitative research tends to be limited to a more observable 'what, where and when' focus.

The nature of qualitative research requires the researcher to interpret complex data that is not simply a case of adding up numbers. The inherent subjectivity of all researchers (as humans) can impact on the outcomes of the study. This phenomenon is known as reflexivity and is particularly important to consider in qualitative studies where the researcher may interact more with the participants (Fitzpatrick and Boulton 1994).

Constructionism refers to the phenomenon that observed scientific observations are purely conceptual and are affected by the people that are considering and describing them. Context is important to allow meaning to be derived.

Table 2.2.3 summarises the theoretical perspectives relevant to this project.

Table 2-2-3 Theoretical perspectives of qualitative research

Constructivism	Aims to understand multiple participants meanings; theory generating research
Pragmatism	Aims to understand consequences of actions; problem centred; set in context

Further to these aims are the manners in which data are interpreted (Bowling 2005):

- Interpretive: the reason for an action is interpreted by the individual themselves
- Naturalistic: assumes multiple interpretations are possible, with a goal of understanding how individuals interpret reality and what forms that reality

2.3.2 Qualitative data collection

Methods of data collection with qualitative techniques vary (Fitzpatrick and Boulton 1994, Bowling 2005).

- Observational: involves a researcher literally observing people in a situation, ideally unobtrusively, to see what happens and draw understanding from this process.

- Interviews: participants are interviewed one-to-one by a researcher, usually digitally recorded and the transcript is the data that is subsequently analysed. Interviews allow individual views to be explored in depth (Denzin N 1994, Fitzpatrick and Boulton 1994).
 - Unstructured interviews allow the participant free rein to talk at length about their experiences and views, ideally with little prompting or direct questioning from the researcher. This technique generates very large amounts of data and requires time and may need several interviews to cover the topic in depth.
 - Semi-structured interviews involve the researcher asking both open and closed questions from a flexible list of questions, not necessarily in order. There are three stages:
 - Introduction: of the interviewer and the broad aims
 - Open questions that become more personal / sensitive with time
 - Rounding off: an opportunity for the participant to add anything they feel is relevant that may not have been covered otherwise.
 - Structured: involves a researcher asking the same set of specific questions in exactly the same way to all participants. It is a form of questionnaire administration and is more likely to be found in quantitative studies than in qualitative, as it is invariably theory verifying and not theory generating.
- Focus groups: involve several participants and a facilitator, are also usually digitally recorded and transcribed with notes to provide the data. Allows group discussion and group views to be explored.
- Other data analysis techniques exist for example documentary analysis (Bowling 2005)

2.3.3 Sampling

Sampling strategies also vary within qualitative studies according to the requirements of the participants: (Kuzel 1986, Murphy E 1992)

- Convenience sampling: For example asking all of the patients attending one clinic
- Purposive sampling: Inviting participants with relevant characteristics to answer a specific question
- Snowball sampling: Participants help to recruit other potential participants

- Theoretical sampling: used to test theories developed from the analysis of data from previous samples (Emerson 1981)

2.3.4 Qualitative data analysis

Perhaps unsurprisingly, data analysis techniques are also varied within qualitative research. (Murphy E 1992)

- Observational / ethnographic approaches aim to immerse the researcher in all forms of possible data related to a topic over a prolonged period of time to gain understanding of that topic.
- Thematic approaches identify themes that summarise the phenomena under study
 - In grounded theory data are collected in batches and compared with previous batches and used to inform further data collection. Theories are generated from inductively created themes, with constant comparison of datasets to explore these theories. (Fitzpatrick and Boulton 1994)
 - The framework method involves simultaneous data collection and analysis with themes being identified from data and a matrix of content used to allow comparisons and associations to be explored. It is flexible and can be more deductive or inductive dependent upon the research question and data analysis process. (Ritchie and Spencer 2003)

There are inherent advantages and disadvantages to the different techniques. The aim of the study to explore the effects of living at increased familial breast cancer risk and women's views towards and experiences of the risk management strategies was felt most likely to be met by interviewing a range of women. Given the intent to explore several different topics, semi-structured interviews were chosen to strike a balance between depth of data and volume of data to analyse. The study aims and objectives did not require theory generation but were pragmatic and phenomenological: aiming instead to understand the essence of the experiences of the women interviewed and the focussing on the outcomes of living with increased familial breast cancer risk. For this reason, the framework method was selected as a technique to guide the study. This technique is described in more depth below.

2.3.4.1 Framework method

Ritchie and Spencer describe the framework analysis technique they developed for large scale policy research in the 1980s, which has subsequently been used widely in health and social research (Ritchie and Spencer 2003). It is one of several methods of thematic analysis, focussing on identifying relationships between parts of the data, aiming to pinpoint descriptive or explanatory conclusions from the dataset. The framework matrix is key to this process and is described further below. This matrix allows researchers to view the dataset in one place and explore relationships, analysing by both cases and by emerging findings. The technique involves (Gale, Heath et al. 2013):

1. Transcription

Interviews (or other sources of data) are transcribed verbatim into a text document with opportunity to add notes, for example non-verbal communication that was significant.

2. Familiarisation with the interview

This step is particularly important for studies where data analysis is not undertaken by the same individuals as were involved in the raw data acquisition (i.e. the interviewers). It usually involves listening to the audio files and reading through the transcripts, making notes during this process.

3. Coding

Coding involves identifying parts of the transcript that are, or may be significant, relevant or important in meaning and labelling them according to the nature of the finding, for example certain behaviours, values or emotions expressed. Coding classifies the dataset so that it can be systematically compared with other parts of the dataset. Coding can follow a pre-existing list of codes (in more deductive studies) or can be open and identify codes as they are met within the transcripts.

4. Developing a working analytic framework

The coding process develops as the first few transcripts are analysed and a set of common codes are identified and developed by the researchers. These are used to code subsequent transcripts. Codes can be grouped into categories and this forms the basis of the analytic framework. New codes may still need to be added up until the final transcript is analysed, so this remains a working framework, subject to change.

5. Applying the analytic framework

The coding framework developed is used to code subsequent transcripts and where necessary, the overall framework is updated to reflect required coding changes. Codes can be abbreviated and computer programmes are available to facilitate this process, for example Nvivo 10 (International Pty Ltd. 2010).

6. Charting data into the framework matrix

The framework matrix is a spreadsheet with cases in rows and codes in columns. The transcript data populate the cells. As interview data is not concise, it is acceptable and also necessary to summarise the relevant sections of the transcripts, aiming to keep the feel and meaning, and often direct quotes are necessary for this integrity of meaning. Without summarising, the volume of data would, however, be impossible to view in this format. The aim is for the matrix to become an intuitively structured overview of the (summarised) data.

7. Interpreting the data

Impressions formed by the data can occur during any of the above stages of analysis and should be noted as and when they are found and discussed with the other members of the research team. Framework analysis allows researchers to explore theoretical concepts, be they pre-existing or based on the findings of the data, and to identify and explore connections between categories. It may be possible to identify causality for a particular phenomenon, or the data may not provide this level of depth.

Framework analysis is highly systematic and is transparent, allowing relatively inexperienced researchers to become involved in complex data analysis, albeit ideally with the benefit of an experienced researcher to guide them. It allows both inductive and deductive methods of data analysis and can facilitate a combination, for example starting coding with labels selected from literature review but then expanding as new ideas are thrown up by the data. The time required for framework analysis is significant, especially if researchers are new to the technique.

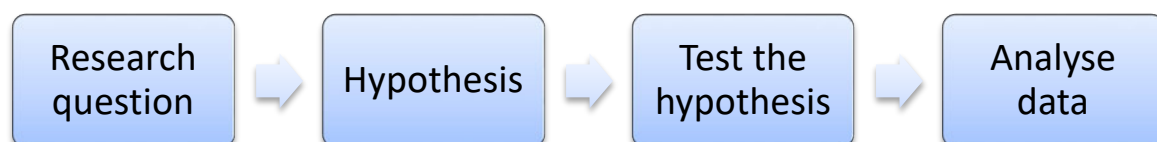
Sampling strategies are sometimes misunderstood. The aim of semi-structured interviews is to gain a greater understanding of a topic by talking to a sample of people who are involved and who may be selected purposefully (as opposed to randomly) (Mays and Pope 1995). Data collected in interviews will not be generalisable as the data are usually specific to the group interviewed. Themes are identified and explored and ideally interviews continued until no new themes emerge from interviews. One potential problem with this method is recruiting, as interviews are time consuming and some people may not feel comfortable discussing potentially emotionally charged issues with a probing stranger. Interviews may, in fact, attract a subgroup of the population being studied, with those who are happy to be interviewed representing only a small proportion of the group.

The questions asked during semi-structured interviews will obviously affect the data provided by a series of such interviews. The three stage semi-structured interview technique described by Seidman in 1998 is used to try to ensure that appropriate topics are covered before moving into a more in-depth stage of the interview (Seidman 1998). Seidman actually recommended three separate interviews be conducted using this approach, however the time demands on participants increase dramatically with this strategy and it is therefore usually modified to a one-interview technique incorporating this structure.

2.4 Quantitative methodology

Quantitative techniques tend to be deductive in nature, used to test theories generated from previously acquired knowledge (see figure 2.2.2 for a schematic of quantitative research).

Figure 2-2-1 - Quantitative methodology



There are a vast variety of quantitative methods described. For the benefit of brevity, this thesis will focus on survey methodology.

2.4.1 Questionnaires

Questionnaires are a tool used to collect responses about a topic from a large number of participants, often comparing one group with another (Sapsford 1999). They sacrifice depth of information for generalisability of results, by sampling a much greater number (Bowling 2005). Appropriate time and thought in questionnaire design is key to the quality of data they will generate. Validated questionnaire tools are widely used and allow direct comparison between studies of similar outcomes, for example the Breast Q measure of patient reported outcomes for surgery to the breast (Pusic). These tools are validated across all spectrums (see below) but are fixed and cannot be adapted. Bespoke questionnaires can be designed but care needs to be taken to ensure they are unbiased, reliable and valid instruments for use to answer the research question effectively.

Psychometric properties to consider with questionnaires (Sapsford 1999, Litwin 2003, Bowling 2005):

- Reliability
 - Test – retest: the questionnaire is re-administered after a short interval when circumstances are not expected to have changed. Cohen's kappa coefficient is used for nominal data, Pearson's correlations for interval data. A score of 1 indicates perfect agreement between the tests, 0 indicates agreement is no better than chance.
 - Inter-rater: this applies more to questionnaires that are administered by a researcher asking the questions and indicates the correlation between two or more interviewers with the same population.
 - Internal consistency: assesses the questionnaire questions' ability to explore the area they are intended to, by comparing answers to questions aiming to tap into the same area. See Cronbach's alpha.
 - Internal consistency measures the extent to which all items measure the same concept or construct (Tavakol and Dennick 2011). Cronbach's alpha – a measurement of internal consistency of a test or scale, is expressed as a number between 0-1, where higher scores indicate greater reliability.

- Validity

- Face: in essence, does the questionnaire look like it contains appropriate questions and formatting?
 - Content: This is an extension of face validity, assessing the questionnaire content for evidence of a balanced and comprehensive set of questions that will answer the research question.
 - Criterion: This assesses the questionnaires correlation with another validated measure of the same topic, which of note, does not always exist, and proxy measures can be used instead.
 - Construct: Reflects the questionnaire's ability to answer the research question
- Bias and error
 - Response style bias: also known as 'automatic-yes-saying' where participants tick the yes box without thought (or always tick the left column or 'strongly agree'). This can be minimised by changing the questions phrasing to force participants to think more carefully about the answer, or by alternating positives and negatives in questions.
 - Random measurement error: where participants may give a different answer on different days due to uncertainty or guessing an answer. It is assumed that in a big enough sample, positives will be balanced by negatives.
 - Reactive effects: by inviting their participation, the participants change how they respond, either becoming more interested in the phenomenon being studied or by trying to make a good impression.
 - Recall bias: describes the difficulty in accurately recalling memories of events and experiences
 - Reporting bias: describes the gaps in participants' answers due to difficulty in answering some questions, for example because of embarrassment or the sensitivity of the information.
 - Systematic error: This is the sum of the biases and errors inherent in the design of the questionnaire. These can stem from selection bias, information bias and other confounding factors and tends only to be described for very large, population based studies.

2.4.2 Questionnaire design

Questionnaires vary widely in both how they are administered (for example in person, by post, online) and by the type of tools they use to measure the participants' responses (including Likert scales, visual analogue scales, ordering lists etc.) Choosing the right means of delivery and questions is clearly important for validity of the questionnaire. Design should follow the steps outlined below in figure 2.2.3 (Sapsford 1999, Gillham 2000, Bowling 2005).

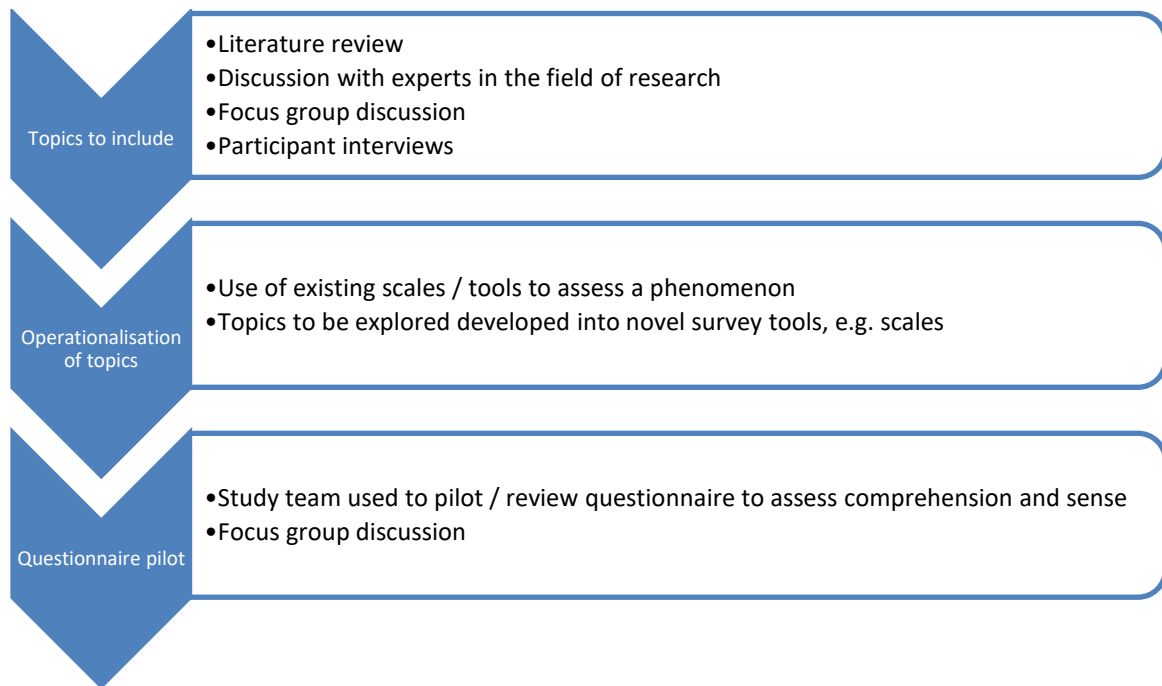


Figure 2-2-2 Questionnaire design steps

There are steps that can be incorporated into the study design that can improve response rates, for example use of stamps (instead of franking) on envelopes, hand signed letters (instead of photocopies) and use of coloured paper (Edwards P. 2001). Sending written reminders to non-respondents is another technique recognised to improve response rates by this group.

A power calculation can be performed using the size of the population being studied, along with the desired confidence interval and confidence level to determine the sample size that allows confidence that the results represent the population (Creative-Research-Systems 2017). A difficulty with using power calculations for surveys is that sample size calculations require assumptions that can rarely be estimated in advance of data collection.

Determining the size of sample necessary to be confident in the views expressed being representative of the whole population being studied is challenging. Clearly the bigger the number the greater the chance that all views held within the population are expressed in the results. Some view sample size as being flexible and determined by the responses given. If all respondents agree on a point and the sample technique did not introduce bias, then the results of a small sample may be identical to those of a bigger sample. When more subgroup analyses are planned, a greater number of responses are required, to populate each group (Oppenheim 1992).

Response scales:

These ask participants to select an option to which a number can be attached (either obviously within the questionnaire design or more commonly during data analysis) to simplify the analysis process. Examples include:

- Dichotomous option: Questionnaires represent a good method of gaining understanding? Yes / No?
- Selecting from a continuum, e.g. Likert scales: 1=strongly agree, 2=agree, 3=neither agree nor disagree, 4=disagree, 5=strongly disagree.
- Selecting one response from a range of options: Which one of the following do you think ... Option 1=statement, Option 2=statement, Option 3=statement.
- Visual analogue: The pain I experienced was:



where participants put a mark along the line to represent their view. The marks are subsequently measured to provide a numerical response.

Care needs to be taken to ensure that an appropriate option is available to all participants when this type of question is used. It is also important to consider how the question is phrased with inclusion of both positive and negatives statements about the same phenomenon, for example, "I feel confident that breast screening is likely to recognise cancers early" and "I worry that screening may not detect cancers at an early stage" to reduce the likelihood of participants being swayed by the very inclusion of the statements. It

also forces participants to consider their answers and avoid automatic endorsement of all statements provided by the researchers.

Another point of note applies to Likert scales. Where a middle option is offered, for example:

- Strongly agree
- Agree
- Neither agree nor disagree
- Disagree
- Strongly disagree

up to 20-30% will 'sit on the fence'. If this option is moved to the end and/or the label changed:

- Strongly agree
- Agree
- Disagree
- Strongly disagree
- Undecided

fewer participants select it (Dillman 2000). Some advocate removing this option completely, producing a modified (forced) Likert scale where participants are forced to select an either positive or negative response.

Ordering of questions:

Each section, or 'cluster' of questions should begin with a brief explanation of what is to come, for example, "In this section, we will ask questions about your general health". A funnel approach is usually used, where questions begin broadly with simple responses, then narrowing into the area of interest with more probing, sensitive questions (Vaus 2002). Questions should aim not to skip between topics, which is frustrating for participants.

Question wording:

Ambiguity needs to be avoided. Questions need to ask one question only and all of the words should be simple and generic, even if this necessitates the inclusion of further questions. Where questions are exploring a potentially sensitive or embarrassing topic, an option to reduce this impact is to include an opinion question before one asking about the participants behaviour, for example: “Risk reducing breast surgery may have an impact on their desire for sexual intimacy, agree / neutral /disagree” before “Since surgery, I have been sexually intimate more / less / about the same”.

Finally, open questions with space for respondents to write freely can be included. Participants may respond differently in open and closed questions about the same topic. This may reflect the question’s phrasing but may also reflect a characteristic of question format and the likely responses. Free text boxes present some challenges for analysing results, particularly if the researchers wish to demonstrate the instrument’s validity, but they allow respondents to include their thoughts and feelings about a topic that may not otherwise be captured in the close ended part of the questionnaire. A ‘final comments’ box is often offered for participants to add any further insights or comments on the questionnaire itself.

2.4.3 Questionnaire interpretation

Before interpreting the responses themselves, the quality of the questionnaire itself can be assessed. Cronbach’s alpha is a frequently reported measure of internal consistency of a questionnaire tool. It can be assessed on a single administration of a test and is easily calculated on most statistical software programmes (Kaplan 2004) with values falling between 0-1. Scores nearer 1 suggest higher internal consistency, a measure of good reliability. Similarly the response rate needs to be calculated and responder bias addressed, at least in the discussion of the ultimate findings (Bland 2015). The power of a questionnaire will determine the reliability of it’s findings. An underpowered study is likely not to represent the population adequately and results are likely to include error, accordingly. Power calculations take into account the size of the population being studied, the desired confidence interval and confidence level (Creative-Research-Systems 2017).

In order to analyse the responses of a questionnaire, the data need to be translated into a form that allows tabulation (Fink 2003). With the aim of a questionnaire study being to allow measurement and quantification (Oppenheim 1992), it is necessary to change responses to

questions that have non-numerical responses, for example Yes / No and Likert scales into numerical code. A code is created for the questionnaire, listing the questions, the responses and the numerical codes to enable data from questionnaires to be transcribed into a database accurately, where questionnaire respondents are given identities, for example 'Surgery1' and form the rows with each question becoming a column within the database. A coding framework is created to cope with free text responses, creating categories that responses fall into (Oppenheim 1992, Litwin 2003). Where no response is given, a separate code is required to allow meaningful data interpretation.

As questionnaire data tend to be categorical, most begin to report findings using simple descriptive statistics, which allow data to be presented and groups compared. Median and interquartile range are used to describe the data and provide context (Bland 2015). Cross-tabulating nonparametric data allows direct comparison and where applicable also allows statistical analysis between groups using Chi squared or Fisher's Exact tests (when the expected value is less than 5 and where Chi squared approximation of the p value becomes less appropriate), which assume no difference between groups and assesses whether figures are as expected (without a statistical difference) or not as expected (statistically significant difference between groups) (Sapsford 1999, Hart 2001, Bland 2015). McNemar's Q test can similarly be used to compare dichotomous information, for example Yes / No responses. These data can be presented in graphical form using bar charts, percentage component bar charts, pie charts and line charts.

2.5 Mixed methodology research

The combination of qualitative and quantitative methods is known as mixed methods. As a concept it is not new and the overarching premise is that by combining methods, a greater understanding of a phenomenon can be gained than by using one approach alone (Bowling 2005) (Tashakkori A 1998). The methods can be carried out either sequentially or concurrently. The aim of using both can be either to complement each other, for example using qualitative techniques in the pilot phases of a (mainly quantitative) project, or one can be used to triangulate against the other, that is, checking the findings from one limb of the study against the findings in the other. In reality, a combination of both aims is likely to be present (Creswell JW 2007).

Typology of mixed methods

This refers to the way in which mixed methods are used, examples include (Bowling 2005, Teddlie 2009):

- Sequential exploratory strategy: qualitative work informs the subsequent quantitative study, for example questionnaire design
- Sequential explanatory strategy: qualitative work is used to help explain quantitative findings
- Concurrent triangulation strategy: qualitative findings are compared with quantitative findings at the end of the study.

A major challenge for researchers is the need to be proficient in both qualitative and quantitative techniques and to understand the options available in both and to choose appropriately. In short, mixed methods researchers need to be well versed in methodological approaches generally prior to embarking on a specific project. They then need to design a study that is appropriate to the research question, including thought to sequential or concurrency of the study arms.

2.6 Rationale for use of mixed methods

This study aimed to understand the psychosocial outcomes for women and partners of women at increased familial breast cancer risk when undergoing enhanced screening or following risk reducing surgery. A mixed methods strategy was chosen to allow the benefits of the different component and to avoid the weaknesses of each from impacting on the overall findings. An initial review of the literature was undertaken, followed by systematic review of the psychosocial outcomes for the two groups, risk reducing surgery and screening. This process was deductive, assuming that both screening and surgery have a psychosocial impact on women living at increased risk.

Particularly for screening women and partners, there was a paucity of published work looking at psychosocial outcomes. In order that a broader picture could be established, identifying similarities and differences between the groups, an exploratory phenomenological approach was selected, and the study moved onto semi-structured

interviews, aiming to understand the essence of women's and partner's experiences in both the surgical and screening groups.

The findings from the interview phase of the study were then used to design the final part of this body of work: a quantitative questionnaire study. This utilises an exploratory, sequential strategy, using the benefit in understanding acquired in the qualitative study to inform the subsequent work, allowing design of a bespoke questionnaire that would provide greater inferential understanding of the phenomena identified in the interviews and adding to the existing literature.

Having explored the methodological options, the next section will outline the methodological choices and rationale.

Study development

2.7 The gap in knowledge

The inclusion of MRI breast screening to the options available to women at increased familial risk was felt by the group of experienced clinicians and researchers involved in this study (see acknowledgements), to significantly alter the nature of the decision facing women needing to decide on how to manage their risk of breast cancer. Review of the literature has identified a wealth of information about risk reducing surgery but a relative paucity of data pertaining to the impact of enhanced screening on women at increased risk. The focus of this study was broad, aiming to redefine the psychosocial outcomes for women at increased familial breast cancer risk and their partners, with the change in context from previous studies, which focussed on either *BRCA* carriers alone, or on the outcomes of risk reducing surgery. How this study will address gaps in knowledge is summarised below and in diagrammatic form in figure 2.1.

- The introduction (Chapter 1) and systematic literature reviews (Chapter 3) outline the background to the study, underpinning why it is important to study the outcomes for women and partners of women at increased familial breast cancer risk.
- Chapter 2 presents the research question with the aims and objectives of this thesis before going on to describe the methodological and philosophical approaches used to address these.
- Chapter 4 reports the findings of semi-structured interviews with women at increased familial risk and (separately) with their partners, focussing on
 - The impact of living at risk
 - Views of screening and surgery options for managing risk
 - Outcomes of their risk management strategy and decision satisfaction
- Chapter 5 describes the design and validation of a bespoke questionnaire, using themes developed in the interview study and a focus group discussion to refine and validate.
- Chapter 6 describes the questionnaire administration and results
- The discussion summarises the main findings from the study in relation to the aims and objectives.
- The conclusion summarises the key findings

2.8 The research question

What are the psychosocial outcomes for women and the partners of women at increased familial breast cancer risk when undergoing either enhanced imaging surveillance or risk reducing surgery?

2.9 Study aims

To explore the impact of living at increased familial breast cancer risk and to identify the factors affecting choice of risk management strategy and satisfaction levels associated with these decisions.

2.10 Study objectives

- To establish the impact of living at increased risk for women and their partners
- To explore views toward risk management options in women and their partners
- To explore the decision making process and factors affecting decisions
- To identify the psychosocial outcomes for women at increased familial breast cancer risk
- To quantify the outcomes identified in the qualitative study with a wider cohort of women

2.11 Study components

This is a sequential exploratory mixed methods study, comprising of both qualitative and quantitative methods, including: (see figure 2.4)

- Systematic review (Chapter 3)
- Semi-structured qualitative interviews: (Chapter 4)
- Questionnaire survey (design, validation and application): (Chapters 5 and 6)
- Integrative analysis of these 3 components

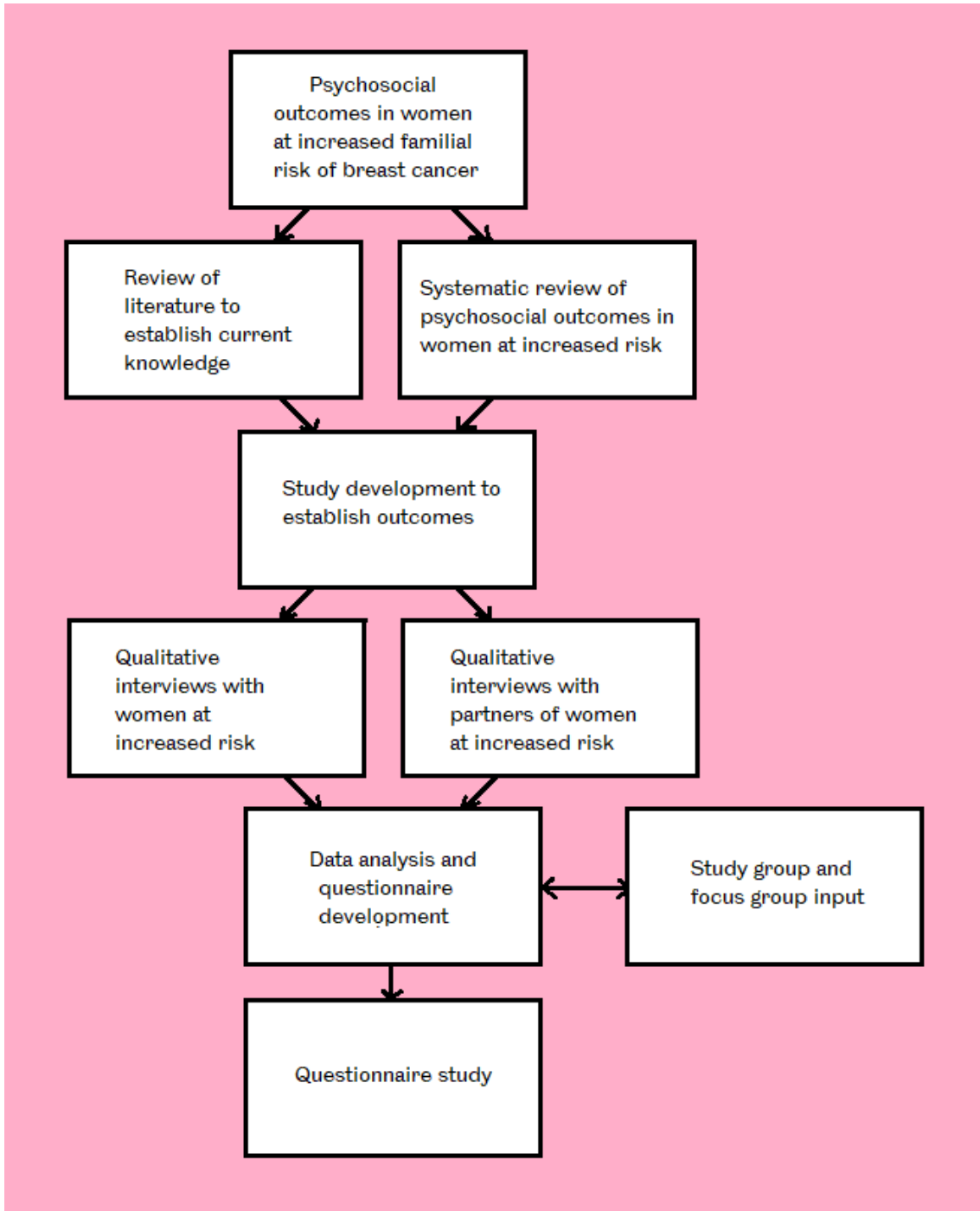


Figure 2-4 - Schema of MD

2.12 Project development

The decision was made to use a sequential exploratory mixed methods approach, starting with exploratory interviews to establish the impact of living at risk, the risk management decision making process and the outcomes of these decisions. The findings of the interviews were used to develop a questionnaire which was used to quantify the findings and allow subgroup analysis between gene mutation carriers and those without genetic mutations. Focus group assessment was also used to refine and validate the questionnaire, which was expected to contain recognised tools to measure psychosocial outcomes initially but this plan was amended after focus group discussion.

2.13 Methodological approach

The aim of this study was to explore and redefine the psychosocial outcomes for women and the partners of women at increased familial breast cancer risk. The first stage of the study involved a systematic review of the existing literature, guided by the overarching aims of the study. It is worth noting that the literature review will highlight issues identified in previous research but will be limited to reported data which may be selective, including where qualitative methods have been used to explore the topic. The experience and expertise of the study group (see acknowledgements), together with an aim to explore experiences and outcomes in a novel setting was felt most appropriately met by, at least initially, a qualitative approach. It was also felt necessary to start with a qualitative methodology to avoid creating a research study where the basis of the study is an assumption, for example, body image or cancer anxiety, as is commonly seen in previous studies. The use of qualitative methods can help to eliminate the effect of researcher assumptions and is one that is frequently employed when considering health related outcomes.

There are many different techniques described to facilitate the acquisition and analysis of qualitative data. Methodology choices can have a substantial impact upon a study's findings and the theoretical backgrounds to these techniques are explored earlier in this chapter (Methodology).

The expert reference group had experience in mixed methods research and in particular with using framework analysis of qualitative data. Given the exploratory nature of the first

step of this study, a framework approach was well suited to the aims. As a results, a series of semi-structured interviews were conducted to ensure a comprehensive range of topics were identified that could be explored in greater depth in the questionnaire phase of the study. By using the findings of the initial qualitative study to guide the development of a questionnaire, the advantages of both techniques are preserved and the weaknesses, to some extent, minimised. The inclusion of focus group discussion was added to further strengthen the study. The combination of results from this mixed methods study will provide an overall comprehensive picture of the outcomes for women with an increased risk of familial breast cancer, which may be used to guide future care and information provided to patients.

2.14 Ethics and research governance

The study was approved by the tertiary Teaching Hospitals Research Governance Unit and was awarded Ethical Approval for the initial study and for the second round of questionnaire invitations (Abridged protocols and ethics approval letters are included in appendices 1 and 5).

2.15 Funding

This study was funded by the University of Sheffield.

2.16 Summary

The first two chapters have provided the evidence base to the study and to the methodology. The next chapter describes the process of systematic literature review for the psychosocial outcomes for both risk reducing surgery and enhanced surveillance. This is followed by the interview and questionnaire phases of the study.

3 Chapter three – Systematic Literature Reviews

This chapter describes the process followed and the outcomes of two separate systematic reviews: one to identify the psychosocial outcomes of risk reducing breast surgery and the other the psychosocial outcomes of enhanced breast surveillance. The findings are explored together and with reference to broader literature in an summary discussion.

Women who discover that they have an increased familial breast cancer risk face the difficult decision of risk management. Broadly, the options are risk reducing surgery or non-surgical measures; predominantly surveillance. RRM is a massive undertaking for a woman who does not have cancer with permanence and irreversibility that can have long-reaching psychosocial consequences. Non-surgical risk management options include surveillance, chemoprophylaxis and lifestyle modification. Familial risk is not binary, there are differing levels of risk and a risk management strategy that may be suitable for one may not be appropriate for another. Individual women also need to understand how their risk management decisions are likely to affect them and their families, both in the short and long-term, and how their choice will affect their actual risk.

Two systematic literature reviews are presented below with an aim to understand better the psychosocial outcomes of the two main risk management strategies offered to women at very high levels of risk with a secondary aim of recognising women at particular risk of psychosocial distress.

3.1 A systematic review of the literature pertaining to the psychosocial impact of risk reducing mastectomy in women at increased familial breast cancer risk

3.1.1 Abstract

3.1.1.1 Introduction

This systematic review aimed to establish the psychosocial outcomes for women undergoing risk reducing mastectomy for increased familial breast cancer risk. There is a wealth of published evidence pertaining to the outcomes of risk reducing mastectomy in high risk women. This review aimed to systematically assess these data to present a comprehensive overview.

3.1.1.2 Methods

A systematic search of databases was undertaken in accordance with PRISMA guidelines, identifying studies of women assessing the psychosocial outcomes for women who have undergone risk reducing mastectomy (with or without reconstruction) due to increased familial risk of breast cancer. Studies of women being treated for cancer, review articles and those in which psychosocial outcome assessment was not a primary aim were excluded. Studies were subject to quality review. Meta-analysis was not performed due to heterogeneity of outcome measures and participants.

3.1.1.3 Results

14 studies were identified as suitable for inclusion.

3.1.1.4 Conclusion

RRM is generally well tolerated with minimal psychosocial distress reported in the majority. Women at increased risk of a poor psychosocial outcome include those who over-estimate their breast cancer risk, those who have high baseline cancer related anxiety / distress, those with poor body image at baseline, younger women and those without good social support. Following surgery, women with complications are also at increased risk. Provision of

information was often felt to be inadequate. Improving access to information and identifying women at risk of a poor outcome and targeting additional support may improve psychosocial outcomes.

3.1.2 Introduction

Breast cancer is the most common cancer to affect women (Cancer Research 2016). Those at increased familial risk have often seen relatives suffer and die of the condition. The discovery of *BRCA* genes in the 1990s (Miki, Swensen et al. 1994, Wooster, Bignell et al. 1995) alongside an increase in public awareness (Evans, Barwell et al. 2014) has resulted in a larger number of women at increased risk seeking risk reducing mastectomies to prevent development of breast cancer. There is good evidence that RRM is an effective strategy to reduce risk (Hartmann, Schaid et al. 1999) but the effects of this irreversible operation are broader than simply reducing risk: studies have demonstrated some women suffer long-term psychosocial sequelae following RRM.

This review aimed to systematically assess the psychosocial outcomes associated with RRM for women at increased familial breast cancer risk. Specifically, it aimed to describe areas of psychosocial distress and factors that are associated with this outcome. Rapid review methodology was employed limiting searches to published literature identifiable through searches of bibliographic databases (Tsertsvadze, Chen et al. 2015, Hartling, Guise et al. 2016). Papers were not double screened for inclusion and only information relevant to the review was extracted.

3.1.3 Search methods

The PRISMA statement guided the review process (Moher, Liberati et al. 2009).

Relevant studies were identified by searching the following electronic databases: (see figure 3.3.1)

- MEDLINE
- EMBASE

- CINHAL
- PsycINFO
- CENTRAL at Cochrane

3.1.2.1 Search limits and rationale:

This search is unlimited for start dates to allow all relevant papers to be identified.

- Date: 1946-present day.
- Participants: Humans, Females.
- Language: Articles in English.

Searches were performed using a combination of search terms:

- Familial breast cancer, hereditary breast cancer, familial breast and ovarian cancer, hereditary breast and ovarian cancer, genetic risk breast cancer, inherited risk breast, *BRCA1*, *BRCA2*, gene mutation,
- Breast cancer, breast tumour, breast and ovarian
- Risk, predisposition, tendency,
- Risk reducing mastectomy, RRM, risk reducing surgery, contralateral mastectomy, risk reduction, prophylactic mastectomy, double mastectomy
- Outcomes – Psychosocial, anxiety, depression, distress

3.1.4 Inclusion criteria

Articles were included in the overall analysis if:

Participant factors

- Study included patients with increased risk of familial breast cancer.
- Study included patients who had risk reducing mastectomy or mastectomies with or without reconstruction

Methodological factors

- Original research articles from peer-reviewed journals, including prospective and retrospective, and qualitative and quantitative studies

Outcome factors

- Study pertained to the psychosocial outcomes in high risk women.

3.1.5 Exclusion criteria

Articles were excluded from the overall analysis if:

Participant factors

- Surgery was exclusively for cancer treatment and was not for increased familial risk of breast cancer.

Methodological factors

- Review papers, editorials, case reports, papers published in a language other than English

Outcome factors

- Psychosocial outcomes were not reported

3.1.6 Quality review of papers

Papers were all subject to quality review. Questionnaire based studies were assessed using the Critical Appraisal of a Questionnaire Study tool (Roever 2015) (see appendix 6). Studies using previously validated tools were assumed to meet the quality assessment requirements of the tool itself and analyses were limited to the remaining points. Studies comparing a cohort of RRM women against controls were assessed using the Newcastle Ottawa quality assessment scale (GA Wells 2017). Purely qualitative studies using the Standard for Reporting Qualitative Research tool (O'Brien, Harris et al. 2014). The latter was formulated to allow quality review of qualitative papers although it is not intended to assess methodology due, in part, to the diverse nature of methodologies employed by qualitative studies. It includes 21 points of assessment:

Title and abstract

1. Title – Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g. ethnography, grounded theory) or data collection methods (e.g. interview, focus group) is recommended
2. Abstract – Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results and conclusions

Introduction

3. Problem formulation – Description and significance of the problem or phenomenon studied; review of relevant theory and empirical work; problem statement
4. Purpose or research question – Purpose of the study and specific objectives or questions

Methods

5. Qualitative approach and research paradigm – qualitative approach (e.g. ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g. postpositivist, constructivist/ interpretivist) is also recommended, rationale
6. Researcher characteristics and reflexivity – Researchers' characteristics that may influence the research, including personal attributes, qualifications / experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research question, approach, methods, results and /or transferability
7. Context – Setting / site and salient contextual factors; rationale
8. Sampling strategy – How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g. sampling saturation); rationale
9. Ethical issues pertaining to human subjects – Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues
10. Data collection methods – Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources / methods, and modification of procedures in response to evolving study findings; rationale
11. Data collection instruments and technologies – Description of instruments (e.g. interview guides, questionnaires and devices (e.g. audio recorders) used for data collection; if / how the instrument(s) changed over the course of the study

12. Units of study – Number and relevant characteristics of participants, documents or events included in the study; level of participation (could be reported in results)
13. Data processing – Methods for processing data prior to and during analysis, including transcription, data entry, data management and security verification of data integrity, data coding and anonymization / deidentification of excerpts
14. Data analysis – Process by which inferences, themes etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale
15. Techniques to enhance trustworthiness – Techniques to enhance trustworthiness and credibility of data analysis (e.g. member check, audit trail, triangulation); rationale

Results / findings

16. Synthesis and interpretation – Main findings (e.g. interpretations, inferences and theme); might include development of a theory or model, or integration with prior research or theory
17. Links to empirical data – Evidence (e.g. quotes, field notes, text excerpts, photographs) to substantiate analytic findings

Discussion

18. Integration with prior work, implications, transferability and contribution(s) to the field – Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on or challenge conclusions of earlier scholarship; discussion of scope of application / generalisability; identification of unique contribution(s) to scholarship in a discipline or field
19. Limitations – Trustworthiness and limitations of findings

Other

20. Conflicts of interest – Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed
21. Funding – Sources of funding and other support; role of funders in data collection, interpretation and reporting

An empirical decision was taken based upon critical review of the papers as to whether they were high, acceptable or low quality. A scoring system was not used as the included studies were so diverse, however the quality review tools were used to inform this decision, for example, studies that had met the majority of the quality review points were rated higher than those that hadn't provided evidence for several points.

3.1.7 Results of the search

A total of 188 results were generated by these initial searches and 22 records identified by other means. Abstracts and titles were reviewed for relevance and compared to the inclusion criteria and full text articles were obtained for relevant papers. Where it was unclear from the title/abstract whether the studies met the inclusion criteria, full text articles were also obtained and a decision made based on the entire paper.

Figure 3.3.2 shows the review process in diagrammatic form.

After excluding ineligible and duplicate abstracts, 57 papers were deemed potentially eligible and the full papers were retrieved.

References of relevant papers were hand searched to identify additional studies missed by the primary search.

Records identified through database searching (n = 188)

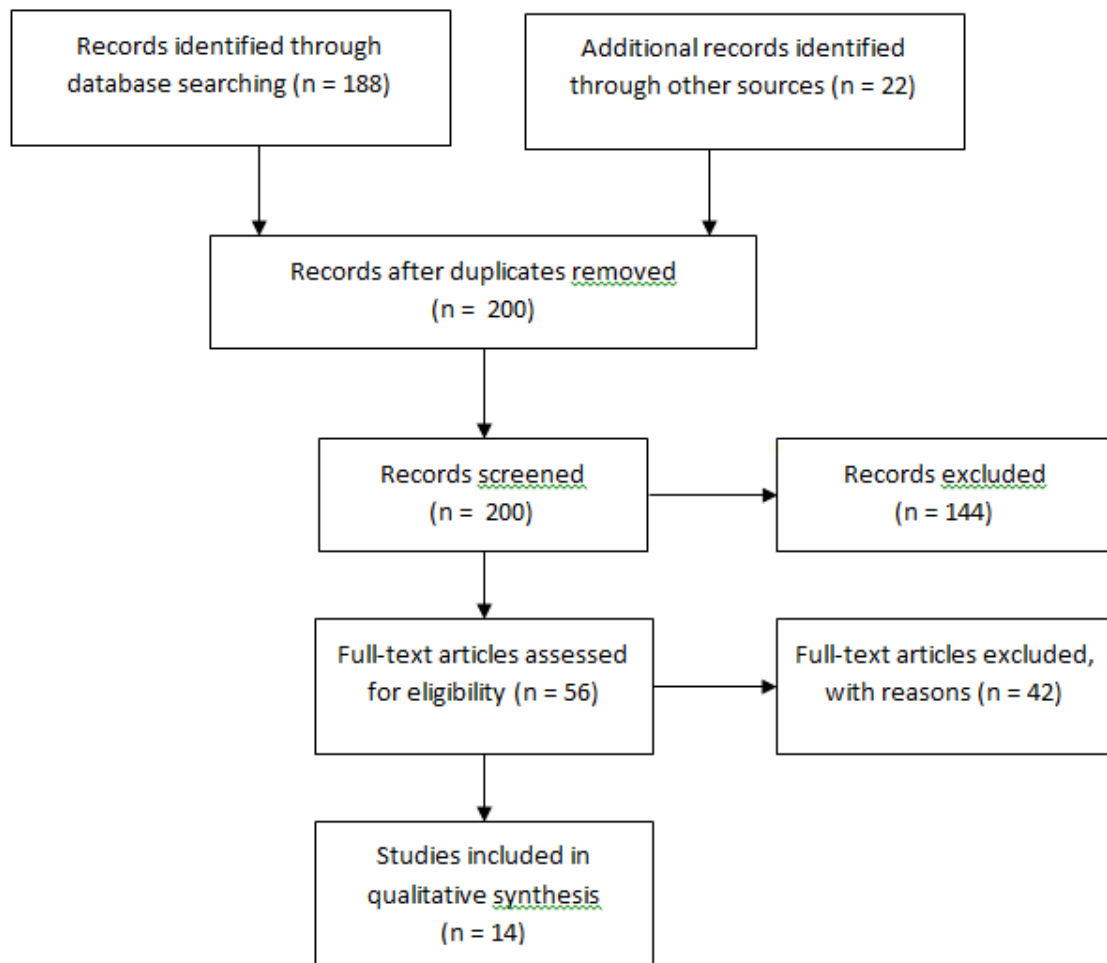
Additional records identified through hand searching references (n = 22)

Total number of citations assessed (n = 201)

Excluded based on title or information in abstract (n = 144)

Full-text articles retrieved for the review (n = 57)

Figure 3-3-1 Flow chart for systematic review as per PRISMA guidelines (Moher, Liberati et al. 2009)



3.1.8 Characteristics of included studies (see table 3.3.1)

Study methodologies

- 10 were questionnaire based studies, some using validated tools and some bespoke questionnaires
- 2 combined interviews with questionnaires
- 2 used interviews to explore the topic
- 7 were purely retrospective
- 7 included pre-operative assessment and prospective data collection

Study participants

- 11 limited participation to women who had / were having purely risk reducing surgery, whereas 2 combined RRM with women having CRRM and one did not state the nature of surgery

- Participant numbers varied from 10 to 684
 - Interview studies participant numbers varied from 10 to 154
 - Questionnaire studies participant numbers varied from 36 to 684
- Participants level of risk varied with 6 stating women were at high risk (some stating *BRCA* carriers or similar level of risk), 4 including women at high or moderate risk and 4 not categorically stating risk (although all had been offered RRM for familial risk)

Quality review

- 5 studies were rated as acceptable quality
- 9 studies were rated high quality

Papers dated between 2000 and 2015 (although some data collection included women operated on in the 1980s.

Table 3-3-1 Study characteristics and findings

Author, year and study key	Study sample	Quality review notes	Data collection method and follow up period	RRM / CRRM / combined	Study aims	Summarised findings
1. Heiniger 2015	32 women who had RRM +/- RRSO (a separate RRSO only group were investigated) with 69 high risk women who had not had surgery	Acceptable quality study 70% response rate Very wide range of risks (RR of breast cancer 0.7 <i>i.e. below normal</i> to 65.7) so questionable generalisability to a <i>BRCA</i> or equivalent risk group	Pre-op / baseline questionnaires with 3 year follow up questionnaires	Not stated if any women had CRRM or if all RRM (+/- RRSO)	To investigate long-term psychosocial outcomes for women who have RRM +/- RRSO	RRM women reported reduced breast cancer risk and reduced cancer anxiety. Regret was uncommon but was associated with greater changes in body image scores
2. Gopie 2013	50 <i>BRCA</i> or high familial risk women from Holland	High quality study Prospective cohort study, initial response rate 68%. Unusual statistics analyses.	Questionnaires sent pre-op, 6 months and 21months post op	RRM	Prospectively explore body image, sexual relationship satisfaction and cancer distress after bilateral RRM and immediate reconstruction	Body image and sexual relationship satisfaction deteriorated from baseline
3. den Heijer 2012	36 high risk women (>50% risk of breast	Acceptable quality study. Small sample size. No mention of response rate	Psychological distress and body image assessment by postal	RRM	To explore psychosocial distress and body image after RRM at long-term	Psychosocial distress was reduced by RRM with reconstruction at the cost

	cancer or BRCA carriers)	/ representativeness of sample. Those in whom reconstruction had failed and implant been removed were excluded from the study.	questionnaire: preop, early post op and late post op		follow up and to identify risk factors for poor body image	of long-term body image issues
4. Geiger 2007	106 moderate to high risk women who had RRM previously and 62 moderate to high risk women who had not had RRM	Acceptable quality study Retrospective case – control study. Heterogeneous sample. Up to 20 year follow up 58% response rate Results have questionable application to very high risk women	Postal questionnaires using some validated and some sections of validated tools	RRM	To examine the long-term quality of life after RRM	Most were satisfied with their surgery. RRM did not appear to impact upon psychosocial outcomes compared to the non-surgical group
5. Rolnick 2007	684 women who had RRM or CRRM in the past	High quality study. 71% response rate, large numbers. Very variable risk, majority were CRRM and were likely 'normal' risk. Results have questionable application to very high risk women	Postal survey asking 2 open questions	Combined	Explore what women wished they had known before having RRM	Information needs, especially images of reconstruction results post op.

6. Metcalfe 2005	60 women at variable familial risk levels who had undergone previous RRM	High quality study although based on the same cohort and questionnaire data as study 12 so likely some repetition and the same limitations apply.	Postal questionnaires included validated tools (with telephone interviews purely to clarify risk)	RRM	To assess quality of life in women who had had RRM and to determine which factors affect quality of life.	Poor quality of life correlated with cancer-related distress, body image difficulties and psychological distress. Social support was associated with better quality of life.
7. Metcalfe 2004	60 women at variable familial risk levels who had undergone previous RRM	High quality study 80% response rate 6-117 months since surgery, likely greater recall bias with longer interval participants	Postal questionnaires included validated tools (with telephone interviews purely to clarify risk)	RRM	To explore the current psychosocial functioning of women who had undergone RRM	Most did not experience psychological distress, body image or sexual difficulties after mastectomy. Reconstruction and older age were associated with higher satisfaction.
8. Bebbington Hatcher 2003	60 women who had RRM at high risk and 20 women that opted against RRM	High quality study Robust sampling strategy and large numbers Analysis of a subgroup from the (same authors') 2001 questionnaire study cohort	Semi-structured interviews	RRM	To explore the attitudes and beliefs of high risk women who accepted or declined RRM	Clear need for tailored information and for emotional support
9. Lodder	63 women with a 50%	Acceptable quality study 67% participation rate	Interviews and questionnaires 1-3 weeks	RRM	To explore the emotional impact of gene test	Raised distress levels in the RRM group had almost

2002	risk of carrying <i>BRCA</i> gene, 14 of whom chose RRM	Study methodology adjusted based on preliminary findings to strengthen findings validity. Some non-validated tools with no mention of internal validation. No presentation of interview data.	after gene testing and 6 and 12 months later with 1 week pre-op and 1 month post RRM phone interviews		outcome and decisions on risk management (including RRM)	disappeared at one year follow up. Most were satisfied with their decision. RRM group had adverse effects in body image, intimate relationships and physical wellbeing.
10. Bebbington Hatcher 2001	154 women at increased familial risk and offered RRM	High quality study. 92% response rate, Transparent data analyses.	Questionnaires pre-op and at 6 and 18 months post op compared against women who decided not to have surgery	RRM	Investigate psychosocial impact of RRM and identify risk factors for post op distress	Psychological morbidity decreased in the women who chose RRM but not in the group who declined surgery
11. Frost 2000	572 women at increased familial risk of breast cancer (214 high risk, 425 mod risk)	High quality study Large numbers, mean 14.5 years long-term follow up 94% response rate Results have questionable application to very high risk women	Questionnaire sent post op (up to 14yrs later)	RRM	To evaluate long-term satisfaction, psychological and social function after RRM	Decreased breast cancer emotional concern with favourable psychosocial outcomes but some reconstruction problems and some poor psychosocial outcomes
12. Hopwood	45-52 women at increased	High quality study Predominantly	45 interviews and 52 questionnaires preop and	Combined	To assess mental health and body image outcomes	For most women there are no significant mental health

2000	familial risk and who had decided to under risk reducing surgery	questionnaire data with interview comments to expand on questionnaire responses ad hoc. 79% initial response rate, short follow up	1 year post op		after prophylactic mastectomy in women at increased familial risk	or body image issues in the first 3 post op years. Women with complications warrant extra psychological support
13. Josephson 2000	15 women at increased familial risk	Acceptable quality study. Lifetime risk of breast/ovarian cancer >20%, only just above normal 88% participation rate, follow up varied from <1 to >3 years post op. No raw data presented.	Semi-structured interviews	RRM	To explore experiences with decision making and satisfaction with care before RRM	Women struggled to translate the genetic information provided and felt care lacked psychological support. None regretted RRM.
14. Lloyd 2000	Women at increased familial risk who had previously undergone RRM	High quality study 91% participation rate. Follow up varied from 6 weeks to 3 yrs post op.	10 women and 8 partners were interviewed	RRM	To explore the psychosocial implications of bilateral prophylactic mastectomy	Highlighted cancer related anxiety, isolation, social obligations, lack of regret in having RRM, depression, lack of support

3.1.9 Findings

Baseline psychosocial function

Interviews with women (after RRM) describing some of the feelings women had prior to surgery, included fear of cancer, fear of losing their breasts and more generic concerns about surgery including fear of anaesthetics (Lloyd, Watson et al. 2000). Clearly there is likely to be some degree of recall bias incorporated but it does add some context to the 'baseline' pre-RRM assessments of general anxiety. Another study found that women choosing RRM had greater concerns with body image and intimate relationships than a control group who did not undergo RRM (Lodder, Frets et al. 2002) (although the study included very small numbers of women choosing RRM).

Bebbington-Hatcher noted a tendency of women who declined RRM to have higher anxiety traits than those who accepted surgery (Hatcher, Fallowfield et al. 2001) with significant anxiety and psychosocial morbidity at baseline in both groups, with particular reference to intrusive thoughts (Bebbington Hatcher and Fallowfield 2003). The opposite effect was noted in another study that found baseline anxiety and cancer related distress were higher in women choosing surgery (Lodder, Frets et al. 2002) than in those not choosing surgery, and whilst this study incorporated some methodological weakness, including a small sample size, anxiety and distress were measured with validated tools.

When personality traits were assessed, women with more 'problem focussed' coping strategies were more likely to choose RRM over screening, whereas those who tended to use detachment to cope, were more likely to choose screening (Bebbington Hatcher and Fallowfield 2003). A higher perception of breast cancer risk was reported, as was elevated cancer related anxiety in those who chose surgery compared with matched controls who did not have RRM (Heiniger, Butow et al. 2015), although small numbers and risk heterogeneity limited this study.

Short-term outcomes

Women described feelings of loss, sadness and lack of womanliness during the immediate recovery period (Lloyd, Watson et al. 2000) with associated difficulty in coming to terms

with the fact that it was something they decided to do to themselves. Complications were a source of distress for women interviewed (Lloyd, Watson et al. 2000) with some women attributing responsibility for complications to themselves.

Women felt poorly prepared for the degree of incapacity they felt post-RRM (Lloyd, Watson et al. 2000, Bebbington Hatcher and Fallowfield 2003). Some expressed overwhelming tiredness and pressure to get back to work quicker than was comfortable. Most expressed relief with the reduction in cancer related anxiety following RRM, although ongoing concerns included risk to children and ovarian risk (Bebbington Hatcher and Fallowfield 2003), which perhaps manifest in some other studies measuring cancer-related anxiety following surgery.

General distress and cancer-specific distress both fell significantly ($p=0.03$ and 0.01 respectively) from pre-op values when measured at six months following surgery (den Heijer, Seynaeve et al. 2012). It should be noted, however, that the pre-op assessment was carried out 2-4 weeks before a major operation, which could impact on general distress considerably. These findings were mirrored by another group (Lodder, Frets et al. 2002). General physical health was negatively impacted by RRM when assessed at 6 months post op. This effect had almost disappeared at ~ 2 year follow up (Gopie 2013).

The proportion of women who were 'highly anxious' before RRM (71%) dropped significantly following when reassessed 18 months after surgery (41%). This effect was not apparent in a matched control group who did not have surgery (52% at baseline, 50% at 18 months).

Long-term outcomes

Contentment with quality of life was reported in 61% of women post RRM, but interestingly, also 61% for a matched control group that did not have surgery (Geiger, Nekhlyudov et al. 2007). Quality of life (6-117 months post RRM) was generally above average and correlated with good social support. It was however, negatively affected by vulnerability and, perhaps unsurprisingly, by psychological distress (Metcalfe, Esplen et al. 2005). Vulnerability in this context included feelings of susceptibility of the body to illness and cancer and a loss of trust

in the body as a healthy and functioning organism (Baxter 1997.). Psychological distress was also influenced by over-estimation of ongoing cancer risk (Metcalfe, Esplen et al. 2005).

General distress and cancer-specific distress, which were measured shortly before surgery, then at 6 months post operatively and finally between 6-9 years post RRM. Distress levels fell at the early post-op visit and fell substantially further at the third assessment, suggesting long-term benefit is derived from surgery in terms of distress, (both cancer-specific and general distress) (den Heijer, Seynaeve et al. 2012). However measuring baseline distress levels shortly before a major operation may give erroneously high baseline levels and the number of subjects in this study was small.

Another study found that, at post-RRM follow up, there was no difference between women who had RRM and those who did not in terms of cancer related anxiety (Heiniger, Butow et al. 2015), although this study was also limited by small numbers.

Psychological distress symptoms consistent with the need for psychological counselling were present in 32.2% of women on long-term follow up (Metcalfe, Esplen et al. 2004). This was more likely in women who over-estimated their ongoing risk of breast cancer.

Deleterious effects on emotional stability (9%), levels of stress (14%) and self-esteem (18%) were reported in 572 women at various levels of risk surveyed between 7 and 40 years after surgery (Frost, Schaid et al. 2000)

Two studies describe a process of acceptance: processing loss, recognising the positives and adjusting to the negatives and moving on. This process is necessary for recovery and varies between individuals (Lloyd, Watson et al. 2000, Lodder, Frets et al. 2002). Those with greater difficulty, for example, looking at or touching their breasts, are likely to require longer to recover in the broader sense. This theory holds parallels with the well described stages of bereavement, which is not surprising.

Body image

A study of 36 women who had RRM with immediate breast reconstruction (IBR) found that body image and breast-specific body image scores both worsened significantly at 6 months post-RRM compared with baseline scores. At 6-9 years, the result was slightly closer to baseline but still negatively affected, for both general and breast-specific domains (den Heijer, Seynaeve et al. 2012). Lower general body image baseline scores correlated with lower scores post RRM, although this was not the case for breast related body image, which seemed to be more sensitive to surgical changes, likely reflecting scars and other aesthetic differences (den Heijer, Seynaeve et al. 2012). Long-term follow up of women who had RRM for various reasons (not all exclusively familial risk) found that 36% expressed diminished satisfaction with body image following RRM (Frost, Schaid et al. 2000). Some operations dated from the 1960s and pre-op counselling is likely to differ substantially from that provided today, limiting the generalisability of these findings. An interesting finding, also from Frost's study, was that women who chose not to have reconstruction had fewer adverse outcomes in both femininity and body image domains than those who had reconstruction.

In contrast to these studies, body image was found not to be affected by RRM and IBR in other studies (Hatcher, Fallowfield et al. 2001{Heiniger, 2015 #811}), possibly due to methodological issues, for example small samples, or reflecting differences in the experiences between groups of women in different studies. Heiniger comments that it could also be due to long follow up in her series, reflecting inevitable changes in body image over time. Metcalfe found half of women reported no change in self-image, with the other half equally split between those who thought it was improved and those who thought it was worsened by surgery (Metcalfe, Esplen et al. 2004). Reconstruction did not influence this finding.

Body image concerns and regret were more common when there were complications following surgery (Frost, Schaid et al. 2000, Hopwood, Lee et al. 2000, Metcalfe, Esplen et al. 2005). Women with reconstruction had a trend to better body image views than those who

did not have reconstruction (Hopwood, Lee et al. 2000) and although small numbers limit this study, a similar finding was reported by Metcalfe, with body shape and appearance satisfaction scores higher in women who had reconstruction than those who did not (Metcalfe, Esplen et al. 2004). Women with better physical health were less likely to report adverse effects on body image (Gopie 2013), however somewhat conflicting with this was the finding that women with a lower BMI tended to have a less positive body image after RRM and IBR. Persisting body image issues reported in one series (Gopie 2013) included:

- Problems with naked appearance 30%
- Difficulties touching breasts 17%
- Feeling sexually unattractive 32%
- Uncomfortable when partner touched breasts 39%

The authors note that many of these issues existed prior to surgery, adding context to the findings of similar studies that did not include a baseline assessment. An interview study found that many women were surprised by the long-term lack of sensation in their reconstructed breasts but felt it was 'a small price to pay' for peace of mind. There were some, however, for whom it had a negative impact on sexual pleasure (Bebbington Hatcher and Fallowfield 2003).

Cancer related anxiety

RRM was demonstrated to decrease breast cancer anxiety substantially in most studies (Frost, Schaid et al. 2000, Bebbington Hatcher and Fallowfield 2003, den Heijer, Seynaeve et al. 2012, Gopie 2013, Heiniger, Butow et al. 2015). A long-term follow up study comparing women at increased risk (due to family history but also including other risks e.g. ADH, previous benign biopsies) who had RRM with those who did not have surgery found no difference in cancer related anxiety between the groups, which the authors do not explain although they do point out that the lack of a baseline for comparison makes interpretation challenging (Geiger, Nekhlyudov et al. 2007).

Relationship impact

Changes in sexual relationships were reported by 23% of a cohort surveyed many years after RRM (Frost, Schaid et al. 2000) with feelings of femininity negatively affected in 25%. Reduced sexual attractiveness was reported by 55% and reduced physical attractiveness by

53% (although not to a great extent) in another study (Hopwood, Lee et al. 2000). Another study found no change in satisfaction with overall partner relationship following RRM but sexual satisfaction did reduce (Gopie 2013) and this effect had not changed at later follow up. Sexual pleasure and sexual function did not appear to be affected by RRM with or without reconstruction in other studies (respectively) (Hatcher, Fallowfield et al. 2001) and (Metcalfe, Esplen et al. 2004) although in the latter, around a third reported a worsening in sex- life after surgery.

An interview study reported, for a few, an improvement in sex life following RRM which the women attributed to a reduction in cancer anxiety (Bebbington Hatcher and Fallowfield 2003). Others in the same study reported a significant negative impact on their relationship and sex life following surgery. Another interview study found several women reporting a change in relations with a spouse, although they did not elaborate or explore this further (Josephson, Wickman et al. 2000).

Support needs

The need for better emotional support and information (including pictures) was highlighted in many of the studies (Hopwood, Lee et al. 2000, Josephson, Wickman et al. 2000, Lloyd, Watson et al. 2000, Bebbington Hatcher and Fallowfield 2003, Rolnick, Altschuler et al. 2007) with two thirds wishing they had had access to more information, particularly about reconstruction and implants (Rolnick, Altschuler et al. 2007). Health-care professionals' lack of understanding of the specific needs of women undergoing risk reducing surgery (in contrast to those of women undergoing cancer treatment) was raised during interviews of women post RRM (Bebbington Hatcher and Fallowfield 2003). Women felt isolated and vulnerable not knowing anyone else in the same position and many would have liked access to a support group (Lloyd, Watson et al. 2000, Bebbington Hatcher and Fallowfield 2003, Rolnick, Altschuler et al. 2007). Increased social support and seeking social support (family and friends) correlated with better outcomes (Metcalfe, Esplen et al. 2005, den Heijer, Seynaeve et al. 2012).

Women in two interview studies expressed concern that one pre-operative consultation with their surgeon was inadequate time to cover everything (Josephson, Wickman et al. 2000,

Bebbington Hatcher and Fallowfield 2003) and found that women wanted more information prior to RRM specifically on pain, the nature of implants, scars and numbness (Josephson, Wickman et al. 2000). Some women expressed feelings of guilt (that they were able to have risk reducing surgery and avoid cancer, unlike affected family members) and some felt it impaired their ability to talk to, and get support from, their family (Bebbington Hatcher and Fallowfield 2003).

Decision satisfaction

High levels of decision satisfaction were reported in women who chose RRM (Josephson, Wickman et al. 2000, Lloyd, Watson et al. 2000, Lodder, Frets et al. 2002, Metcalfe, Esplen et al. 2004, Geiger, Nekhlyudov et al. 2007, Rolnick, Altschuler et al. 2007). One interview study, exploring decision satisfaction, found that women felt that they'd had no choice and so regret was a moot point (Josephson, Wickman et al. 2000). Women with an active coping style as measured using the Utrecht Coping List tool (and who were hypothesised to have sought more information about what to expect from surgery and the likely changes that would follow it) were noted to have greater satisfaction than those who were not 'active copers' (den Heijer, Seynaeve et al. 2012). Women who reported insufficient support were more likely to be dissatisfied with their decision to undergo RRM (Frost, Schaid et al. 2000). Young women were less likely to feel satisfied with their decision to have RRM (Metcalfe, Esplen et al. 2004). This did not seem to be due to body image or sexual function changes.

Regret

Lack of regret was common in most studies (Hopwood, Lee et al. 2000, Josephson, Wickman et al. 2000, Lodder, Frets et al. 2002, Bebbington Hatcher and Fallowfield 2003, Metcalfe, Esplen et al. 2004) with interviews finding that lack of regret was because women felt the relief from cancer anxiety to be paramount (Hopwood, Lee et al. 2000, Josephson, Wickman et al. 2000). Frost looked at a cohort of women whose surgery dated from between 1960 to 1993. This group reported dissatisfaction in 19%, with only 67% saying they would choose RRM again. This was not influenced by risk status, time since surgery, or age. Regret was

more common where body image was perceived as having changed more (Heiniger, Butow et al. 2015).

Women at increased risk of a poor psychosocial outcome

Women who rated their general body image negatively before surgery were more likely to rate it negatively following surgery (den Heijer, Seynaeve et al. 2012) The authors suggest that this demonstrates that RRM minimally affects general body image, which is already well established. Women with high pre-RRM cancer distress were more likely to have long-term body image concerns (Gopie 2013). Psychosocial distress symptoms were more common in women who over-estimated their ongoing risk of cancer following RRM (Metcalfe, Esplen et al. 2004). Women lacking support or who felt unable to talk to family for whatever reason, were at increased risk of psychosocial morbidity following surgery (Bebbington Hatcher and Fallowfield 2003). Quality of life suffered in women with psychological distress symptoms and vulnerability (a perceived threat to health and life) following RRM (Metcalfe, Esplen et al. 2005).

3.1.10 Discussion

The studies included in this systematic review are diverse in both methodology and time frame relating to risk reducing surgery. The tools and techniques used to explore the associated psychosocial outcomes were also very variable. The findings however, are broadly similar. A majority of women who undergo this drastic risk modifying strategy remain well with little evidence of long-term psychosocial distress and with high levels of decision satisfaction apparent. In a minority however, (and figures vary from study to study), up to a third, suffer long-term body image related concerns and suffer physically and emotionally. There appears to be a correlation between women who experience complications from their surgery and feelings of regret and poorer psychosocial outcomes, but this is not always apparent and some women who have had a challenging time surgically remain satisfied and un-distressed. That surgery usually reduces breast cancer anxiety is well documented and unsurprising. One other consistent comment related to the need for better emotional support both in preparing for surgery and in the post-operative period. Figure 3.3.3 summarises these findings.

There are several possible sources of bias to note, most commonly the introduction of recall bias particularly in the purely retrospective studies, where in some cases the time from surgery to the study was over a decade. Some women interviewed had previously been treated for breast cancer, which may impact upon psychosocial outcomes and indeed the motivation factors to have further surgery. Similarly, the participants' risk of cancer varied between studies with some including women whose risk was moderate or high. The benefit derived from risk reducing surgery in women at moderate risk is objectively (but perhaps not subjectively) lessened and this also has the capacity to impact on reported outcomes. The fact that some of these women will have had reconstruction and some not, may also have impacted significantly on the results of studies considering decision satisfaction and psychosocial outcomes, as body image has been demonstrated to be an important factor for some women, in determining these views. Information on reconstruction uptake was not available for some of the included studies and so has not been a focus of this review and is explored separately in chapter 1 in a narrative review.

Identifying women at increased risk of a poor outcome must be a priority for healthcare professionals involved in risk reducing breast surgery, putting in place additional support to minimise distress. The findings of this review identify a subset of women who are at greater risk of a poor psychosocial outcome:

- Poor body image scores at baseline
- High cancer-related anxiety / distress at baseline
- Over-estimators of breast cancer risk, both at baseline and following RRM
- Women without access to good social support
- Younger women (although this was not a consistent finding)
- Women who have surgical complications

The highly individualised, complex trade offs of one negative for a less unacceptable alternative is key to understanding the decision making process and subsequent satisfaction. Provision of tailored, personalised information (for example of year-by-year breast cancer risk with and without surgery, or likely surgical outcomes including pictures, for the specific woman in clinic, taking into account her breast shape and size, her body weight, co-morbidities and reconstruction wishes) alongside targeted psychological support to fully

inform women of the likely outcomes of their individual decisions and to detect problems early and support them through the process is imperative to improving psychosocial outcomes.

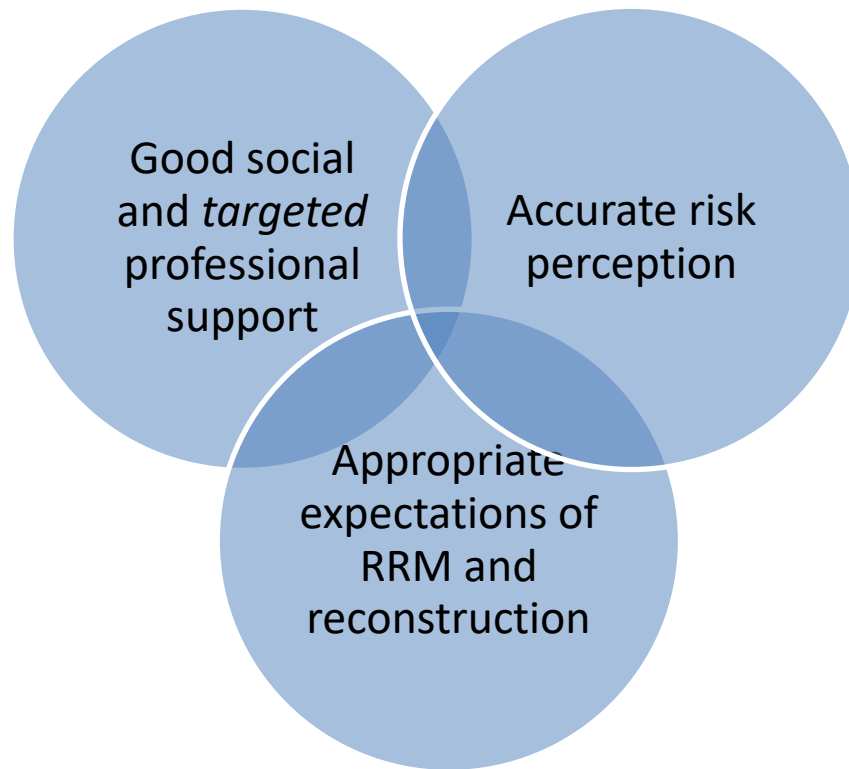


Figure 3-3-2 Factors affecting psychosocial outcome of RRM

3.2 A systematic review of the literature pertaining to psychosocial outcomes associated with enhanced breast surveillance in women at increased familial breast cancer risk

3.2.1 Abstract

3.2.1.1 Introduction

Women at increased risk of familial breast cancer may opt to undergo a programme of enhanced surveillance in order that cancers may be detected at an earlier stage. Cancer related anxiety is well documented in women at increased familial risk. This systematic review aimed to establish whether participation in surveillance including MRI and mammography has an impact on psychosocial quality of life.

3.2.1.2 Methods

A systematic search of databases was undertaken in accordance with PRISMA guidelines, identifying studies of women engaged in screening for familial risk. Studies of women being followed up for previous cancer and review articles were excluded. Studies were subject to quality review. Meta-analysis was not performed due to heterogeneity of outcome measures and participants.

3.2.1.3 Results

6 studies were identified as suitable for inclusion.

3.2.1.4 Conclusion

There is a lack of evidence to suggest that women at increased familial breast cancer risk derive any psychosocial benefit from surveillance. Generally, they do not appear to suffer psychosocial distress but with some notable exceptions, including women subject to recall, who suffer a temporary increase in cancer-related anxiety / distress, those younger than 40, those who over-estimate their risk of breast cancer, those who self-examine very regularly, those with immediate family being treated for cancer, and those with high baseline levels of anxiety. These women may benefit from additional support and counselling.

3.2.2 Introduction

The discovery of *BRCA* genes in the 1990s (Miki, Swensen et al. 1994, Wooster, Bignell et al. 1995) and subsequent increasing public awareness has led to increasing numbers of women finding that they are living at increased risk of breast cancer. Managing this risk presents women with choices, broadly: risk reducing surgery, screening and-or chemoprophylaxis. Women who have chosen screening may have done so to delay risk reducing breast surgery or because they do not wish to undergo surgery at all (Lodder, Frets et al. 2002). Women in this group also include those at increased risk, but for whom surgery may not be offered as their risk is unclear or thought to be less. There will also be women for whom screening was an active choice as opposed to 'the alternative to surgery'.

Whatever the reason for choosing to undergo surveillance, women at increased familial risk partaking in enhanced surveillance face regular visits to screening units and hospitals to undergo tests that have been described as 'painful', anxiety provoking and unpleasant (Rijnsburger, Essink-Bot et al. 2004). Women living at increased risk of familial breast cancer may have pre-existing high levels of cancer-related anxiety (Lodder, Frets et al. 2001, van Oostrom, Meijers-Heijboer et al. 2003). In addition to the fact that their risk of breast cancer is not reduced by this risk management strategy, introduces the potential for the screening process itself to cause distress and compromise psychosocial quality of life. Conversely, the fact that these women are having screening may have a positive impact on them psychologically by providing reassurance that they are 'disease free', more likely to survive an earlier detected cancer or may safely defer surgery until it better suits their lifestyle and future plans.

This review aimed to systematically assess the psychosocial outcomes associated with enhanced breast screening for women at increased familial breast cancer risk. Specifically, it aimed to describe areas of psychosocial distress or reassurance and factors that are associated with distress or reduced anxiety. Rapid review methodology was employed limiting searches to published literature identifiable through searches of bibliographic databases. Papers were not double screened for inclusion and only information relevant to the review was extracted (Tsertsvadze, Chen et al. 2015, Hartling, Guise et al. 2016).

3.2.3 Search methods

The PRISMA statement guided the review process (Moher, Liberati et al. 2009).

Relevant studies were identified by searching the following electronic databases: (see figure 3.3.4)

- MEDLINE
- EMBASE
- CINHAL
- PsycINFO
- CENTRAL at Cochrane

Hand searching of references was also performed in an attempt to identify all relevant studies.

3.2.2.1 Search limits and rationale:

Breast screening out-with a population screening programme due to increased familial risk is a relatively new phenomenon. The National Institute of Clinical Excellence (NICE) first published recommendation for screening out-with the NHSBSP for high risk women in 2006.

The search start date precedes this by ten years for inclusivity.

- Date: 1996-present day.
- Participants: Humans, Females.
- Language: Articles in English.

Searches were performed using a combination of search terms:

- Familial breast cancer, hereditary breast cancer, familial breast and ovarian cancer, hereditary breast and ovarian cancer, genetic risk breast cancer, inherited risk breast, *BRCA1*, *BRCA2*, gene mutation,
- Breast cancer, breast tumour, breast and ovarian
- Risk, predisposition, tendency,

- Mammogram, mammography, mammographic, MRI magnetic resonance, screening, surveillance
- Outcomes – Psychosocial, anxiety, depression, distress

3.2.4 Inclusion criteria

Articles were included in the overall analysis if:

Participant factors

- Study included patients with increased risk of familial breast cancer.
- Study included patients having regular breast screening out-with a population screening programme

Methodological factors

- Original research articles from peer-reviewed journals, including prospective and retrospective, and qualitative and quantitative studies

Outcome factors

- Study pertained to the psychosocial outcomes in high risk women.

3.2.5 Exclusion criteria

Articles were excluded from the overall analysis if:

Participant factors

- Screening was following up previous cancer treatment and was not for increased familial risk of breast cancer.

Methodological factors

- Review papers, editorials, case reports, papers published in a language other than English

Outcome factors

- Psychosocial outcomes were not reported

3.2.6 Quality review of papers

Papers were all subject to quality review. Questionnaire based studies were assessed using the Critical Appraisal of a Questionnaire Study tool (Roever 2015) (see appendix 6). Studies using previously validated tools were assumed to meet the quality assessment requirements of the tool itself and analyses were limited to the remaining points. Studies comparing a cohort of screening women against controls were assessed using the Newcastle Ottawa quality assessment scale (GA Wells 2017). Purely qualitative studies using the Standard for Reporting Qualitative Research tool (O'Brien, Harris et al. 2014). The latter was formulated to allow quality review of qualitative papers although it is not intended to assess methodology due, in part, to the diverse nature of methodologies employed by qualitative studies. It includes 21 points of assessment: (see section 3.1.5 for details).

3.2.7 Results of the search

A total of 63 results were generated by these initial searches and 7 identified by other means. Abstracts and titles were reviewed for relevance and compared to the inclusion criteria and full text articles were obtained for relevant papers. Where it was unclear from the title/abstract whether the studies met the inclusion criteria, full text articles were also obtained and a decision made based on the entire paper.

Figure 3.2 shows the review process in diagrammatic form.

After excluding ineligible and duplicate abstracts, 17 papers were deemed potentially eligible and the full papers were retrieved.

References of relevant papers were hand searched to identify additional studies missed by the primary search.

Records identified through database searching (n = 62)

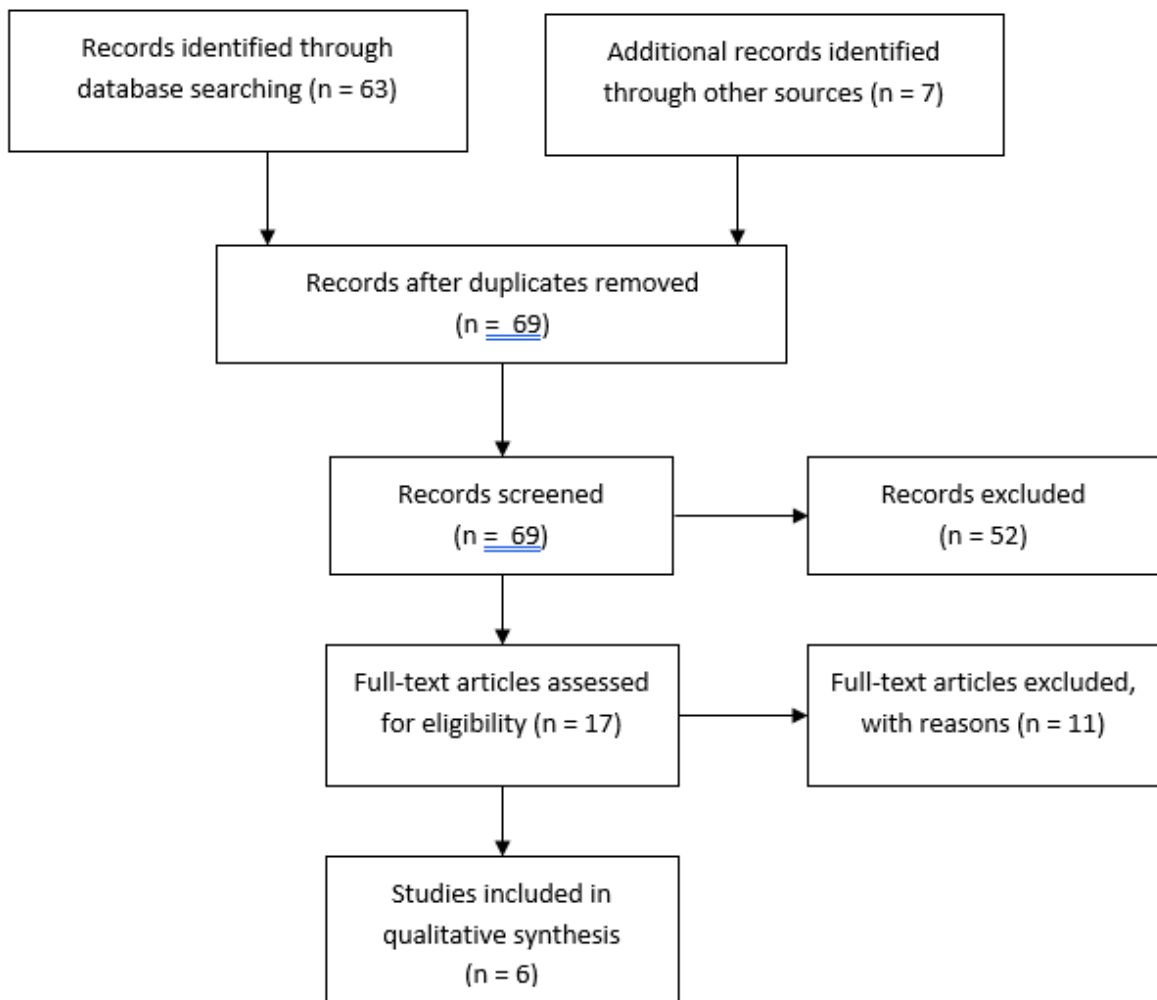
Additional records identified through hand searching of references (n = 7)

Total number of citations assessed (n = 69)

Excluded based on title or information in abstract (n = 52)

Full-text articles retrieved for the review (n = 17)

Figure 3-2 Flow chart for systematic review as per PRISMA guidelines (Moher, Liberati et al. 2009)



3.2.8 Characteristics of included studies

Studies were very heterogenous in nature and of variable quality, using different populations, screening modalities, sample sizes, levels of risk and outcome measures. Not all had the assessment of psychosocial impact of surveillance as the primary aim.

Study methodologies

- All 6 were questionnaire based studies, all using validated tools with one study (Drossaert, Boer et al. 1996) using a *de-novo* questionnaire tool as well as an non-validated abbreviated Boer scale (measure of cancer related anxiety).
- All of the questionnaire studies were prospective
- Not all looked at the impact of the surveillance results on subsequent anxiety (Rijnsburger and van Dooren did not correlate imaging results with psychological findings).

Study participants

- Mode of surveillance varied: some were very high risk women undergoing a programme of annual MRI scans (Rijnsburger, Essink-Bot et al. 2004, van Dooren, Seynaeve et al. 2005, Spiegel, Esplen et al. 2011, Bredart, Kop et al. 2012). Others were much lower risk (any affected first degree family member) in a mammographic programme where the interval between encounters was unclear (Valdimarsdottir 1995, Drossaert, Boer et al. 1996).
- Participant numbers varied from 26 to 1561
- Participants level of risk varied: 1 study included women at high risk with a confirmed genetic mutation conferring risk (Spiegel, Esplen et al. 2011), 3 including women at high or moderate risk (Rijnsburger, Essink-Bot et al. 2004, van Dooren, Seynaeve et al. 2005, Bredart, Kop et al. 2012) and 2 used one first degree family member with breast cancer as a proxy measure of familial risk (Valdimarsdottir 1995, Drossaert, Boer et al. 1996).

Papers dated between 1995 and 2012. See table 3.2.

Table 3-2 Study characteristics and findings

Author, year and key	Study sample	Quality review notes	Data collection method and follow up period	Mode of surveillance	Level of risk	Study aims	Summarised findings
1. Bredart 2012	900 women at very high risk having MRI compared with 661 moderate risk women having MMG	Acceptable quality study. Controls not closely matched. Up to 43% data excluded due to protocol requirement on QN administrative timing – may introduce bias.	State trait anxiety inventory, IES and avoidance subscale QNs before, just after and 2-3/12 after screening	MMG with USS or MRI	High risk in the MRI cohort (with a control group of moderate risk women having MMG alone)	To compare psychological distress between MRI with a control group having MMG and USS	MRI does not convey more harmful psychological effects than standard imaging. Specific support req'd for women with high psychological distress scores. Recall (any modality) associated with increase in anxiety.
2. Spiegel 2011	55 women <i>BRCA</i> gene carriers in an MRI surveillance programme	High quality study 48% participation. Subscale abandoned due to low internal consistency.	HADS, Lerman's breast cancer worry scale, breast cancer worry interference scale, QoL all measured pre, after and 6/12 after screening.	MRI	<i>BRCA</i> mutation with MRI screening	Is MRI surveillance (esp recall) associated with increased anxiety / depression / BC worry/distress	Temporary increase in anxiety associated with false positive recall. Generally MRI surveillance did not have a detrimental psychological impact
3. Rijnsburg-	519 women in MRISC study	High quality study Impact of recall	Health related QoL QNs (SF36, EQ5D) a 3	MRI and MMG	15% lifetime risk of breast cancer	To determine the short term effects of	General distress and QoL remained

er 2004		was not assessed Excellent response rate (>94%)	time points within surveillance programme			screening high risk group	unchanged, generally better health related outcomes than general population
4. Valdimars-dottir 1995	26 women with FH risk having MMGs	Low quality study Small numbers and significant loss to follow up Control group not adequately matched (no risk and no intervention) All screening test results were normal, not typical of larger scale screening programmes	QN (postal) study comparing women at FH risk having MMGs vs women at normal risk not undergoing MMGs (POMS, IES, BSI)	MMG	As per (Garber 1991)	To assess causes of psychological distress in FH women	Women at FH risk had higher BC anxiety immediately before MMG than after normal results and generally higher levels of non-specific distress and BC anxiety
Drossaert 1996	389 women aged 50-69yrs at moderate FH risk (total n=3684)	Acceptable quality paper. Large numbers but variable risk. Shortened Boer	Postal QNs 6 weeks after MMG (shortened Boer scale with denovo MMG distress score)	MMG	affected 1st degree relative	Compare FH women with normal risk women re risk perception, BC anxiety, surveillance choices	Slight increase in psychological distress at time of MMG but rare to have more profound

		scale not validated. Anxiety measured 6 weeks after MMG may miss the effect.					distress.
van Dooren 2005	357 women in MRISC study	High quality study 82% participation Large numbers Timing of questionnaires was not consistent (some 1 week after MRI, others up to 4 weeks later)	IES (BC spec) and HADS pre and post surveillance x2	MRI and MMG	15% lifetime risk of breast cancer	Course of psychological distress during BC surveillance programme	Generally psych distress within normal limits and decreased after screening. BC spec distress worse for risk over-estimators, young women who tend to over BSE and women with sisters with BC. Vulnerable subgroups may need extra care.

3.2.9 Findings

Baseline psychosocial function

Elevated baseline distress was noted in several studies (Valdimarsdottir 1995, Drossaert, Boer et al. 1996, Rijnsburger, Essink-Bot et al. 2004, Spiegel, Esplen et al. 2011, Bredart, Kop et al. 2012). Bredart noted a higher baseline level of anxiety in the group having mammograms than in the (higher familial risk) group having MRIs. They acknowledge that the groups are not matched, with a greater number of women with a personal history of cancer in the MMG group, of whom 43.6% over-estimated their breast-cancer risk. In contrast the MRI group were younger women with higher levels of education and these women had also benefitted from psychological support, which was not available to the MMG women (Bredart, Kop et al. 2012).

In contrast to Bredart, Spiegel used Miller's Behavioural Style Scale to divide women into two groups according to their coping style; 'high monitors' (who want more information in the presence of increased mental stress) and 'low monitors' (who prefer less information) (McGraw-Hill 2002). These groups had differing baseline anxiety scores with the 'high monitors' having higher baseline anxiety than the 'low monitors'. Age, level of education, personal breast cancer history and recent life events had no statistical effect on baseline anxiety, suggesting that baseline anxiety is a reflection of personality (Spiegel, Esplen et al. 2011). There was little change in this series between baseline anxiety and anxiety measured after surveillance.

Interestingly, the baseline quality of life measurements in high risk women were found to be higher than age / sex adjusted reference scores in one study, suggested by the authors as likely reflecting the background and personality attributes of women who engage in enhanced screening (Rijnsburger, Essink-Bot et al. 2004).

Beneficial effects

One paper mentions that *"positive psychological effects of intensive breast surveillance have also been observed, such as reassurance related to frequent contact with healthcare professionals, a high level of confidence in the efficacy of intensive breast surveillance and a*

preference for MRI over mammography" quoting (Warner, Plewes et al. 2004), although the study describing these effects does not have data to support these findings (Bredart, Kop et al. 2012).

Neither Valdimarsdottir nor Drossaert reported a positive effect of screening on psychosocial outcome (Valdimarsdottir 1995, Drossaert, Boer et al. 1996). Spiegel did not describe any positive effects of MRI screening on psychosocial outcomes, although the study was not designed to assess the benefit and instead focussed on the psychosocial impact of recall (Spiegel, Esplen et al. 2011).

Two possible benefits of MRI screening in terms of psychosocial outcome have been identified:

- Generic health-related quality of life was better than that of age and sex adjusted reference scores. The authors suggest this may reflect participation in enhanced screening leading to a feeling of having done everything they can to handle their risk (Rijnsburger, Essink-Bot et al. 2004) although it may also reflect a self-selected, motivated and generally well-educated group.
- Both general and breast cancer-specific distress are described as appearing to reduce slightly (although this was not statistically significantly) from one scan to another a year later. The data supporting this finding were weak.

A difficulty in interpreting benefit and a possible explanation for the lack of evidence of this phenomenon is that the true 'baseline' will, for most, be the time of risk management decision making, a time fraught with uncertainty and high levels of anxiety. Longitudinal studies following women through several years of MRI surveillance, crucially, including the impact of recall and development of disease within family members, will be necessary to objectively assess whether there is an actual beneficial psychosocial effect of surveillance.

Short term effects

Three studies (Valdimarsdottir 1995, Drossaert, Boer et al. 1996, van Dooren, Seynaeve et al. 2005) found an increase in breast cancer related anxiety / distress immediately before surveillance which quickly returned to normal afterwards (except in excessive breast self-

examiners (van Dooren, Seynaeve et al. 2005)). A small minority had moderate or severe anxiety scores with the majority suffering mild anxiety (Drossaert, Boer et al. 1996) although this study had several weeks between screening encounter and questionnaire completion in some cases, potentially affecting the validity of this finding. Valdimarsdottir also noted increases in non-specific distress, intrusive and avoidant thoughts immediately before mammography and persisting at one month after receiving normal results. Other studies found no significant differences in health related quality of life measurements, generalised or cancer-related anxiety in women having either MMG or MRI screening, between at the time of the test and after communication of results (Rijnsburger, Essink-Bot et al. 2004, van Dooren, Seynaeve et al. 2005, Bredart, Kop et al. 2012).

Longer-term psychosocial distress

Van Dooren found a non-significant trend of reduction in cancer specific anxiety over time, suggesting that women may find ongoing surveillance has a cumulative reassuring effect. The impact of recall did not appear to translate into long-term psychosocial distress (Bredart, Kop et al. 2012) although this study had a number of weaknesses and no other studies have corroborated this finding. Higher baseline psychosocial distress persisted across all measurements (pre and post surveillance) when compared to non-familial risk controls (Valdimarsdottir 1995).

Differences between screening modalities

Women undergoing MRI screening had slightly higher anxiety levels both at baseline and at all subsequent time points (Spiegel, Esplen et al. 2011) but this is in contrast to another study that found higher anxiety levels in the mammography group (Bredart, Kop et al. 2012), although this study did acknowledge over-estimation of risk in the mammography group. Rijnsburger found that screening modality had no effect on pre and post surveillance quality of life measurements, with no change in any modality noted, albeit the 'post' measurement was taken up to 4 weeks after the screening encounter by which time any temporary increase in anxiety may have resolved. Neither Bredart nor Spiegel found a difference in change of anxiety levels pre and post surveillance in either the mammogram or MRI group and these conflicting findings make it hard to ascribe greater anxiety levels to the mode of surveillance.

Impact of being recalled for further assessment

Any need for further investigation after surveillance was also associated with an increase in anxiety and intrusive thoughts (Bredart, Kop et al. 2012). Spiegel (Spiegel, Esplen et al. 2011) described an increase in anxiety associated with a false positive result. The proportion of women concerned about their risk of developing breast cancer 'often or almost all of the time' rose from 22% to 39% (in contrast to the non-recalled group who reported this falling from 16% to 8%. At 6 months there was still a slight increase in cancer-related worry (although the authors note that for at least half of the recalled women, this coincided with the time they were due for repeat imaging, likely to impact upon this finding).

Groups at increased risk of psychosocial distress

There were conflicting findings on the impact of age. Younger women at increased familial risk were particularly noted to have a greater increase in anxiety around the time of mammography (Valdimarsdottir 1995, Drossaert, Boer et al. 1996, van Dooren, Seynaeve et al. 2005) but older women (over 50 years) had greater anxiety in another study (Bredart, Kop et al. 2012). Women who over-estimate their risk of breast cancer (van Dooren, Seynaeve et al. 2005, Bredart, Kop et al. 2012), women who self-examine their breasts very frequently (van Dooren, Seynaeve et al. 2005) and those with immediate family being treated for breast cancer were also noted to be at increased risk of psychosocial distress (van Dooren, Seynaeve et al. 2005). High baseline anxiety correlated with higher anxiety scores associated with tests as well (Bredart, Kop et al. 2012).

3.2.10 Discussion

Breast cancer anxiety and general distress are generally high in groups of women at increased familial breast cancer risk. Surveillance, for most women, seems not to have a significant impact on this, either adverse or beneficial. Some studies did report an increase in breast cancer related anxiety at the time of surveillance (Valdimarsdottir 1995, Drossaert, Boer et al. 1996, van Dooren, Seynaeve et al. 2005), but others did not (Rijnsburger, Essink-Bot et al. 2004, Spiegel, Esplen et al. 2011, Bredart, Kop et al. 2012). Women who were subject to recall did consistently have an increase in anxiety around this time with a negative effect on psychological wellbeing. Given MRI surveillance, particularly in the prevalent scan, has a high rate of false positives, women at increased risk of distress may benefit from identification and additional support.

In contrast, none of the studies showed any defined beneficial impacts of surveillance but rather degrees of avoidance of negatives, suggesting that for many women, surveillance is far less effective than surgery at reducing cancer anxiety, although there are no directly comparative trials. As shown in section 3.1, RRM is usually associated with significant reductions in anxiety and distress levels in the longer term. These 2 groups of women may not be comparable as there may be significant 'baseline' differences in both anxiety and motivational and personality types between women who undergo RRM and those undergoing surveillance.

Limitations

The small number of papers and diversity of included participants (some at near-normal level of risk undergoing mammograms, others at vastly increased risk undergoing MRIs) limit the conclusions that can be drawn from this systematic review. Some studies had very small numbers for questionnaire based research (Valdimarsdottir 1995) and the tools used and the way in which they were used and correlated to the participants specific circumstances also varied. Some studies had contradictory findings, for example the level of psychological distress noted at baseline which was quoted as normal (van Dooren, Seynaeve et al. 2005), or as elevated (Valdimarsdottir 1995) likely reflecting the differences between the groups being studied or the methodology applied.

Teasing out the impact of surveillance from overall anxiety presents challenges for studies using tools that are essentially measuring both (alongside any other causes of distress present of the day of assessment). Those studies that did not have well matched controls to compare the results of questionnaire data with, are potentially presenting composite findings of both generalised and cancer-specific anxiety, *and* test-specific anxiety.

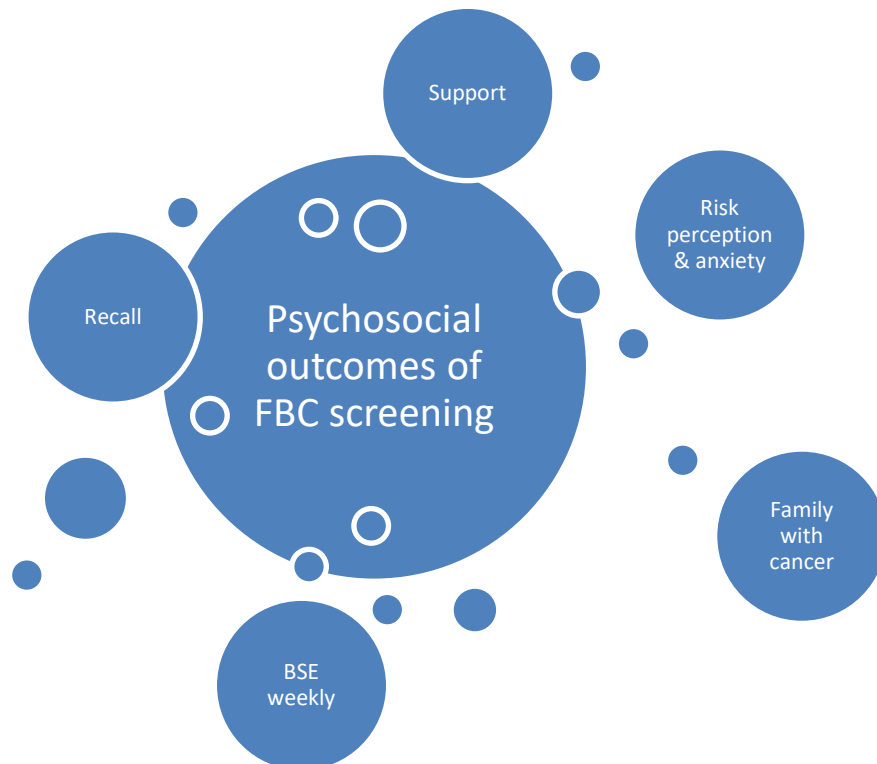
In spite of these limitations, there appears to be consistency in the finding that surveillance of women at increased familial risk rarely causes significant or long-lasting psychological distress but nor is there evidence that it offers any psychosocial benefit. Surveillance recall is associated with an increase in anxiety, more so in women at increased risk than in a normal risk population (Lerman 1993, Cockburn, Staples et al. 1994, Valdimarsdottir 1995, Spiegel,

Esplen et al. 2011, Bredart, Kop et al. 2012). Women at increased risk of psychological distress include (Valdimarsdottir 1995, Drossaert, Boer et al. 1996, van Dooren, Seynaeve et al. 2005, Bredart, Kop et al. 2012):

- Young women
- Women who over-estimate their breast cancer risk
- Women who self-examine weekly or more often
- Women who have baseline increased anxiety
- Women who have family members currently undergoing breast cancer treatment.

Recognising these women and offering additional support within the surveillance programme may prove to be of benefit, although this has not yet been demonstrated. Before enrolling women in surveillance, it would seem incumbent upon the referring clinician to consider these factors and discuss the potential effect of surveillance with their patient. There is no data about any differential impact between women in terms of their motivation for selecting surveillance rather than surgery (delaying RRM, avoiding RRM, afraid of RRM, don't regard RRM as necessary, relevant or appropriate for them) and further work would be beneficial. Figure 3.3.5 summarises these findings.

Figure 3-3-3 Factors affecting outcome of screening



3.3 Discussion: Review of literature on psychosocial outcomes of both RRM and surveillance strategies

RRM may have significant cosmetic, physical and sexual impacts and is irreversible, with potentially significant long term psychosocial effects. Most women undergo risk reducing surgery without developing major emotional distress, but post-operative distress scores are not infrequently raised to clinically relevant levels (Bresser, Seynaeve et al. 2007). Mutation carriers who opted for RRM were significantly more distressed pre-operatively than carriers opting for screening, or non-carriers. When followed up at one year this effect had disappeared (Lodder, Frets et al. 2002), possibly explained by cancer risk-reduction ameliorating the negative effects of surgery.

A personal previous history of breast cancer predicted for subsequent choice of risk reducing mastectomy and similarly women with a family history of ovarian cancer were more likely to consider RRSO (Uyei, Peterson et al. 2006). Garcia and colleagues studied the risk management strategies of gene mutation carriers and women at increased risk without a recognised gene mutation. They found the uptake of risk reducing measures was lesser in the latter group and advocate these women be encouraged to use surveillance, chemoprophylaxis and RRSO due to the high number of women in whom risk is reclassified with time as lower than initially thought (Garcia, Lyon et al. 2014). It is worth noting that with expanded panel testing, lower testing thresholds, reduced costs and better knowledge of the clinical impacts of various mutations, women who have a high familial risk but remain untested are reducing in numbers and those with VUS after testing are diminishing. Therefore women with uncertain risk estimates are fewer now than previously making risk stratified management easier and reducing the number of moderate or uncertain risk women having RRM.

A qualitative study of British women explored their views towards risk reducing surgery at the time they were informed about their increased risk. They found some common motivations for surgery (in order) (Hallowell 1998):

- To fulfil obligations to (their) family
- To reduce risk and contain their fear of cancer

And similarly, they noted common concerns about undergoing surgery including:

- Compromising social obligations
- Upsetting the body's natural balance
- Not offering protection from cancer
- Complications
- Menopause onset
- Body-image, gender and personal identity effects
- Potential effects on sexual relationships

A similar study noted that most women anticipated that risk reducing mastectomy would result in a reduction in their quality of life (Wagner, Moslinger et al. 2000).

The majority of women were however, satisfied following RRM in a study with up to 33 years of follow up, but a significant number of women (up to a third) reported negatives effects including:

- Self esteem
- Satisfaction with appearance
- Feelings of femininity
- Sexual relationships
- Stress in life and overall emotional stability (Frost, Schaid et al. 2000)

Data need to be interpreted with care, as the comparison is being made retrospectively, in some cases with several decades since surgery. Higher levels of satisfaction were associated with low stress levels, no or uncomplicated reconstructive surgery, reduced cancer-worry and in those who elected to have surgery due to family history.

A similar but prospective study (Hopwood, Lee et al. 2000) found psychological or body-image concerns in the following areas, especially when women had suffered complications after surgery:

- Reduced sexual attractiveness
- Reduced physical attractiveness
- Self-consciousness about appearance

- Reduced femininity

Up to half of the women undergoing RRM will suffer negative effects on body-image and sexuality (McGaughey 2006), although this finding is very variable. Most studies are retrospective introducing recall bias. Overall happiness (in a sample of American women) significantly correlated with three factors pertaining to body-image, including sexual attractiveness (along with weight concern and physical condition) (Stokes and Frederick-Recascino 2003). Older women tended to rate their body-image as worse than younger women (Franzoi and Koehler 1998), suggesting the impact of perceived poor body-image after RRM in these studies may also be affected by age.

Psychological morbidity decreased significantly in women who had RRM, remaining static or increasing in those who opted for screening (Hatcher, Fallowfield et al. 2001). Higher baseline anxiety levels were apparent in women who declined surgery (Hatcher, Fallowfield et al. 2001, Geiger, Nekhlyudov et al. 2007), with equivalent decision satisfaction in women who had chosen between RRM and screening (Geiger, Nekhlyudov et al. 2007). Dissatisfaction with sex life, depression and-or poor general health were associated with reduced satisfaction, whilst RRM was not (directly). Interestingly, no difference was apparent between women undergoing RRM (most of whom had reconstruction) and women who were screened with respect to body-image, sexuality and self-consciousness (Geiger, Nekhlyudov et al. 2007). A study looking at sexual activity found that psychological morbidity in groups at increased risk of ovarian cancer was associated with reduced sexual pleasure (Atkins and Fallowfield 2007).

High baseline general and cancer-related distress predicts high levels occurring after RRM (Bresser, Van Gool et al. 2007). Pre-operative psychological distress and vulnerability on the body-image scale was associated with reduced quality of life after RRM, whilst those with greater levels of social support had better quality of life (Bresser, Van Gool et al. 2007). Providing accurate risk information to women may be beneficial, as risk over-estimation is thought to compound vulnerability (Metcalf, Esplen et al. 2005). Identifying such women in advance can enable these women to receive additional support.

A psychological benefit of RRM experienced by many women is the feeling of relief and freedom from cancer worry (Bebbington Hatcher and Fallowfield 2003, van Oostrom, Meijers-Heijboer et al. 2003, Heiniger, Butow et al. 2015), but some report feeling stigmatised (i.e. different to 'normal' society) aiming to conceal their surgery (Kenen, Shapiro et al. 2007). This effect is likely to diminish as broader public awareness of familial risk increases, partly due to a surge of media interest following celebrities who have chosen RRM (Evans, Barwell et al. 2014). This increased awareness has also impacted on the number of women presenting to units to discuss RRM.

Generally women are satisfied with their decision (to undergo RRM) due to the diminishing effect it has on cancer worry and anxiety, regardless of any associated negative effects (Hopwood, Lee et al. 2000). Altschuler and colleagues studied satisfaction in women who had undergone risk reducing mastectomy comparing the response to a closed question about satisfaction with open ended questions. They found that 70% of women who stated they were satisfied in the closed question, then provided either negative or disparate responses to the open questions (Altschuler, Nekhlyudov et al. 2008), raising questions about the high levels of satisfaction with RRM reported in other studies. A systematic review looked at satisfaction following RRM with or without reconstruction in 22 studies. Their summarised findings are illustrated below in figure 3.3.6:

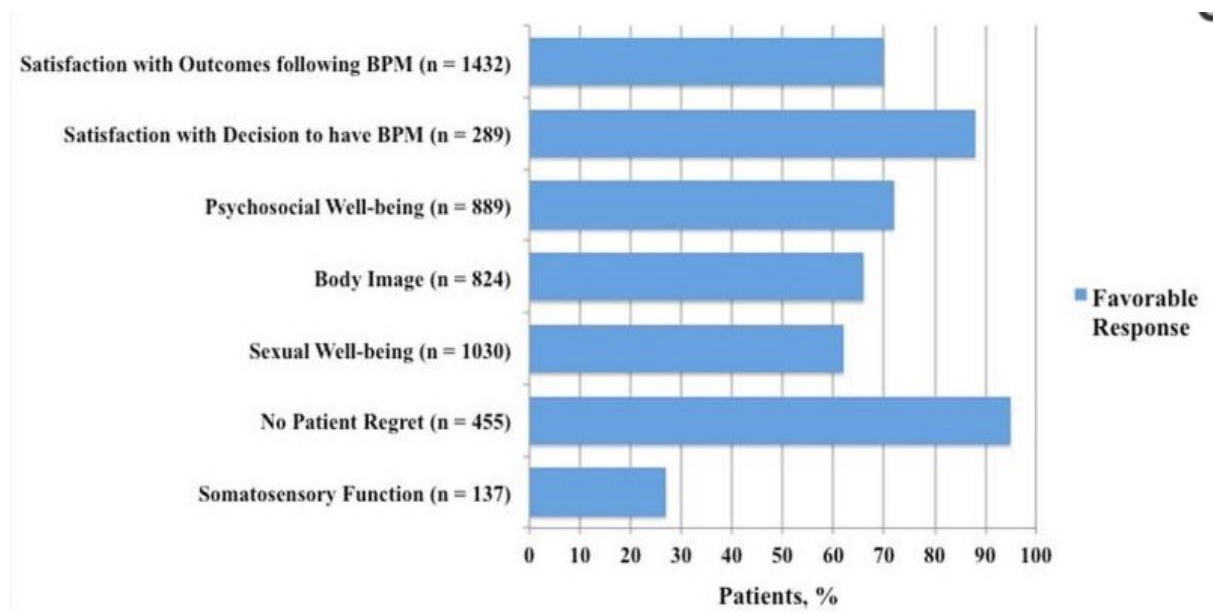


Figure 3-3-4 Satisfaction following RRM: Razdan 2016 systematic review ((Razdan, Patel et al. 2016) open access)

Feelings of regret regarding contralateral mastectomy were apparent in 6% of high risk women and more likely if the idea of contralateral surgery had been raised by the patient as opposed to by their physician (Montgomery, Tran et al. 1999). This contradicts other studies, showing regret to be more likely if the decision to have risk reducing surgery was strongly led by or even taken by their doctor (Frost, Schaid et al. 2000, Nekhlyudov, Bower et al. 2005).

The majority of literature pertaining to breast surgery in a high-risk setting is risk reducing but there are a small group of patients who first present as being at increased risk at the time of a cancer diagnosis. There are mixed feelings about how best to proceed for these women. Rapid genetic counselling and testing is described and, where done, increases the number of women who choose to have bilateral risk reducing mastectomy at the outset (Cortesi, Razzaboni et al. 2014). This is relatively newly available and long-term follow up is not yet published but the large amount of emotive information these women need to process in a short period of time raises questions about their ability to make a truly informed decision, although a recent study found no increase in adverse psychosocial effects (Wevers, Ausems et al. 2016). An obvious advantage to this is the reduction in women choosing breast conserving surgery and undergoing adjuvant radiotherapy, then shortly after electing to have risk reducing mastectomy with reconstruction in a scarred and irradiated breast, negatively impacting on cosmesis and satisfaction.

Metcalfe and colleagues showed that women who kept their NAC had higher satisfaction and sexual well-being than a similar group of high risk women who did not (Metcalfe, Cil et al. 2015). Another study noted that skin sparing (i.e. nipple preserving) risk reducing mastectomy in high risk women had higher levels of satisfaction than a non-nipple preserving technique, however they also noted most nipples are insensate and that separate nipple reconstruction therefore presents a balanced alternative option (van Verschuer, Mureau et al. 2014). The very broad range of breast reconstruction options need to be carefully explained and recommendations made for individual women to allow them to choose something suitable for their body shape and to match what is possible to their expectations.

It has been well documented that immediate breast reconstruction (IBR) reduces the distress associated with the decision to undergo mastectomy (Goin and Goin 1982), with decreased anxiety and depression and improved body-image, compared to those who had delayed reconstruction (Al-Ghazal, Sully et al. 2000), however this correlation is not straightforward. Metcalfe showed that cancer patients who had mastectomy with or without delayed breast reconstruction (DBR) had improved psychosocial functioning, which did not appear to be related to whether or not the woman had undergone DBR (Metcalfe, Zhong et al. 2015). Satisfaction following reconstruction is reduced if the cosmetic result is compromised by complications (Frost, Schaid et al. 2000). Women who did not have reconstruction, reported, perhaps surprisingly, fewer negative outcomes relating to body-image and femininity than those who had reconstruction in one study (Frost, Schaid et al. 2000). This is in contrast to Metcalfe and colleagues who found that women who had undergone IBR with RRM were generally more satisfied in terms of appearance and body shape than those who did not (Metcalfe, Esplen et al. 2004). This probably relates to baseline attitudes towards body image and lower expectations. Were they not able to have reconstruction, some women said they would not have had RRM (Bebbington Hatcher and Fallowfield 2003), whilst other women choose not to have reconstruction.

In women who have had risk reducing contralateral mastectomy with reconstruction, regret was associated with poor cosmetic results, a diminished sense of sexuality and the feeling that the surveillance options had not been fully explained (Montgomery, Tran et al. 1999). Some women in this retrospective questionnaire study stated that had they known the cosmetic outcome from reconstruction pre-operatively, they would not have chosen to have the mastectomy. Others reported being unaware of alternative options, and similarly may not have undergone mastectomy. These data are based on women with very variable risk levels, generalising these findings to a high risk group may not be appropriate. A systematic review of patient reported outcomes of breast reconstruction after mastectomy (mostly done for cancer) found that reconstruction was associated with worse quality of life, body image and sexuality compared to a mastectomy-only cohort (Lee, Sunu et al. 2009). It does note that most studies were observational and introduce bias accordingly, with no evidence of pre-operative assessment of quality of life, body image or sexuality with which to compare against the reported poor outcomes after surgery, making it hard to know whether the reason for poor quality of life is the reconstruction or whether the cohort having reconstruction had pre-existing reduced quality of life compared to the mastectomy-only

cohort. Without this understanding, it is hard to draw meaningful conclusions from these findings.

Data regarding regret after reconstruction in a risk reduction setting vary. One study reported no regret, nor any negative physical or psychological impact (Isern, Tengrup et al. 2008), in contrast to other studies, where RRM and IBR are associated with both physical and psychological negative effects in a larger proportion of patients. One small study found none of 15 women interviewed regretting their RRM and IBR, all being more focussed on the positive step in risk reduction, feeling there had been no other viable option (Josephson, Wickman et al. 2000). High levels of satisfaction are especially common in older women after RRM and IBR (Metcalfe, Esplen et al. 2004). A recent systematic review of patient reported outcomes after RRM (including women with and without reconstruction) found that quality of life scores were generally higher in women who had RRM without reconstruction, an effect the authors suggest could be explained by patients' pre-operative expectations (Razdan, Patel et al. 2016).

3.4 Summary

Two systematic reviews looking at the psychosocial outcomes for risk reducing breast surgery and breast screening in women at increased familial breast cancer risk have demonstrated that a majority of women do not suffer *significant* distress but nor do they appear to derive any benefit in terms of reduction in anxiety. A minority, and figures vary widely (from none up to about a third) do suffer long-term psychosocial distress. The majority who are not significantly distressed are not, however, *un-distressed*. This group of women manage to carry on with life, but many have adapted to changes related to their choice of risk management strategy, for example persistently high levels of cancer-related anxiety in screening women or adverse body image effects of surgery. Healthcare professionals involved in providing care for women at increased familial risk should be aware of these adaptations.

The systematic reviews identified women at increased risk of a poor outcome, summarised visually at the end of each subchapter (figures 3.3 and 3.5). Common risks include over-estimation of risk, limited social support and high baseline cancer-related anxiety / distress.

Assessing for these factors and being alert for factors that develop during the process of risk management, whatever strategy that may be, will allow additional support to be provided that may improve psychosocial outcomes for women at risk both of cancer and at risk of the adverse effects of cancer risk reduction strategies.

Further work is needed to assess the long-term effects of enhanced breast surveillance in this high-risk group. The impact of recall, which occurs commonly in MRI screening, alongside the impact of likely cancer diagnoses within family members will have upon a woman who has chosen screening remains to be seen. It could be assumed that women derive a benefit from undergoing screening, in terms of the 'acceptance' process described in 3.1, but this is as yet unproven. Longitudinal studies following cohorts of women over many years will be necessary to capture the effects of screening on women living at risk.

This chapter has used a process of systematic review to provide data to allow analysis and a greater understanding of the psychosocial outcomes for women at increased familial breast cancer risk. Chapters 4 and 5 describe the interview and questionnaire phases of the study, adding to these data, which are pooled and interpreted in the discussion (Chapter 7).

4 Chapter four – Semi-structured interview study with women and the partners of women at increased risk of familial breast cancer

4.1 Abstract

4.1.1 Introduction

Women carriers of familial breast cancer genes face difficult choices about managing risk. Risk reducing surgery is effective but with associated surgical morbidity, cosmesis, sexuality and potential long-term psychosocial impact. MRI breast surveillance has minimal morbidity and although does not reduce risk of cancer, provides a viable risk management strategy, although the impact of the ongoing risk is poorly understood.

This study explored views of women at high familial risk, and their partners, towards RRM and MRI breast screening and explored factors that impact upon their risk management decisions and subsequent outcomes and satisfaction.

4.1.2 Method and analysis

Semi-structured interviews were undertaken with women at increased risk from a tertiary UK Breast Unit. Interviews focused on views of, choice of, and satisfaction with, preferred risk management strategies (RMS). Framework analysis was used to analyse data.

4.1.3 Findings

32 women and 6 partners of these women were interviewed. Themes identified included: perception of risk and impact of increased risk; risk management decision making; impact of screening and RMS, impact upon partners and support needs and satisfaction.

4.1.4 Conclusion

Most women were satisfied with their RMS. Factors influencing choice were related to fear of cancer, past negative experiences of family and a desire to survive for their children.

Some women used MRI breast screening to delay surgery and some as their only planned management. Those who chose surgery either wanted to reduce their risk or were concerned about efficacy of screening. Partners aimed not to influence RMDM and provided support. Availability of time off was a frequent frustration expressed by partners. None of the women interviewed had regrets about breast surgery and most were satisfied with the cosmetic result.

4.2 Introduction

Use of qualitative techniques in health related research is recognised to have benefits over quantitative techniques when the research question remains open. There are a variety of techniques available including observation of clinical experiences, focus group discussions and use of individual, one-to-one interviews. There are advantages and disadvantages to each of these, including but not restricted to the impact of the researcher on the findings and the time taken to obtain the necessary data. For this study it was felt a series of semi-structured interviews with women at increased risk of familial breast cancer would be most appropriate for many reasons. The nature of the topic means that many of the questions being posed could be highly sensitive and not necessarily suitable for focus group discussion. Similarly, observation of clinical encounters would be unlikely to provide the level and depth of understanding that was required, exploring the underlying feelings related to the increase in risk and the reasoning for decisions taken in this context.

The aims of the interviews were:

- To explore the views of women and their partners at high familial breast cancer risk about the impact of their risk and their choice of risk management strategy on their lives
- To determine the significant issues that relate to coping with a high risk of developing breast cancer
- To explore the factors that impact upon decisions about risk management
- To explore women's satisfaction with the decisions they have made and the outcomes of these decisions.

An advantage of interviews over a questionnaire to explore these issues is that women are free to express their personal views without the influence of preconceived ideas or opinions, which may affect the views expressed if a more structured approach is used (Black 1994). It should lead to a better understanding of key issues surrounding coping with an increased risk of developing breast cancer. A disadvantage of interviews is that each woman may not mention all of the factors expressed by the group as a whole, even if they are important, but since the aim of the interviews was to explore issues relevant to the individual women in particular rather than to answer specific pre-defined questions this effect is not important.

In order to establish how the issues identified in each of the individual interviews impacts on the population of women at increased risk, the interviews formed just the first stage of a mixed methods study, guiding the development of a structured questionnaire sent to a greater number of women. In addition to review of relevant literature and the study teams' expertise and knowledge of the field, the combination of methodologies makes the overall study findings more representative.

In addition to interviewing women at increased risk, this study also interviewed partners of women at increased risk, who may be significantly involved in and affected by both cancer risk and risk management strategies.

4.3 Research, Design and Procedures

4.3.1 Ethics and research governance

The study was approved by the tertiary Teaching Hospitals Research Governance Unit and was awarded Ethical Approval (ref 09/H1308/121) (Abridged protocols and ethics approval letters are included in appendices 1 and 5).

4.3.2 Funding

This study was funded by the University of Sheffield and recruited women and partners of women between 2010 and 2012.

4.3.3 Sample

Women at risk

Women were identified from a locally held database and prospectively in breast clinics and only those with a very high risk of familial breast cancer were considered (see inclusion and exclusion criteria below). Purposive sampling aimed to include women who decided to have RRS and those who opted for enhanced screening, across a wide range of ages (Pope 2006). No account was taken of socio-economic status or race, as this information was not available.

In practice, certain groups remained poorly represented, in spite of efforts to recruit greater numbers, including younger and older women (40-59 years was well represented) and those who had surgery but did not have reconstruction. Challenges in recruitment largely reflect participant interest in the study and subsequent engagement.

Partners of women at risk

Women who had taken part in the interview study and who were in a relationship were asked if they were comfortable with their partner being invited to a partner interview. Those who agreed were asked to give their partner a study information pack. This recruitment strategy limited opportunity to recruit a greater number than those who initially responded positively and similarly prevented expanding the range of partners being represented. Again, participant interest and engagement limited recruitment.

4.3.4 Saturation of themes

Recruitment of interviews with women at risk ceased once data saturation had occurred. Essentially, no new information or themes were generated in interviews undertaken once themes were saturated. This occurred at around 30 interviews, although 2 further interviews were undertaken as they had already been scheduled (and these confirmed saturation of themes). 30 interviews is consistent with theme saturation in previously described qualitative interview studies and corroborated by Mason who reviewed a large number of such studies and found that 30 is a frequent number required to saturate themes (Mason 2010). Partner interviews, although only representing a subsection of the wider population (of partners of women at increased risk) also reached saturation of themes with just 6 partners. This is explored further in the discussion and likely reflects the similarity of partners who participated.

4.3.5 Inclusion and exclusion criteria

Women at risk

Inclusion Criteria

- Female

- Known to be at high risk of developing breast cancer and have attended a family history clinic to discuss this risk
- Have been offered a risk reducing mastectomy as part of their options for risk reduction (even if they subsequently chose screening)
- Able to speak and write in English
- Able to give informed consent in the opinion of their clinician

Exclusion Criteria

- Inability to give informed consent
- Terminally ill
- Inability to speak and write English
- Significant cognitive impairment or history of severe mental health disorder (if this was known to impact on their decision making)
- Recent cancer diagnosis

Partners of women at risk

Inclusion Criteria

- Male or female
- In a relationship with a woman known to be at high risk of developing breast cancer who had attended a family history clinic to discuss this risk
- In a relationship with a woman who had been offered a risk reducing mastectomy as part of their options for risk reduction (even if they subsequently chose screening)
- Able to speak and write in English
- Able to give informed consent in the opinion of the interviewer

Exclusion Criteria

- Inability to give informed consent
- Inability to speak and write English
- Significant cognitive impairment or history of severe mental health disorder (if this was known to impact on their decision making)

- In a relationship with a woman with a known recent cancer diagnosis

4.3.6 Recruitment

Women at risk

Eligible women were identified as above and sent a study pack etc

Study packs comprised:

- An Introductory Letter from the research study team outlining the study and inviting participation
- A Patient Information Sheet explaining the study
- A Study Reply Form and consent form to indicate whether or not they wish to take part in an interview
- A FREEPOST envelope

Study packs were given to eligible women in clinic by their clinician or were sent via the post.

Women who consented to being interviewed were contacted to arrange a mutually convenient time and place for the interview, either in the hospital or at the woman's home or workplace, or by telephone at their request. Informed, written consent was taken at the start of the interview and the purpose of the study re-explained. A digital dictaphone was used to record the interviews. Travelling expenses were reimbursed and refreshments offered to those women who were interviewed in the hospital. Participants were not paid for their time.

Partners of women at risk

During interviews with women, they were asked if they would consent to their partners being approached by the study team. Only if they were comfortable with this would their partners be invited to participate. Women were asked to hand a pre-prepared pack to their partners containing:

- An Introductory Letter from the research study team outlining the study and inviting participation
- A patient Information Sheet explaining the study
- A Study Reply Form to indicate whether or not they wish to take part in an interview

- A FREEPOST envelope

Partners, if interested in participating, were then invited to interview either at the hospital or at a place they found more convenient. Expenses were offered but they were not paid for their time. Similar issues were explored and a separate interview schedule was used to ensure the same topics were covered in each interview, which was conducted by a single researcher (EM). Topics including their involvement (both in attendance and in decision making) in their partner's discovery of risk and risk management decision making, their views of screening and surgery and the impact that their partner's risk had upon them and their relationship, both emotionally and physically.

4.3.7 Conduct of the interviews

The semi-structured interviews were conducted by one of two researchers (EM and SE) who worked closely together and were familiar with the technique generally and specifically within the context of this study. Interview schedules were developed based on the available literature by the study team and were used to ensure that all of the interviews covered the same basic themes but without prescribing the order in which topics were discussed (see figure 4.4.1). Three versions of this prompt sheet are included as appendix 7 (one for women in screening; one for those who have had surgery; one for partners of women at increased risk). The interviews focused on personal choice of, and satisfaction with, their risk management strategy. Other topics that were explored included: regret, body image, relationships and cancer anxiety. Women were also asked about the influence of health care professionals and their partners on their decisions. Other factors that shaped their choices were explored. Partners were asked about their involvement in risk discovery and risk management choices, their views of the risk management options, their view of the outcomes and the impact upon them and their partner in terms of relationships and emotionally.

SE undertook the first few interviews with a researcher not linked to the project who had extensive experience in the conduct of semi-structured interviews. EM and SE worked together for the majority of the remaining interviews with partners. EM undertook all of the partner interviews and some of the latter interviews with women alone.

Interview prompt sheet – screening women

Beginning

- Introductions
- Brief overview of study
- Explain purpose of interview
- Check had time to read information leaflet
- Any questions
- Check they have signed a consent form
- Confidentiality and anonymity issues
- Check okay to tape record discussion
- Ensure participants feel free to stop interview at any point or turn off tape.

Issues to explore

- Discovery of risk – how, when, who else was involved
- Decisions regarding surgery and screening
 - Thoughts regarding surgery
 - Thoughts regarding screening
- Risk perception
- Waiting for results/anxiety
- If offered surgery, what puts you off
- Have you thought what you would do re surgery if you are diagnosed with cancer.....one or both breasts removed/breast conserving surgery/reconstruction
- Oophorectomy / screening thoughts (and awareness of risk)
- Experience of screening so far
 - Timing, anxiety, painful, benign recalls, claustrophobia, flexibility etc
- Long-term plans (e.g. continue screening or surgery)
- Family history – how other women have managed risk, been affected etc.
- Effects of increased risk
 - Cancer worry, risk perception, body image, feeling re breasts, general anxiety etc.
- Effects on relationships – partner, children, other family, friends, colleagues etc

Figure 4-4-2 Interview prompt sheet sample – partners. Full version available in appendix 7.

Interview prompt sheet – partners

Beginning

- Introductions and general chat to break the ice/offer tea/cake/how did they get here and check re travel expenses and if they need them to be reimbursed.
- Brief overview of study
- Explain purpose of interview
- Check had time to read information leaflet
- Any questions
- Check they have signed a consent form
- Confidentiality and anonymity issues
- Check okay to tape record discussion
- Ensure participants feel free to stop interview at any point or turn off tape.

Issues to explore

Initial question about the background to your relationship with X....how did you meet, how long together? Do they have kids....how many, how old etc.

- Discovery of partner's risk – how, when, who else was involved
- How did confirmation of risk affect them?
- Were they together at the time? If so, was he involved, attending appointments?
- Did he ever feel he was being ignored/out of the female issues loop
- Awareness of family history
- Did he want her to go for gene test or not
- Did he want her to have surgery/screening

4.3.8 Analysis of interview transcripts

Interviews were transcribed verbatim, in full and without abbreviation, and checked against the recording for accuracy. Notes taken at the conclusion of the interviews were added in to create the final transcribed interview document. Analysis followed the National Centre for Social Research 'Framework analysis' approach, identifying recurrent themes (Ritchie and Spencer 2003). Nvivo10 was used to facilitate this process (International Pty Ltd. 2010). Transcribed interviews were initially read and then re-read and a process of coding developed, initially on paper, developing initial themes. The range of topics explored and volume of data meant that paper analysis quickly became unmanageable. Options for digitally working included Microsoft Excel or a dedicated platform to allow framework analysis. The latter was chosen for the benefits outlined below:

- Ability to cope with large volumes of source data
- Coding simplified (no requirement to note source or position of coded text)
- Automatically links coded text back to the source, preserving context
- Allows complete coded dataset to be examined as one and facilitates sub-group analyses

As the coding matured, the data were transferred into an Nvivo file and coding then done electronically, linking coded parts of text back to their origin to allow context to be preserved (see figure 4.4.3 and 4.4.4). Two researchers (EM and SE) analysed all of the interview data and worked together closely to ensure familiarity with each other's approach to coding and theme development.

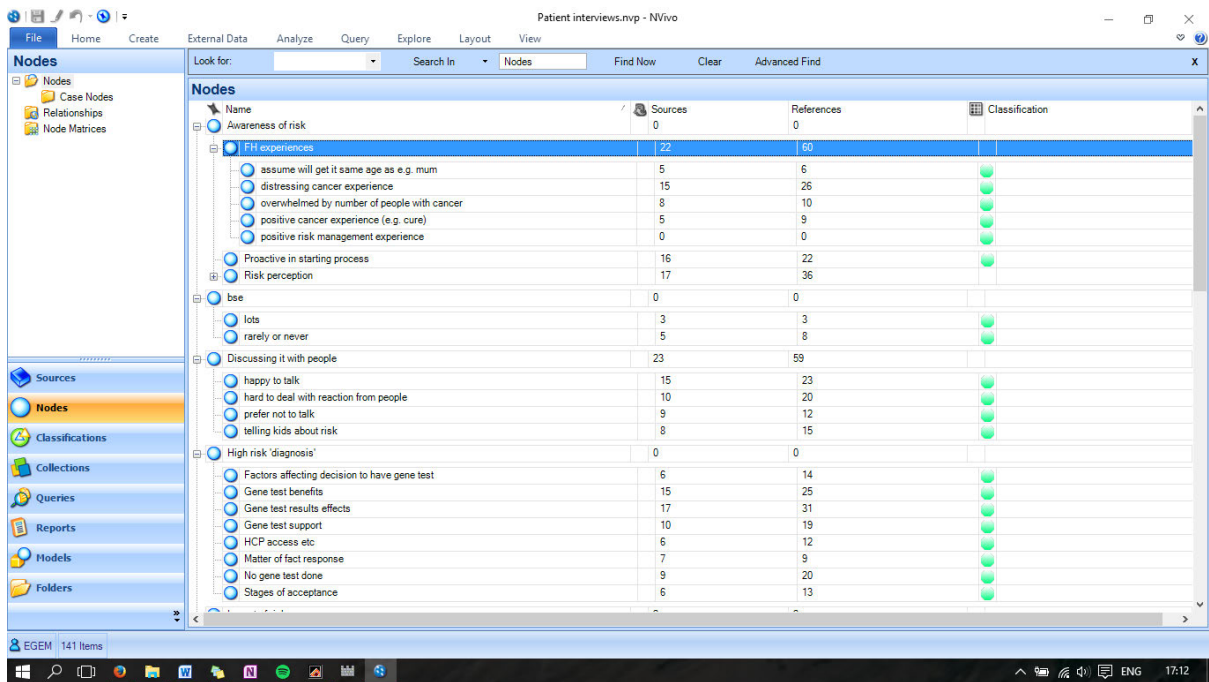


Figure 4-4-3 Nvivo screenshot: coding and sources

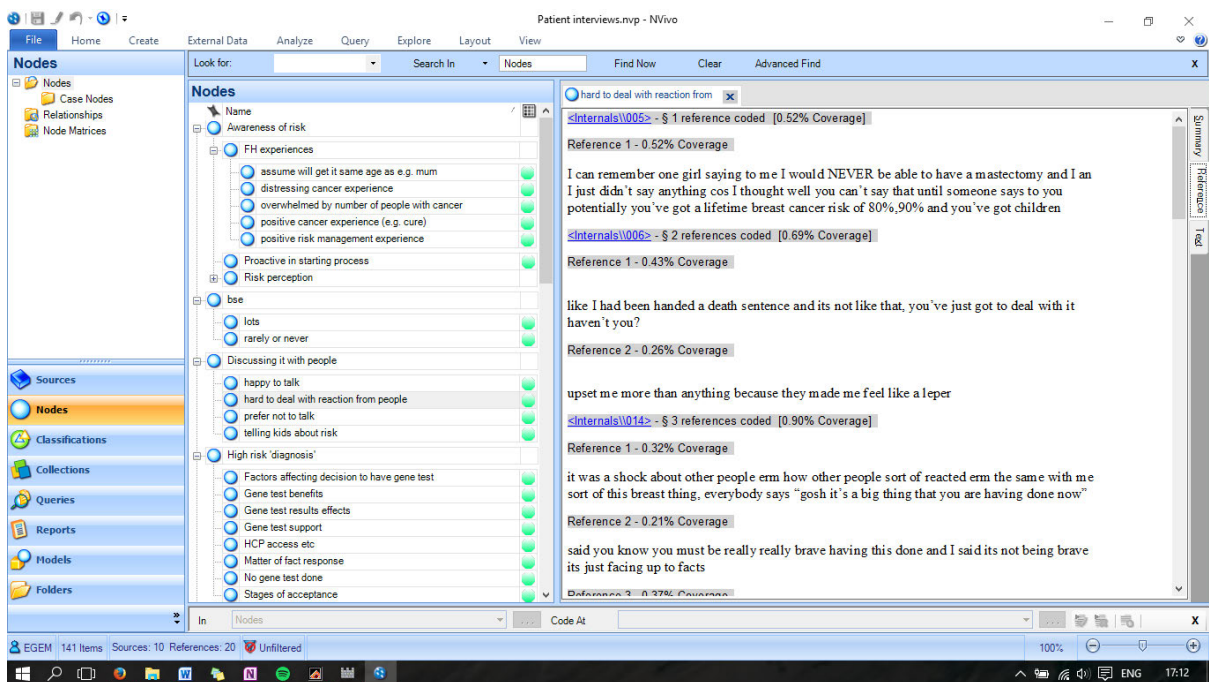


Figure 4-4-4 Nvivo screenshot: Example of one code and the sources

Another function of Nvivo (International Pty Ltd. 2010) is the ability to add labels to the sources, in this case, the interview transcripts, (see figure 4.4.5). This allowed associations to be readily identified and meant that tables could be created of one group alone, for example women who chose screening, to examine a sub-group of views on a specified topic.

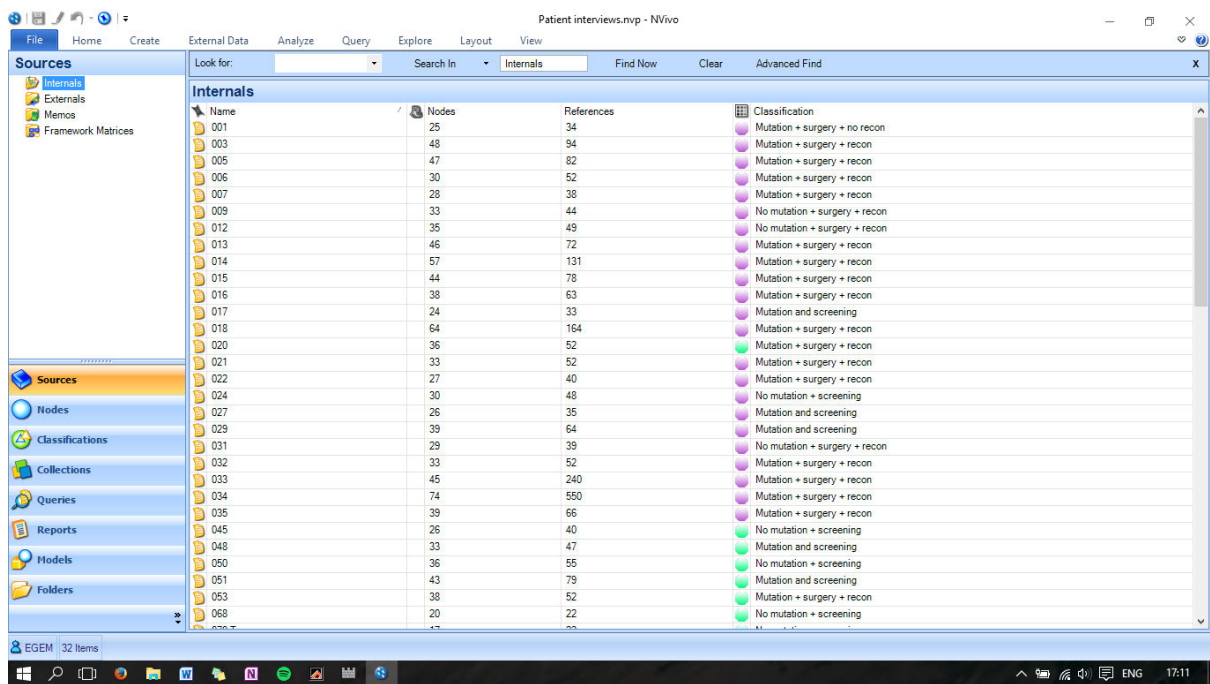


Figure 4-4-5 Nvivo screenshot: Participant characteristics

As coding took place, framework matrices were created, essentially forming two spreadsheets (one for women at risk and one for partners) detailing all of the coding points from all of the interviews (see appendix 9). These spreadsheets developed and grew as themes from more interviews were added and themes refined, until a point was reached when no new themes were being identified (saturation of themes). The tables enabled themes to be linked and associations noted.

Ranges of responses were noted and associations between findings identified, for example the likelihood of women who had children to feel that surgery was their only option. Data were then explored further to provide explanations for the findings (Gale, Heath et al. 2013).

4.4 Results

4.4.1 Quality of data

Table 4.1 summarises the processes and reviews the quality of the interview phase of the study.

Table 4-1 Summary of findings

Findings	Appraisal question	How it is addressed
Findings	How credible are the findings?	Samples of the interview data are available, along with samples of the framework matrix in appendix 9. Findings are corroborated by further work (see chapter 7).
	How has knowledge/ understanding been extended by the research?	Literature review (see chapters 1 and 3) is presented and findings referred back to existing knowledge. Findings that are new are highlighted as such.
	How well does the evaluation address its original aims and purpose?	Aims and objectives are stated in chapter 2 and the discussion refers back to these aims, identifying how the data meet the aims.
	Scope for wider inference	Purposive sampling was used with an aim of representing as wide a variety of women and partners as possible. Limitations are discussed.
Design	How defensible is the research design	Methodological choices are discussed in chapter 4, with information about the options and justification of choices.

Sample	How well defended is the sample design?	Sampling is discussed in chapter 4 and choices justified in chapter 5
Sample (cont'd)	Sample composition – how well is the eventual coverage described?	Limitations in recruitment are explored in the discussion
Data collection	How well was the data collection carried out?	Data collection methods are described above, full transcription of interviews was performed and notes added by the interviewers.
Analysis	How well has the approach to, and formulation of, the analysis been conveyed?	Nvivo is specifically designed to facilitate qualitative data analysis. The coding framework and theme charts are displayed below.

4.4.2 Recruitment and demographics (see table 4.4.2)

A total of 32 high risk women who had opted for either risk reducing breast surgery or enhanced surveillance with MRI and/or mammography were interviewed. Women were aged between 22-68 years (median age 44). 20 women had undergone risk reducing surgery, of whom 5 had a previous breast cancer diagnosis. 12 had opted for enhanced surveillance with a wide range of time in different screening programmes. 27 were in a stable relationship at the time of their risk management decision.

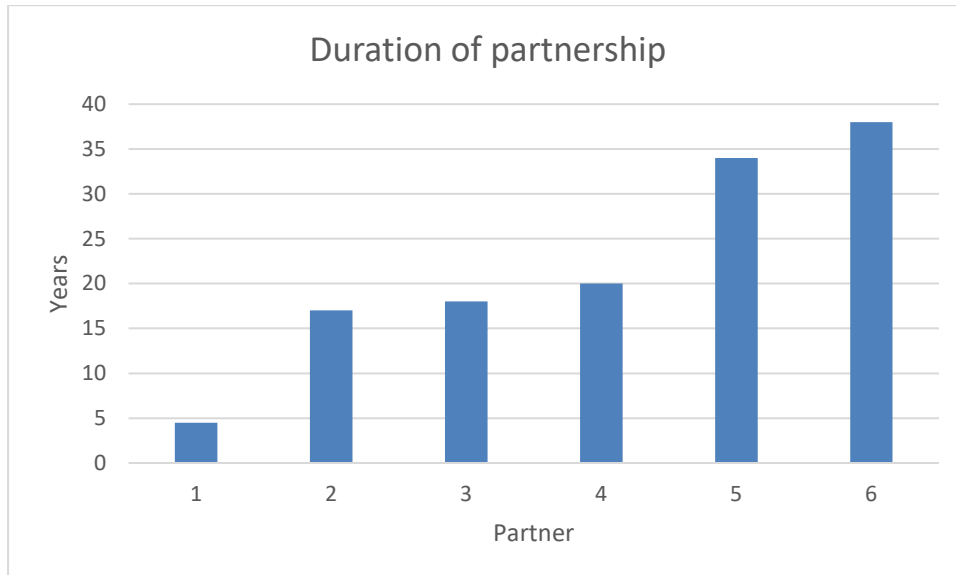
Table 4-4-2 Participant characteristics

Characteristic		Number of women
Age in years (at interview)	20-39	4
	40-59	25
	60+	3
Risk management choice	MRI breast screening	12
	Risk reducing breast surgery	20 19 had reconstruction 12 LD, 2 TRAM/DIEP (1 salvage for failed LD), 5 implant only, 1 IGAP
Type of risk	<i>BRCA</i> mutation	22
	No demonstrated mutation but <i>BRCA</i> gene carrier risk level	10
Previous breast cancer diagnosis	Yes	5
	No	27
Risk reducing oophorectomy		15

26 of 27 women with partners (who had been with them during their risk management decision) agreed to allow the study team to contact their partners and to their partner being given (or sent) an interview invitation. In total 7 partners (27%) responded positively and 6 were ultimately interviewed (one could not be contacted after the initial contact). Five were partners of women who had undergone risk reducing breast surgery, 2 of whom had chosen not to have a reconstruction, the sixth was a partner of a woman who was awaiting risk reducing surgery. The length of relationship at time of interview varied from between 4-38

years with risk management decisions occurring after between 2 and 30 years together (see 4.4.3). Partner demographics were not collected but all were aged over 18 and all were male.

Table 4-4-3 Duration of partnership



Interviews with women and with partners were analysed separately.

4.4.3 Themes of interviews with women at risk

An example of an interview transcript is included in appendix 8. The full framework NVivo table is not included in the thesis but sample sections are included in figures 4.4.3 to 4.4.6. The full NVivo analysis is available to examiners if requested.

Data were analysed using *Nvivo10 (International Pty Ltd. 2010)* software. Interviews were transcribed as soon as possible after completion, often by one of the interviewers or by a medical secretary (VP). Notes were added, where necessary to clarify points or add to the data things that would not be noted from the transcript alone. Framework analysis tables developed as interviews went on, with themes being identified and refined. Table 4.4.4 shows the node classification that was used initially, where the number of sources is the number of interviews that have been coded to the heading and the number of references the total number of individual references from all interviews. These initial nodes, or early themes developed into four final themes:

1. Perception of risk and the impact of increased risk;
2. Risk management decision making;
3. Impact of screening and risk management strategy and
4. Support needs and satisfaction

The final coding index is below in table 4.4.5 and demonstrates the process by which the framework analysis developed.

Table 4-4 Initial node classification

Topic	Initial theme	Initial subtheme	Sources	References
Awareness of risk			0	0
	FH experiences		22	60
		assume will get it same age as e.g. mum	5	6
		distressing cancer experience	15	26
		overwhelmed by number of people with cancer	8	10
		positive cancer experience (e.g. cure)	5	9
		positive risk management experience	0	0
	Proactive in starting process		16	22
Risk perception			17	36
	better since surgery or screening		2	2
	cancer risk perceived as very high		4	4
	hopefully I won't get cancer		9	10
	I look like an affected relative		2	2
Breast self examination			0	0
	Lots		3	3
	Rarely or never		5	8
Discussing it with people			23	59
	happy to talk		15	23

	hard to deal with reaction from people		10	20
	prefer not to talk		9	12
	telling kids about risk		8	15
High risk 'diagnosis'			0	0
	Factors affecting decision to have gene test		6	14
	Gene test benefits		15	25
	Gene test results effects		17	31
	Gene test support		10	19
	Healthcare professional access		6	12
	Matter of fact response		7	9
	No gene test done		9	20
	Stages of acceptance		6	13
Impact of risk			2	2
	Avoidance		15	26
	Cancer related anxiety		6	13
		hard to live with it	11	15
		minor or none after surgery	15	19
		not a big issue	6	10
		prefer this to cancer worry	1	1
		significant	15	27

		still worry after surgery	10	15
		worry reduced by screening	3	3
	Effect of knowing		0	0
		benefits of knowing risk	12	29
		detrimental effects	6	15
	Effect on family		0	0
		difficult interfamilial relationships caused	10	15
		improved relationships	6	7
		no change	2	2
		worry about kids	19	30
		worry about my screening or surgery affecting them	7	13
	Guilt		1	3
		Guilt re kids	13	26
		Guilt re not having cancer	6	7
	How it has changed you		17	23
	Isolation		10	20
	Partner		0	0
		effect on getting a new partner	6	9
		effect on partner	12	19
		opinion on surgery	10	83
		partner role in decision	18	33

		sex	12	17
	Shock		10	16
		Not a shock	4	6
	Time bomb		7	7
	Upset		14	26
Ovarian risk			0	0
	cancer is a death sentence		2	2
	fear of ovarian cancer		4	5
	oophorectomy experience		6	9
	options and decision		13	20
	ovarian screening		6	8
	provision of oophorectomy info		10	18
Risk management decision			0	0
	Access to information		26	59
		internet	17	26
	Be there for kids		13	21
	Desire for control		9	19
	Making it a harder decision		0	0
		conflicting views of friends and family	1	1
		fear of surgery and outcome	8	12

		impact on family	5	9
		uncertainty	11	14
	Making it an easier decision		0	0
		reconstruction availability	17	27
		supportive family etc	5	5
		would reduce risk of cancer	20	36
	Timing		7	15
		get on with it	8	14
		when I was younger maybe	3	5
	Your own decision		16	27
		felt pushed	6	11
	Satisfaction		0	0
		Positive	9	17
		Negative	18	43
Screening			0	0
	Efficacy		0	0
		Not considered good enough	7	10
		Reassuring	10	16
	Experiences of screening process		0	0
		Good points	11	17
		Bad points	9	12

	Inconvenience of screening		5	8
	Views of screening		0	0
		against	9	15
		other	7	10
Suggestions			0	0
	re service		7	19
	to other women at high risk		7	12
Support needs			0	0
	didnt want support		9	13
	needs that were met		16	29
	re support group		19	42
	role of family and friends		14	20
	unmet needs		10	23
Surgery			0	0
	Body image		1	1
		negatives post op	14	26
		pleased post op	14	24
		pre op thoughts	12	19
		trade off for cancer risk or surgery risk	7	8
		want to look normal or have breasts	18	33
	Complications		15	31

	Expectations of surgery		0	0
		did not meet expectations	6	13
		expectations met or exceeded	13	27
		general	11	13
		preoperative images etc	12	29
	Experience of surgery		0	0
		Negatives	9	22
		Positives	7	11
	Inconvenience of surgery		17	27
	Longterm		0	0
		late effects	12	40
		re feeling normal	10	31
	Pain		9	21
	Reconstruction		0	0
		having had it thoughts	8	15
	Views of role of surgery		0	0
		No way!	1	1
		Not yet	4	7
		Only if I have cancer	5	9
		The only thing that makes sense	8	11

Table 4-4-5 Coding index

Topics discussed	Initial themes	Refined themes	Final themes	Core concepts
Awareness of risk	<p>Family history experiences</p> <ul style="list-style-type: none"> - Assume will get it at same age as e.g. mum - Distressing cancer experience - Overwhelming number of affected relatives - Positive (i.e. cure) cancer experiences - Positive risk management experience <p>Proactive in starting process</p> <p>Risk perception</p> <ul style="list-style-type: none"> - Better since surgery / screening - Cancer risk perceived as very high - Cancer risk perceived as low - Cancer risk high because of appearance similarity with affected relative 	<p>Women's experience of cancer management and risk management affects their behaviour</p> <p>Risk perception is widely variable and can be distressing</p>	1. Perception of risk and impact of increased risk	<p>Distress / anxiety</p> <p>Uncertainty</p> <p>Guilt</p> <p>Isolation</p>
High risk diagnosis	Factors affecting decision to have gene	Women's decision to explore their		

	<p>test</p> <p>Gene test benefits</p> <p>Gene test results effects</p> <p>HCP access</p> <p>Matter of fact response</p> <p>No gene test done</p> <p>Stages of acceptance</p>	<p>risk could be described as traumatic or run-of-the-mill</p> <p>Discovery of high risk was often traumatic</p>		
Impact of risk	<p>Avoidance</p> <p>Cancer related anxiety</p> <ul style="list-style-type: none"> - Hard to live with it - Minor or none after surgery - Not a big issue - Prefer 'this' to cancer worry - Significant cancer fear - Still worry after surgery - Worry reduced by screening <p>Effect of knowing</p> <ul style="list-style-type: none"> - Benefits of knowing risk - Detrimental effects <p>Effect on family</p> <ul style="list-style-type: none"> - Difficult interfamilial relationships result 	<p>Profound for some, much less for others</p> <p>Impact of risk seemed to correlate with a decision to have surgery</p> <p>Effect on family often significant</p> <p>Guilt was common especially for women with children</p>		

	<ul style="list-style-type: none"> - Improved relationships - No change - Worry about children - Worry about risk management strategy affecting children <p>Guilt</p> <ul style="list-style-type: none"> - Regarding children - Regarding not having cancer <p>How it has changed you</p> <p>Isolation</p> <p>Partner</p> <ul style="list-style-type: none"> - Effect on getting a new partner - Effect on partner - Opinion on surgery - Partner role in RMD - Sex <p>Shock or not</p> <p>Time bomb effect</p> <p>Upsetting</p>			
Ovarian risk (where relevant)	<ul style="list-style-type: none"> - Cancer is a death sentence - Fear of ovarian cancer - Oophorectomy experience 	Again, profound for some, less worrying for others.		

	<ul style="list-style-type: none"> - Option and decisions - Ovarian screening - Provision of oophorectomy information 	Availability of information frequently a source of frustration		
Risk management decision	<p>Access to information</p> <ul style="list-style-type: none"> - Internet <p>Wish to 'be there' for children</p> <p>Desire for control</p> <p>Factors making RMD harder</p> <ul style="list-style-type: none"> - Conflicting views of family / friends - Fear of surgery / outcome - Impact on family - Uncertainty <p>Factors making RMD easier</p> <ul style="list-style-type: none"> - Reconstruction availability - Supportive family - Would reduce the cancer risk <p>Timing</p> <ul style="list-style-type: none"> - Get on with it - When I was younger perhaps <p>Your own decision or felt pushed</p>	<p>Desire to reduce risk or be there for children was frequent</p> <p>Feeling that surgery was unnecessary or would be too great a hurdle for them or their family</p> <p>Impact of RMD on family</p>	2: Risk management strategy decision making	Uncertainty Conflicting views

Screening views and experiences	<p>Efficacy views – either reassuring or not felt good enough</p> <p>Good and bad experiences of screening</p> <p>Inconvenience of screening</p> <p>Reasons for not choosing screening</p>	<p>Variable views of efficacy</p> <p>Varied experiences</p>	<p>3: Impact of risk management strategy decision (screening or risk reducing surgery)</p>	<p>Cancer related anxiety</p> <p>Body image</p> <p>Privacy</p>
Surgery views and experiences	<p>Regarding a role for surgery as a RMD</p> <ul style="list-style-type: none"> - No way! - Not yet - Only if I have cancer <p>The only thing that makes sense</p> <p>Expectations of surgery</p> <ul style="list-style-type: none"> - Did not meet expectations - Expectations met / exceeded - General thoughts - Preop images views <p>Experience of surgery</p> <ul style="list-style-type: none"> - Negatives - Positives <p>Inconvenience of surgery</p> <p>Long term</p>	<p>Some feel surgery is their only risk management option, others feel it could never be appropriate without cancer</p> <p>Variable expectations and outcomes</p> <p>Some unresolved longterm consequences</p> <p>Reconstruction crucial for some considering risk reduction surgery</p> <p>Body image issues common</p>		

	<ul style="list-style-type: none"> - Late effects - Feeling normal <p>Pain</p> <p>Reconstruction views</p> <p>Body image</p> <ul style="list-style-type: none"> - Negative post op - Positive post op - Expectations - Trade off description - Want to look normal or have breasts <p>Complications</p>			
Discussing risk and experiences with people	<p>Happy to talk</p> <p>Hard to deal with reaction from people</p> <p>Prefer not to talk</p> <p>Telling kids about risk is a huge thing</p>	<p>Some very loquacious</p> <p>Other people's reactions challenge their risk management decision</p> <p>Talking to children challenging</p>		
Support needs	<p>Didn't want support</p> <p>Needs that were met</p> <p>Regarding a possible support group</p>	<p>Widely variable needs and views of possible sources of support</p>	<p>4: Support needs and satisfaction</p>	<p>Support group</p> <p>Privacy</p> <p>Ongoing impact</p>

	Role of family and friends Unmet needs			
Satisfaction	Negative Positive	Frequently satisfied despite compromise		
Suggestions	Regarding the service provision For other women at increased risk			

4.4.3.1 Theme 1: Perception of risk and the impact of increased risk

This theme involved two distinct subgroups: women's awareness and perception of risk and their account of their risk being confirmed. Women frequently described feeling shocked and traumatised by the confirmation or discovery of their increased risk of breast cancer.

The perception of risk varied and was often based upon the timing of previous cancer diagnoses among relatives and their subsequent outcomes. Those who had known (and not purely known of) family members who had died of breast or ovarian cancer often had a deeply held fear of cancer.

"I was bound to have it already, I was going to die, basically history was going to repeat itself... ..Intense fear of cancer." (ID2: BRCA, surgery)

"I look in the mirror and think I'm turning into my mum you know and we are just physically so similar and the fact that she died, you know, relatively young, 59, erm that does worry me" (ID15: BRCA, surgery)

However, some who had not had this experience described their cancer risk in more objective terms regarding their risk management strategy.

"Yes, my family's got this predisposition thing, but that's way off in the future and that's how I feel, so you know, perhaps concerned enough to look out for signs but not to do something such as [surgery]" (ID32: No demonstrated gene mutation, screening)

There was an ongoing impact of familial experience with women diagnosed with the gene initially choosing screening and then changing their mind when a close relative was diagnosed with cancer or died of cancer.

"Both my mum and my auntie were both screened regularly, they both had mammograms done regularly... but it came in such an aggressive form with my mum and her sister that in between screenings they had missed it and it was too far advanced too quickly." (ID20: No demonstrated gene mutation, initially screening, then surgery)

Women frequently described feeling shocked and traumatised by the confirmation or discovery of their increased risk of breast cancer.

"...as if she'd told me I'd got cancer, that's how bad I felt. I went to pieces, didn't go to work for a week because I couldn't sleep, I was panicking, tut, er, I just felt that suddenly there was a switch that told me I was bound to have it already, I was going to die" (ID2: BRCA, surgery)

For some women, the initial shock and anxiety of discovering their increased risk seemed not to abate, whilst for others, the discussion appeared to be based on an historical event. This was not divided clearly between women who had had surgery and those in screening.

“Do you worry yourself about the possibility of something developing in the future?”

“...yes I do... and I think it’s so deep that Ican’t really begin to tell you” (ID28: BRCA, screening)

“I was checking every day, twice a day, was on my mind, couldn’t live with 90% chance of breast cancer” (ID16: BRCA, surgery)

Women with children frequently described feeling guilty about the possible inherited risk they may have passed on. This guilt seemed to restrict some families from discussing possible risk to future generations.

“I felt as if I was handing them a poisoned chalice and I felt um, responsible and guilty although I know there’s no need, but that’s how I felt” (ID28: BRCA, screening)

Some women expressed mixed feelings when asked how their risk affected them. Having their risk confirmed meant that they were forewarned and therefore also forearmed. They were able to take proactive steps to manage the condition and gain some sense of control.

“Very keen obviously to get tested because I wanted to be in control of what happened not the other way” (ID4: BRCA, surgery)

Several women described difficult interfamilial relationships during the time that their risk was established, with differing opinions on how to manage risk causing angst for some.

“One of my sisters was angry with the way one of my other sisters had reacted to it and one of my sisters questioned my way of reacting to it” (ID14: BRCA, surgery)

4.4.3.2 - Theme 2: Risk management strategy decision making

The decision of how to manage their risk was, for some women, seemingly straightforward, whilst for others it was a distressing time. Previous experiences of family members played an important role for some women in deciding what risk management strategy to take. Fear of cancer was, in some, paired with their fear of hospitals and surgery, further complicating the decision. Most women felt the decision had been their own.

“I tried to get feedback from my husband and a couple of close friends but each one of them wouldn’t commit on the decision, claiming it was entirely up to me” (ID2: BRCA, surgery)

However, 5 women felt they had been pressurised into surgery/reconstruction, either by family or by following the advice of their doctor. On reaching a decision some women described their continued sense of uncertainty. This was particularly the case for women without a recognised gene mutation, who felt that their risk was less certain.

“...like shall I shan’t I, yeah I’m going to do it, no I’m not and it’s still like that now” (ID17: No demonstrated gene mutation, screening)

The availability of reconstruction was an important factor in making a decision for some, but not for all, women who chose surgery.

“I think I’d have felt totally different if I couldn’t have had the reconstruction. I think I struggled enough as it was with the decrease in size” (ID13: BRCA, surgery)

4.4.3.3 - Theme 3: Impact of risk management strategy decision

Women broadly fell into one of three groups: those who had already undergone risk reducing surgery (*“it’s the only thing that makes sense”*), those who might consider it in the future (*“not yet”*) and those who felt they would never consider it (*“no way!”*).

Surgery decision

Not all of the women who had surgery felt that they ‘had’ to do it, although many did, usually quoting either the need to be there in the future for their children or a feeling that it was their only choice given the risk of cancer they had been presented with.

"To me it was just a case of you can't live with risks so high so you had to do something about it...I mean for me [surgery] was the lesser of two evils" (ID9: BRCA, surgery)

"We've all got children, you know, what's your choice really? For me, I didn't really have a choice" (ID3: BRCA, surgery)

For some, opting to undergo surgery allowed them to exercise some control, albeit with reservations about the options available. Women who opted for surgery more frequently noted that screening could not reduce the risk of cancer developing in the future and expressed concerns about the effectiveness of the test or whether it would miss something.

"I didn't want to wait for it to happen, I wanted to be proactive about it I guess" (ID13: BRCA, surgery)

Those women who had had surgery expressed the trade-off between having breasts and having the constant worry of cancer.

"I wanted rid of them as soon as I'd made up my mind that they had to go because they just seemed... unnecessary" (ID2: BRCA, surgery)

"I just didn't want to take the risk...especially as the alternatives looked reasonable and aesthetically good" (ID29: BRCA, surgery)

Although, most women expressed a welcome reduction in cancer worry following surgery, several felt that their cancer worry was merely reduced and not gone. Dealing with the loss of their natural breasts and the impact of the operation itself was a frequent cause of distress.

"Cosmetically you look fine but dealing with the feelings and the sort of anguish that comes with reconstruction, it's not, you never get back to normal" (ID9: BRCA, surgery)

"I liked my back. I think my back was probably (my) nicest bit and now I hate it" (ID8: BRCA post Latissimus dorsi flap reconstruction)

Screening decision

For some women the decision to undergo enhanced breast surveillance was an active choice and one with which they felt satisfied. For others, screening was merely accepted as an alternative to surgery (or to delay that decision).

“I might go through life and never get it and I might have this big operation you know for nothing and its not just a case of, er, of breast removal; Its all the other things that what go with it, psychological and things like that” (ID27: No demonstrated gene mutation, screening)

Some women felt that surgery was too drastic an option given that they may not have or ever develop cancer, with many stating that they would leave surgery until that situation changed.

“if I get breast cancer I’ll deal with it.” (ID12: BRCA, screening)

Others were more concerned with the actual effects of surgery and the loss of their breasts.

“I wouldn’t put myself through that because I think, I just can’t imagine a woman without, er, bre...[breasts] I can’t imagine me without breasts” (ID25: No demonstrated gene mutation, screening)

Most women with experience of screening were circumspect about any inconvenience of the screening process, acknowledging the process as being necessary and worthwhile for the peace of mind it provided. The wait for results was described by some as a period of increased worry. The vast majority felt that MRI was a better test (than mammography) offering a more thorough assessment of their breasts and this seemed to equate to greater levels of reassurance from the screening process.

“[MRI is] a more in depth test you know so that it shows up early” (ID27: No demonstrated gene mutation, screening)

“What’s a bit of discomfort for peace of mind that you know you’ve been checked” (ID32: no demonstrated gene mutation, screening)

4.4.3.4 - Theme 4: Support needs and partner relationship issues

A number of women felt that a support group or one-to-one meetings with someone in a similar position would be a potentially useful means of ongoing support following their risk management strategy discussions.

“I don’t think I was prepared for how I was going to feel afterwards [re surgery] and I think I would have liked to have spoke(n) to someone who had had it done” (ID20: No demonstrated gene mutation, surgery)

“You don’t meet anyone else with the condition you don’t kind of get to talk it over with anyone else at all just, that’s it now we’ve told you, goodbye. I found that a bit weird I thought it was all a bit weird; the counselling was all one side” (ID20: No demonstrated gene mutation, surgery)

The over-riding view of the women interviewed (and the 6 partners interviewed) was that the partners’ role in decision making was supportive and regardless of their own views, any decision needed to be made by the woman (at increased risk).

“He just wasn’t happy but he’ll just have to, you know, it’s my decision in the end, it’s my body, he said ‘but it’s your decision in the end but I don’t agree with it’” (ID8: BRCA, surgery)

Those who opted for surgery described a greater impact on their relationships.

“I think he’s lost a bit of confidence in our relationship or in how he performs in our relationship” (ID2: BRCA, screening)

The impact of their risk and their choice of RMS that some women describe observing in their partners is also a cause of distress for some.

“when I went for my results my husband obviously got upset because he had to deal with the aftermath” (ID14: BRCA, surgery)

“When I first found out about it, I think he struggled a bit erm and he couldn’t talk about it because I think he was worried about what might happen... ...he just thought I was going to get cancer” (ID15: BRCA, surgery)

Women who opted for screening tended to discuss the role of their partners less, perhaps reflecting a lesser need for support in this group or a lesser effect on partners.

“I think it worries him more than me actually. I mean, when I go for the MRI scan... ...he doesn’t go off worrying about it every day but I think he, it’s always in the back of his mind” (ID31: No demonstrated gene mutation, screening)

Very few partners seemed to have offered opinions or to have been involved in making risk management decisions. This is reflected in the partner interviews and also perhaps in the very low uptake by partners to take part in the study.

Effects on relationships varied.

“he has very little interest in my breasts anymore, which for a breast man is obviously a change because... I think he sees them as they aren't really me, they're just bags of salt water” (ID3: BRCA, surgery)

“it has not made a difference because erm only that he can't touch them. Erm its not a problem that way. He completely understands” (ID23: BRCA, surgery)

“it's not affected sex, at all.” (ID29: BRCA, surgery)

“I – Okay. And do you think it's affected your sexual relationship at all?”

P – No” (ID6, no demonstrated gene mutation, surgery)

“...probably brought us closer together to be honest” (ID21: BRCA, surgery)

4.4.4 Themes of interviews with partners of women at risk

Data were analysed using *Nvivo10 (International Pty Ltd. 2010)* software. Interviews were transcribed as soon as possible after completion, often by one of the interviewers. Notes were added, where necessary to clarify points or add to the data things that would not be noted from the transcript alone. A framework analysis table developed after completion of the six interviews, with themes being identified and refined during analysis. Table 4.4.6 shows the node classification that was used initially, where the number of sources is the number of interviews that have been coded to the heading and the number of references the total number of individual references from all interviews. These initial nodes, or early themes developed into three final themes:

1. Views of and role in RMDM
2. Relationship effects
3. Support

The final coding index is below in table 4.4.7 and demonstrates the process by which the framework analysis developed.

Table 4-4-6 Initial node classification (partners)

Topic	Initial theme	Initial subtheme	Sources	References
Discovery of risk			4	6
Involvement in risk management decision			6	30
Screening views	Good points		3	4
	Bad points		5	7
	Bad points and concerns		1	1
Surgery views	Good points and reassurance		2	3
	It was the only option		3	6
	Role of reconstruction		5	6
	Appearance		5	8
Surgery experience	Emotional impact		2	5
	Physical impact		4	11
	Observed in the affected partner		3	8
Impact emotionally	In other family members		2	4
	On partner		4	9
		Worry	4	9
			4	7
Impact on relationship	Sex		6	11
			2	2

Support	Info and general support		5	17
	Role as a supporter		2	3
	Support groups		1	2
	Time off work		3	5

Table 4-4-7 Final coding index (partners)

Topics discussed	Initial themes	Refined themes	Final themes	Core concepts
Discovery of risk	Attending appointments Involvement in decisions	Most are keen to attend in a supportive role Some struggle with work / other commitments	1. Views of and role in RMDM	Supportive role Lack of confidence in screening RRM reassurance Desire for woman's longevity Reconstruction is for woman's benefit, most
Involvement in risk management decision	Involvement in risk management decision	Not my decision Keep my views to myself Supportive role		
Screening views	Good points	Reassurance offered by MRI in addition to MMG		

				partners were ambivalent pre-op.
	Bad points	Lack of confidence in screening sensitivity Not comfortable with a partner at ongoing risk Worry about interval cancers Feeling that cancer is inevitable without RRM		
Surgery views	Good points and reassurance	Reassurance of reducing risk		
	Bad points and concerns	Enormity of the process		
	It was the only option	Desire to take control		
	Role of reconstruction	Concern about the additional risk Reconstruction viewed as being for the benefit of their partner		
Surgery experience	Appearance	“incredible” and “fantastic” Significant scars / deformity Implant feel – cold, hard Not real breasts	2. Relationship effects	Variety of views of reconstructed breasts Awareness of psychological

	Emotional impact	Admiration of their partner Reassurance of clear specimen Pity		impact on affected partner
	Physical impact	Variety of responses from quick to prolonged recovery Pain, tiredness, weakness		Exhaustion and desire to get back to normality Worry Variety of effects on sexual relationship
Impact emotionally	Observed in the affected partner	Battling with ongoing issues Depression, poor confidence Body image concerns		
	On other family members	Worry about children's risk Impact of RMDM on siblings of affected partner		
	On partner	Upset Desire and need to "get on with life" Suffered as a family Exhaustion		
	Worry	Desire for partner's health and wellbeing		

		<p>Lack of control</p> <p>Cancer worry</p> <p>Psychological impact worry</p>		
Impact on relationship	General impact on relationship	<p>Increased distance</p> <p>Feel closer to their partner</p> <p>Irritability</p> <p>Need to “put up with” changes</p> <p>Desire to get back to normal</p>		
	Sex	<p>Strange</p> <p>In limbo</p> <p>Massive change for some, no change for others</p> <p>Generally reduction in sex initiated by woman, thought by partner to be due to tiredness, pain, loss of body confidence</p> <p>Not all happy to discuss this</p>		
Support	Info and general support	<p>Varied opinions on availability of support from “excellent” to “none”</p> <p>Limited preparation for RRM</p> <p>Frustration with HCPs challenging views on RRM</p>	3. Support	<p>Work and availability of time off</p> <p>Variety of views on support availability</p>

		Perceived lack of understanding in others of the difference between RRM and cosmetic surgery Insensitive, “let down”		
	Role as a supporter	Encouragement Perceived inability to sympathise Practicalities – help washing		
	Support groups	Difficulty expressing views to strangers Benefit of other’s experiences		
	Time off work	Lack of support from employers Loss of holidays covering recovery		

4.4.4.1 Theme 1: Views of and role in RMDM

Five of six partners felt that RMDM was something done by the woman independently and most said they would stand by the decision made, irrespective of their (often not expressed) personal opinions.

“Mostly I was there for support. If she asked my opinion, I told her what I thought, but I only told her what I thought when she asked. It wasn’t my decision to make” (Partner 1, surgery)

“P – I think I’d question erm, question her decision as to why she’d go down that route [screening]

I – mmm hmmm

P – and I might even suggest well, do you think it might be better if you if you had the mastectomy” (Partner 5, surgery)

The role of reconstruction was described as being for the benefit of the woman and not from any desire of the partner for reconstruction.

“the reconstruction side of it was more for her than anything else” (Partner 6, surgery)

“the actual reconstructive part is probably cosmetic and its not, like she says there will be no feeling from it as such so in that sense it would purely be the look” (Partner 2, surgery)

4.4.4.2 Theme 2: Relationship effects

Partners expressed a variety of views on the post-operative appearance

“the scarring was a bit sort of ooh in your face and I didn’t know whether that was ever going to go” (Partner 1, surgery)

“it is a bit weird they are there but they are not there” (Partner 2, surgery – reconstruction)

“I suppose it looks ok, its not like it was before” (Partner 4, surgery, reconstruction)

The psychological impact of risk reducing surgery was in some cases profound, affecting both women and their partners, who frequently expressed concern about the impact of RRM.

“well we are different people and we have different breaking strengths and different personalities and you know, I am very worried about her, I suppose [more] psychologically than anything else, the impact it has had” (Partner 6, surgery)

“she just can’t concentrate. Still now she feels a lot, weaker is probably not the right word” (Partner 3, surgery)

Several partners expressed fatigue and a desire for a return to normality.

“although (partner) was a sufferer we felt like we suffered as a family as well in different ways...you have got so much fight in you and then you get to the point where you just need to rest and from my point of view it has changed everybody’s lives” (Partner 6, surgery)

“I just want my wife back home safe and sound... and I want to look after her and do what I can for her” (Partner 3, surgery)

Partners were generally positive about the effect of surgery on their partner’s appearance, although the impact of surgery on their physical relationship was in some cases profound.

“She always turns round when she gets changed and things like that so it makes it, for me it makes it hard” (Partner 3, surgery)

“Its not the same you know erm and I suppose (name) is conscious about it. I don’t know. Its not really something I want to talk about” (Partner 4, surgery)

“marital relationships it has got to have, that’s a massive change, there is no way round that one” (Partner 2, surgery)

4.4.4.3 Theme 3: Support

Availability of time off work was an issue for most of the partners.

“These last two years I have lost my work holidays to this” (Partner 6, surgery)

“the only support I could have done with was my employers. Erm they gave me about three days, they did not understand the enormity of the surgery and the support that my partner needed” (Partner 1, surgery)

There were conflicting views on the availability of support. Whilst some were very positive, the fact that healthcare is free at the point of delivery and public awareness of limitations to healthcare resources are increasing, may have confounded this finding.

“on the care side we could not have asked for anything better... I don't think I really have the right to say we have not had enough... as aware as we are that (name) needs the help we are also aware of how strained the services are” (Partner 6, surgery)

Others were less positive about support.

“I don't think there was any support at all thinking about it” (Partner 4, surgery)

“it is just a patient and another one is going to be walking in the door in 10 minutes” (Partner 3, surgery)

4.5 Discussion

These interviews present new understanding of the impact of management decisions that women at familial breast cancer risk face in the era of enhanced screening. It also presents a novel insight into the effects of familial breast cancer risk management on partners of women at risk.

4.5.1 Interviews with women at risk

The interviews explored topics that have been previously reported upon but with both availability and awareness of the benefits of MRI screening, which were not present at the time of previous similar studies (Frost, Schaid et al. 2000, Hopwood, Lee et al. 2000, Bebbington Hatcher and Fallowfield 2003)

4.5.1.1 Coping with familial breast cancer risk

Discovery of risk was, for many, a traumatic event, in line with published literature (Watson, Foster et al. 2004). The fear of cancer, cancer treatment and a 'bad' cancer death was frequently based on first-hand familial experience and could be overwhelming. For others it was confirmation of something they suspected and was accepted without shock. The knowledge of risk was viewed almost positively by some, enabling them to take action and control.

The presence of children was associated with frequent feelings of guilt: concerning the possibility of their having inherited the risk, the impact of risk management options (for example needing time away for risk reducing surgery) and the impact of the confirmed risk itself.

4.5.1.2 Gene mutation impact

In this series of interviews, women with no gene mutation featured in greater number in the group selecting screening and whilst the methodology employed does not allow for conclusions to be drawn from this fact, it is perhaps unsurprising as there are fewer women without gene mutations who choose surgery.

Women with gene mutations who were undergoing screening numbered five, of whom two were awaiting surgery that they were committed to, two felt they would probably want surgery in the future but were, at the time of interview, too young in their opinion, leaving one who felt she was too old to benefit from RRM at 68, suggesting that women with gene mutations are very likely to at least consider surgery.

The interviewed women who did not have a gene mutation and who were undergoing screening numbered six. They expressed their confidence in modern breast cancer management, a hope that they wouldn't get breast cancer, confidence in screening to detect any malignancy early enough for effective treatment and a desire to keep breasts that were not unhealthy (see table 4.4.8). This is in contrast to the women who chose surgery, who described their breasts as "time-bombs" and a cancer as "inevitable". Whilst gene testing has improved significantly over the past few years, it is not yet possible to assume that women without a confirmed mutation are necessarily at lower risk. The presence of a confirmed gene mutation appears to increase a tendency to choose surgery.

Table 4-4-8 Reasons for choosing screening over surgery

Participant	Summary	Decision to choose screening and not RRM
ID12	Gene mutation Reassured by screening	"I wouldn't have breast surgery, I wouldn't do it. I mean fair enough if I get breast cancer I'll deal with it... if I was younger

	Surgery only if required	definitely I would...I'm 68 I don't know... I don't think I could do it" Regarding screening: "I do really [find them reassuring], I do actually, and I've always gone for them...I really trust them"
ID18	Gene mutation Reassured by regular screening visits Doesn't want to lose breasts	"I know the Government guidelines say that I can't have a MMG once a year when I'm 50 so that might make me choose differently...[starts crying] "the reason why I haven't gone [for RRM] I think is because of the way ... my breasts would have to be reformed ... its not just like having a boob job, it has massive implications and I don't think I am ready for that yet." "yes [I find screening reassuring] and also when I'd found this little lump. You know I was able to ring up and come in straight away. So that was reassuring"
ID19	Gene mutation ID19 was in the pre-RRM counselling stage at the time of interview Couldn't tolerate MRI Feels surgery is not her choice but the only option	"because ... [cousin] has got it now I am thinking 'oh has it started'... I can't leave it now. I feel like I am ... doing something I don't want to ... I am not in control here and that's hard" "I had an MRI last year and then I went again this year... they are just completely, I am claustrophobic and I just had a complete breakdown"
ID26	Gene mutation Wanted to breastfeed Didn't want recovery implications of surgery	"I was thinking about perhaps starting a family so they said we'll do [MRIs] then surgery would still be an option at a later date... I [wanted] to do breastfeeding" "having the surgical procedure itself and then having to stop in and time away from my children... would bother me more than the surgery itself...although it would obviously be worth it"
ID28	Gene mutation Reassured by screening service Changed to surgery once sister diagnosed	"I had more regular mammograms I think every 18 months. I thought it would be every year but it wasn't... when I came here they were so quick and efficient and I got the results very quickly... I knew I would have no hesitation if I found anything ... I'd be on that phone so quick, and I knew that when Breast Surgeon said she'd see me I knew she meant it" "The reason I decided to go for surgery is because my sister's been diagnosed recently"
ID17	No gene mutation Wants to avoid surgical recovery	Regarding surgery: "I think its just the way you are going to look... it is a long operation and then a long recovery afterwards and then ... you are still going to be weak, like a weak back. So

	Reassured by screening	its not just having an operation its everything else as well. At the time when I thought about having it done ... my [children] were at school... what shall I do with the kids, time off and things" "I have had the MRI scan and that has made me feel better because that is a more accurate test and it can show things up a lot earlier and it's ... more accurate than a mammogram."
ID25	No gene mutation Reassured by screening Can't imagine being without breasts RRM unnecessary	Regarding MRI: "it's better because it shows a lot more but it was very uncomfortable" "she said that well you could have breast removal and I said that I wouldn't even consider that... I don't see the point in having something removed when you haven't got it ... I wouldn't put myself through that because I think, I just can't imagine a woman without, er, bre... I can't imagine me without breasts"
ID27	No gene mutation Surgery potentially unnecessary Uncertainty of risk Reassured by screening	"I might have this big operation you know for nothing and its not just a case of er of breast removal its all the other things that what go with it, psychological and things like that... I decided to be monitored... until I knew for definite" "I am quite lucky as I say to be checked twice every year ... I actually find the MRI scan more... reassuring... it shows up more things ... more in depth test you know so that it shows up early"
ID30	No gene mutation Surgery appropriate if gene positive	"I'd have had an elective mastectomy [if the gene test had been positive]... because for me, there was no question with having two small children as to whether I'd have actually done anything about it"
ID31	No gene mutation Surgery unnecessary at her level of risk	"if [cancer risk] had been a higher number ... might have taken it further, ... quite happy just having an annual MRI scan"
ID32	No gene mutation Reassured by screening Hopeful that cancer treatment will continue to improve	"it's been really good ... getting checks twice a year which is quite reassuring ... you know they can screen for it and you can look for it and that gives me a lot of reassurance" Regarding surgery: "if I cop for it ... then hopefully medical treatment would be better and ... it might not be as horrible"

4.5.1.3 Factors that impact upon RMDM

This study supports the findings of previous research (Payne, Biggs et al. 2000) that found that cancer worry was the driving or dominant force among women considering RRS. Some women with children felt it meant they had no choice but to have surgery to reduce the risk of their children seeing them suffer with cancer, or worse, dying from it. This was not the case for all women at increased risk with children. The desire for control also motivated some women to choose surgery. See table 4.4.9.

For some women the decision to undergo enhanced breast surveillance was an active choice and one with which they felt satisfied. For others, screening was merely accepted as an alternative as they felt they were not in a position to undergo RRS, for whatever reason. Women who actively chose screening seemed to do so to have annual (or more frequent) reassurance that they had not developed cancer, with the hope that any cancer would be caught early enough and that it would therefore be survivable. They did still appear to be looking for risk amelioration.

Table 4-4-9 Summarised justification of choice between surgery and screening

	Reasons in favour	Reasons against
Risk reducing surgery	<ul style="list-style-type: none"> Risk reduction More likely to “be there” for children Perception that it is the only option 	<ul style="list-style-type: none"> Loss of natural, sensitive breasts “if it’s not broke, don’t fix it” Too drastic Cancer may never develop Too young May affect ability to find / stay with a partner Inability to breast feed
Enhanced breast screening	<ul style="list-style-type: none"> Detects cancer early Doesn’t rule out other options Straight-forward tests that are easily tolerated Confidence in MRI efficacy Confidence in cancer treatment 	<ul style="list-style-type: none"> Anxiety waiting for results Cancer related anxiety unchanged Concern about efficacy Screening logistics (e.g. length of time waiting for scan results, claustrophobia) Doesn’t prevent cancer development If cancer develops, may not “be there” for children

4.5.1.4 Outcomes of RRS and screening

Surgery

Women following surgery describe a vast array of feelings. Elation was common in the early post-operative period, as was a feeling of loss and a reluctance to look at the chest, which for a minority persisted for years. Later on, feelings were equally mixed. Some still harboured significant cancer anxiety whilst others felt they had done everything they could and were no longer worried. The decision to undergo surgery clearly also impacts upon a woman’s family. Some found interfamilial relationships strained by their choice of risk management strategy, particularly those with siblings, cousins and children who were facing similar decisions.

The operation itself was viewed as being surprisingly straight-forward by some but as being ‘hellish’ by others. Pain, tiredness and seromas were common and a source of frustration.

Several women described feeling miserable due to the inconvenience of the longer-lasting effects limiting their ability to do things they had not anticipated being unable to do, for example driving, looking after their children or going to work.

Reconstruction had mixed long-term outcomes. Some were delighted and described their reconstructed breasts as being an improvement over the originals, with an associated increase in confidence. Others described the feeling that their breasts were not really their own. “Fancy dress” and “barrier” were words used to describe their reconstructed breasts. Those who were more positive expressed feeling more positive about their mastectomies having “come back [from theatre] with something”.

Screening

Women were frequently quite matter-of-fact about the practicalities of their screening experiences. “Just get on with it” and “it was fine” and several were very happy with the care offered. Mammography was rarely praised and was frequently referred to as being unpleasant or worse (“barbaric”, “I felt violated”). The fact that MRI screening requires cannulation was an issue for some and the claustrophobic nature of the scan machine was for a few, too unpleasant to repeat.

A few said their increased risk persisted in their thoughts. This likely reflects the tendency of women who would find this more of a problem choosing risk reducing surgery instead of screening.

Previous studies have highlighted the wait for results as a source of anxiety (Anderson J 2004, Rijnsburger, Essink-Bot et al. 2004). All women interviewed felt that the timeframe was reasonable and a few mentioned it becoming noticeably shorter. Apprehension opening the envelope was mentioned but there was not the same distress between scan and results that had been apparent in these other studies.

4.5.1.5 Decision satisfaction

Within this study although satisfaction with the decision to have surgery was high this was not mirrored in satisfaction with reconstruction, perhaps reflecting the fact that mastectomy is accompanied by reduction in cancer worry with no such effect related to the reconstruction, which is viewed more simply on the merits of its cosmetic outcome. There is also the fact that their mastectomies and reconstructions were not done in the context of a cancer diagnosis. The decision and timing was theirs and the outcome remains one based upon choice and not ameliorating the necessity of mastectomy due to cancer and a doctors' recommendations. The National Mastectomy and Breast Reconstruction Audit found that satisfaction scores were consistently higher in women who had delayed breast reconstruction than in women who had immediate reconstruction. This is in spite of the fact that, objectively, women with DBR often have a cosmetic outcome that is inferior, and is thought likely to be due to the comparison of having 'no breasts' for a period followed by DBR as opposed to going immediately from having 'my own breasts' to having IBR (Jeevan, Cromwell et al. 2014). The majority of women were satisfied with their risk management strategy. In line with previous research the various short and long-term effects of surgery and the psychological impact of increased familial risk varied which is widely in keeping with published literature [10-13].

4.5.2 Interviews with partners

Of 32 women interviewed, 29 women had partners, of whom two had not been together at the time of risk management decision making. Of the 27 who had been together at the time of RMDM, 26 women consented to their partner being invited to participate in the partners study (96%). Seven partners responded positively (27%) and all of these were partners of women who had chosen surgical management. Given the very small numbers, it is not possible to truly interpret this, but perhaps partners of women who choose screening feel less involved or feel they have less to discuss.

The overall response rate was disappointing and merits exploration. One of the few similar studies with which comparisons can be drawn, involved interviews with partners of women who had reconstruction following mastectomy (for cancer). 10 were invited, by way of a letter given to the woman during a clinical review by her breast reconstruction nurse, and 6 responded and were subsequently interviewed (Sandham and Harcourt 2007). One

difference between this study and Sandham's is that, in the latter, women were not involved in a parallel study and perhaps the single invitation to participate in research carried more weight (for women and-or partners) than one that was delivered after women had participated, as in our study. Another crucial difference is that women had been treated for cancer and perhaps partners felt more engaged or felt that they had more to comment on in interview. Another possible explanation is more mundane: the time required for interview (usually at least an hour) or the prospect of sitting discussing breasts and the emotional impact of events openly with a female researcher was off-putting and-or inconvenient for partners.

4.5.2.1 Views of partners

All partners felt that the decision on how to manage risk was one that needed to be made by the affected partner, essentially independently. They all appeared to have an opinion but were reluctant to share this in case they swayed their partner in her decision. One of the six said he would have questioned his partner if she had chosen not to have risk reducing surgery. Similarly consistent was the finding that partners did not appear to want their (affected) partner to choose to have reconstruction for their benefit.

4.5.2.2 Impact upon partners

The impact of supporting their partner through the operation and the (in some cases) lengthy recovery was significant. Access to time off and the need to use holidays from work to provide care was a frequent source of difficulty. Changes to sexual relationship were attributed to post-operative pain, tiredness and reduction in confidence after RRM. Some felt emotionally closer to their partner, having tackled the familial risk "as a team" but others felt their partner had become more distant. Watching their partner deal with the psychological impact of undergoing RRM was difficult and upsetting for some. This finding was also noted in interviews with women, where some described the difficulty of watching their partner cope with the impact of risk and their RMS, particularly surgery.

When asked about availability of support, none of the partners thought the question related to them, and most thought the care their partner had received had been very good (although with a few exceptions) and support was there if their partner needed it. A desire for a

return to normality was common and this mirrored the findings from interviews with women at risk and findings from the systematic reviews. The process of 'acceptance' was described by both Lloyd and Lodder in their studies of women at risk who had RRM. It details the stages that high risk women progress through, similar in essence to stages of grief, in order that they can 'move on' (Lloyd, Watson et al. 2000, Lodder, Frets et al. 2002). It seems, unsurprisingly, that partners of women are equally motivated to get through the process of risk management by the prospect of a return to normality. Several of the partners described simply wanting their partner alive and well, with or without breasts and with surprising ambivalence about breast reconstruction and appearance. This may reflect the nature of the sample of men prepared to participate in this study and may not be consistent with views held outwith the confines of this study. The views of and support provided by partners strongly correlates with good psychosocial outcomes in published studies (Metcalfe, Esplen et al. 2005, den Heijer, Seynaeve et al. 2012). Assessing partners views' as part of the risk management counselling process could be beneficial in providing extra support for women either without a partner or without a supportive, loving partner for whom the partner's physical and emotional health and wellbeing are more important than breasts.

4.5.3 Study limitations

Limitations of this study include the self-selected nature of the women who chose to take part in the study, introducing potential selection bias. Partner interviews were small in number and represent the group of men who were firstly, prepared to talk openly, secondly free to do so and thirdly felt they had something to say (or felt obliged to try) and it could be imagined that there are another group of partners for whom these do not apply and who have not been represented in this study for whom views may have been quite different. The partners interviewed also only represented partners of women who had chosen risk reducing surgery and it could be assumed that a broader range of experiences would have been beneficial to the study. The nature of semi-structured interviews means that, in some interviews at least, the interviewer can find themselves leading the topics and potentially inviting specific responses. Awareness of this phenomenon and the combination of two interviewers aimed to ameliorate this effect.

In order to improve partner participation in this study, were it being repeated, prospective identification of partners would be one possible solution, seeking consent at the initial visit to

contact the partner directly a year or two after the risk management decision had been taken. Another option would be to ask women who had not participated in the research study for their consent to allow direct contact with partners. This strategy would allow purposeful sampling which would address some of the weaknesses of this study. A final option would be to change the methodological technique being used: a questionnaire based on the findings on this study could be used to explore further, or observational data of home visits and appointments could be used, although sampling would again pose difficulties given the need to have consent (and contact details) provided by the affected woman.

4.6 Conclusion

Ultimately, this study has demonstrated in abundance the fact that women are individual and that they experience broadly similar care very differently. Their decisions are based on unique circumstances and a plethora of priorities, experiences and perspectives. It follows that to aid women in arriving at a decision with which they are likely to remain satisfied, it is important firstly to guide and allow them to explore these elements and secondly to fully inform them of the possible and likely outcomes from their decisions. The journey that women and their families face, particularly those choosing RRM, needs to be clearly explained, both at the time a decision is being made and throughout the process. The role of partners should not be underestimated, both as a source of support during the RMDM process and in the ensuing period of time when women and their families adapt to live with the outcomes of these decisions. Practical support for partners is likely to benefit both the partner and the woman involved and would be an interesting area for further research. The issue of taking time off work for caring duties was difficult. It is not clear if this was requested and refused by employers or that the partners felt they did not wish to ask as this is a non-traditional role for a male. Financial considerations may also have been important, especially if the woman was off work at the same time.

A greater understanding of why women choose either screening or RRS in managing increased familial risk could help in provision of more tailored information and guidance to future women faced with this dilemma. Understanding that women (and their partners) at increased familial risk are a diverse group and have differing needs is crucial.

Based on the findings of this study three key areas are identified for further research:

1. Explore the reasons women choose screening and surgery in greater depth – this is addressed in the subsequent questionnaire phase of this body of work.
2. Assess techniques for how best to guide and advise women and partners of women at high risk of familial breast cancer on risk management strategies. Ultimately this would be an area where a decision support tool could usefully be developed and evaluated to assess whether it improved decision quality and satisfaction
3. Explore options for enhancing support for women and their partners once a decision has been made and/or in the post treatment phase.
4. Providing research evidence of the support needs for these women will inform clinical practice/clinical guidelines and hopefully translate into better patient care and outcomes.

Chapter 5 will describe the process of questionnaire design and validation. This is followed by Chapter 6 which explores the findings from this phase of the study. Chapter 5 draws upon the findings of Chapters 1, 3 and 4 to direct the development of the final phase of the study.

5 Chapter five – Questionnaire design and validation

5.1 Abstract

5.1.1 Introduction

Findings from the systematic literature reviews and interviews demonstrated how women at increased familial risk are affected in many different ways by their risk and by their risk management decision. With an aim to better understand how to prepare women in future, these factors were defined and then explored in a bespoke questionnaire, which was refined and validated by a focus group before application to a group of women who had faced this type of risk management decision. The resulting questionnaires are included for reference in appendix 11.

5.1.2 Methodology

Questionnaire tools were identified and bespoke questions drafted based on information derived from systematic literature review, the interview phase of the study and from the expert reference group (ERG, comprising breast surgeons, patient representatives, geneticist, psychologist). The expert reference group expertise in questionnaire research was utilised in developing draft questionnaires, one for women who have undergone risk reducing surgery; one for those who chose screening. Reliability was introduced by exploring the same topic with more than one question. Initial face and content validity was established by piloting within the research team. A focus group was then arranged, with women at increased familial risk invited to review the questionnaires, revise the contents and assess face and content validity and acceptability. A revised version was then developed based on this feedback which was ultimately deployed on a larger group of women (reported in section 7).

5.1.3 Results

The questionnaire content, derived from the literature review and ERG discussions was designed to cover the following key themes: living at risk, risk management options, availability of support and outcomes. A mixture of dichotomous (yes/no), descriptive demographic (age, risk level, surgery type, screening type etc) and Likert type questions were used to explore effect size and to permit both simple descriptive and correlative analysis. The expert reference group made changes to content, order and wording of the

initial draft for face and content validity. The focus group made changes to these, adding construct validity, and also to the overall administration of the questionnaire, adding a letter of invitation to the process to reduce the risk of causing distress.

5.1.4 Conclusion

Two bespoke questionnaires were developed and psychometrically validated (for face and content validity) to assess the factors affecting risk management decision making in high familial risk women. The questionnaire included questions about risk perception, views of screening and surgery, experiences of screening and surgery, body image, ovarian cancer risk, relationship and sexual changes and outcomes including satisfaction.

5.2 Questionnaire study rationale

Both the systematic literature reviews and the qualitative phase of this study identified themes which were, in keeping with their methodologies, non-quantifiable. In order to better understand the phenomena raised, these themes were broadly used to design a pair of bespoke questionnaires, exploring the issues identified in both numbers affected and the extent to which the issues were felt problematic. The advantage of questionnaires in trying to better understand the issues raised in the interviews and systematic reviews include the fact that they are: (Oppenheim 1992, Sapsford 1999, Boynton and Greenhalgh 2004)

- Easy to administer
- Relatively cheap
- A recognised method for exploring attitudes and behaviours
- A method the study team have extensive experience with in quantifying findings from qualitative studies (Collins, Winslow et al. 2010, Burton, Collins et al. 2015, Morgan, Burton et al. 2015)
- Allow generalisability by virtue of the greater numbers of responders and the ability to study the statistical linkage between patient attitudes and attributes
- Ability to quantify the importance or magnitude of a phenomenon

These questionnaires were pre-piloted and refined by the expert reference group, and were then piloted by two service users. Validity and acceptability were improved by a subsequent focus group review, specifically looking at:

- Content
- Question phrasing
- Order of topics
- Questionnaire appearance

The methodological underpinnings of questionnaire design and the specifics relating to the validity and psychometrics of the present questionnaire are described below.

5.3 Questionnaire design

Using questionnaires to collect meaningful data requires the questionnaires to be designed to meet the three broad psychometric requirements of such a tool (Oppenheim 1992, Williams 2003, Boynton and Greenhalgh 2004). Questionnaires must be:

1. Reliable, i.e. they must reproducibly give the same results in the same situation
2. Valid, i.e. they measure what they aim to measure
3. Acceptable, i.e. they are not offensive, distressing, incomprehensible or too long

There are various techniques used to increase the likelihood that questionnaires will provide robust data. Use of pre-existing validated questionnaire tools, such as the various EORTC Quality of Life sub-sets, or the Hospital Anxiety and Depression Scale, or other similar tools are frequently mentioned in studies that have used questionnaires to assess the impact of various aspects relating to familial breast cancer in the past (Foster, Evans et al. 2002, Geirdal and Dahl 2008). The advantages of this include the fact that the tools are already validated for such use and that results between groups can be compared using the recognised, consistent tool. Disadvantages include the fact that the questions may feel irrelevant or may direct the questionnaire to provide only answers for some of the intended questions. Whilst there is already a range of validated tools, this is by no means comprehensive or specific for familial breast cancer.

Previous questionnaire studies of women at increased familial breast cancer risk have focussed on risk reducing surgery outcomes (Frost, Schaid et al. 2000, Hopwood, Lee et al. 2000, Bebbington Hatcher and Fallowfield 2003, Metcalfe, Esplen et al. 2004). This study uniquely adds the perspective of women undergoing breast screening for familial risk and allows comparison of views, experiences and outcomes between these two groups. The design of the questionnaire also sets it apart from other published work, in particular the use of a fully denovo questionnaire rather than the use of several existing questionnaire tools, such as the Body Image after Breast Cancer (BIBC) or Impact of Event (IES) scales. This allows areas identified in interviews of interest to be studied that have not been addressed previously, for example:

- Guilt (around the time of diagnosis, regarding children and post-operatively)
- Views of and limitations that impact upon risk management decisions
 - “I found the wait for [screening] results acceptable”

- “I found getting time off work to go to screening tests difficult”
- “I didn’t want the operation but felt I had to do it for my family’s sake”
- Experiences of risk management options
 - “I was in pain but it was bearable”
 - “Have you ever been recalled from a screening test?”

The questionnaires allow the risk management decision process to be explored, including factors outlined by the interview study that may influence women in one direction or another. The impact that these risk management decisions have (similarly including outcomes identified by interviews, for example body image, relationship changes, confidence, cancer related anxiety) are also examined. The systematic literature review of women engaged in breast screening for increased familial risk included women at near-population levels of risk. Women included in this questionnaire study will be limited to those who are at significantly increased risk, addressing some of the weaknesses of previous work. Figure 5.5.5 summarises the process of questionnaire design.

5.3.1. Initial questionnaire design

The basic questionnaire design was guided by the themes identified in the interviews (which provide an ideal source of content validity), the systematic review findings and the overarching review of literature pertaining to this topic – see table 5.5.1. The following fields were identified for inclusion:

1. Demographics including breast cancer history
 - a. To provide context to answers
2. Evidence of increased familial breast cancer risk (e.g. gene test results)
 - a. To allow subgroup analysis by risk level stratification
3. Effects of living at increased risk and risk perception
 - a. To provide context to the subsequent decision section
4. Risk management option views
5. Risk management option experiences
6. Effects of risk management choices
7. Intimate relationships

Table 5-5-1 Questionnaire topic sources - examples

Category	Topic	Source
Living at risk	Frustration with gene test	Interviews
RMS Screening	Efficacy concerns	Interviews, literature
RMS Surgery	Body image	
RMS Surgery	Sexual relationship changes	Interviews, literature
Living at risk	Insurance	Expert reference group, literature
Intimate relationships	Changes in sexual relationships	Literature, interviews

Following the premise that it is preferable to begin with non-challenging, non-sensitive questions, the first section in the questionnaire included mostly demographic questions. The more detailed questions identified for inclusion in the questionnaire were divided into relevant sections and a funnel approach (Oppenheim 1992) was used for each thereafter, starting again, with a short statement explaining the section, followed by non-sensitive questions that progressed to more in-depth questions.

Two questionnaires were designed, to reflect the fact that participants' experiences were broadly split by whether or not they had undergone risk reducing breast surgery. Initially it was hoped that participants could be guided to appropriate sections within one generic questionnaire (for example, "If you haven't had any breast surgery please move to Q 13") but the two groups (surgery and non-surgery) were so divergent that the number of instructions became overwhelming and two separate questionnaire booklets were designed, albeit with significant duplication. By removing irrelevant questions from participants' questionnaire booklets it was hoped that the length could be limited and uptake improved.

Validated tools were available to assess quality of life, body image and anxiety and depression symptoms. The following tools were initially included:

- The hospital anxiety and depression scale (Assessment 2010)

- EORTC QLQ BR23 (a tool designed to assess quality of life after breast cancer treatment) <http://groups.eortc.be/qol/>

Beyond these common areas for questionnaire focus, were very few validated questionnaire tools and none were felt appropriate for inclusion in these questionnaires. The remaining topics were therefore explored using bespoke questions with the whole questionnaire being validated during the project. A combination of closed questions, selecting from lists, Likert scales and free text boxes were used, in combinations, to allow the desired data to be collected by the novel tool, with the reasons for these choices explored below.

Closed questions were used when responses could be dichotomised to either yes or no (or equivalent). They were generally used to distinguish between experiences (for example, whether or not the participant had had a gene test) however they were also used in areas that could also have used a Likert scale, with an aim of dichotomising the responses fully. An example is:

9.2 Do you avoid looking at your breasts?

Yes	No
-----	----

Figure 5-5-1 Example of a yes-no question

Questions that intended to ascertain the degree to which participants were affected by a phenomenon were generally structured with a Likert scale response. Likert scales are an effective and commonly used way to explore degrees to which someone agrees or disagrees with a statement, and are of particular use in exploring preferences and opinions (Burns 1997, Bowling 2005). They explore one phenomenon only and care needs to be taken to ensure that all participants are able to reflect their views in the limited options available in response. The question wording must be completely unambiguous and lead the participant to reflect their view on the intended topic (Boynton and Greenhalgh 2004). There are two options for Likert scales: forced and unforced, where forced Likert responses are limited to a positive or negative response (Burns 1997).

Figure 5-5-2 Example of a forced Likert type question

4.7 Please tick the boxes below about the support you received:

Poor support / info	Not quite enough	Just enough	Good level of support / info

Unforced Likert scales include a neutral / not applicable / no opinion option. The placement of this option is further open to potential introduction of bias, with the option being placed in the middle (i.e. in between positive and negative) often resulting in a higher 'use' of the neutral option (central tendency bias) compared to when it is placed at one end (i.e. after both positive and negative) (Allen E. 2007). Where possible, a forced Likert response was used but where a neutral option was felt necessary (for example where a patient might genuinely be uncertain about an issue) it was introduced. See figures 5.5.2 and 5.5.3 for examples.

7.3 Please tick the boxes reflecting your feelings about screening below

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I feel confident that screening will identify any problems in my breast at an early stage					

Figure 5-5-3 Example of unforced Likert question

Likert scales are subject to bias and care was taken to ensure that, for similar topics, questions were framed both positively and negatively to avoid bias introduction where participants may simply agree with all (reasonable sounding) statements. Similarly, where possible, the 'neutral' option was left out to avoid the "central tendency" noted, where participants wish to avoid expressing 'extreme' views (Jamieson 2004).

Where we anticipated participants having quite differing experiences relating to a topic, it was explored with questions offering multiple answers that could be selected from a list (see figure 5.5.4). These were generated largely by exploring the qualitative data to identify possible responses, although additional responses were added by the expert reference

group, a team comprised of a breast surgeon, an expert in mixed methods health-care research, a service user, a statistician, a clinical geneticist, a clinical psychologist and research associates.

8.4 If yes, we would like to know why you want to wait. Please tick all that apply

I want to develop my career/job before considering surgery	
I want to be able to care for my children	
I want to be able to breast feed any future children	
I want to have children before considering surgery	
I want the surgery near the age at which my relatives developed cancer	
I want it when I am older so that I won't mind losing my breasts as much	
I want to be in a stable relationship before considering surgery	

Figure 5-5-4 Example of a multiple response question

Finally, being a questionnaire designed for postal administration, the expert reference group suggested it required a visually appealing front page. This was followed by a statement reiterating the nature of the study and what was required of participants. This formed the start of the questionnaire booklet. Appropriate images were purchased to make the booklet more inviting. Typeface and formatting were designed to aid participants using the tool, in line with previous experience in the expert reference group. A closing statement of thanks and a (large) free text box were added at the end for comments and thoughts.

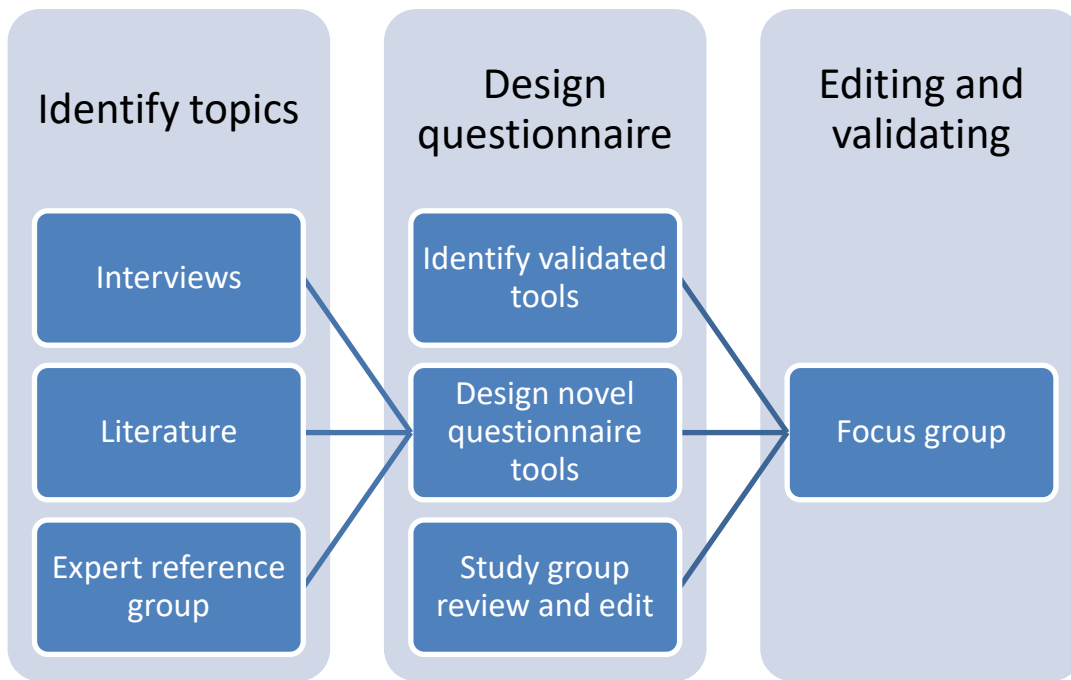


Figure 5-5-5 Questionnaire design

5.3.2. Questionnaire pre-piloting

A final draft pair of questionnaires were then sent to the expert reference group for formal review in a pre-piloting phase. Comments were addressed and the questionnaires were extensively edited. The EORTC QLQ BR23 was removed at this point as many of the questions were felt to lack relevance to this study. Comments from the expert reference group team communication are included below in table 5.5.2.

5.3.3. Questionnaire piloting

Following this the pre-piloting phase, the questionnaire was sent to two service users involved in the study, as a pilot and for further comments and was again edited on the basis of their views. Again, see table 5.5.2.

Table 5-5-2 Questionnaire development – example comments

Comments from:	Comment	Action taken
Study group member	You may want to get rid of the 1 in 100 women etc for this question - this concerns the individual women. Since some people struggle to understand percentages you may want to add some labels to the risk	Changed to nominal labels e.g. "high risk" with percentages in parentheses underneath.
Service user	Add widowed to the options for marital status	Changed
Expert reference group member	Change the wording from Strongly to Very helpful; Moderately to Helpful etc.	Changes made.
Service user	Genes that cause cancer – should be associated with, or linked to an increased risk	Changed
Service user	Should there be a box for 'non-specific / identified genetic disorder'?	Discussed with study team, decision to leave options as they stood
Service user	What if the operation also included oophorectomy, which may have had a big effect on hormones and sexual functioning – would it be useful to know here if relationships have been affected by that more than the appearance/experience of breast surgery?	Decision to put this to the focus group as a question
Expert reference group member	Question over the title of the questionnaire – should it be the title of the registered study or a 'softer' version	Decision to take this to the focus group for discussion
Study team member	Add 'shocked' and 'numb' along with an option for 'took it in my stride' as options	Paraphrased and added
Study team member	Add 'other' to options for some questions	All added

5.4 Focus group validation

5.4.1 Introduction

In order to improve questionnaire validity (face and content) and to assess acceptability of the questions and its suitability for a postal questionnaire, a focus group was arranged to review the draft questionnaires as the next step of the quantitative phase of this study. Understanding what questionnaire recipients think as they read a question and formulate their answer can demonstrate the validity of the questionnaire tool (or lack thereof). If recipients are considering the desired topic in the desired manner, the tool is likely to yield meaningful results. If recipients are confused by the wording or are distracted by a separate topic, the results are going to be much less meaningful. Focus group discussion of a novel questionnaire provides researchers with this level of understanding and allows issues that are likely to compromise results to be explored and adjusted. Overall face validity can be assessed, as can content validity. Individual question validity can be explored and changes made to improve the questionnaire psychometrics.

5.4.2 Methods

The focus group concept was not part of the original study protocol, however it was felt likely to strengthen the study considerably and so the protocol was refined with input from the study steering group. It was resubmitted for and was granted further favourable ethical review from the UK National Research Ethics Service (ref 09/H1308/121) and local research governance re-approval was obtained. Women were identified from the list of participants from the interview phase of this study. Invitation was limited to previous study participants because the focus group would require face-to-face discussion of intimate and potentially very personal issues. Interview participants had already experienced this phenomenon to some degree, whereas newcomers may have found the experience unexpectedly distressing or overwhelming.

Focus group invitation packs comprised:

- An Introductory Letter from the research study team outlining the study (again) and inviting further participation in the focus group
- A Patient Information Sheet explaining the study and the focus group component

- A Study Reply Form and consent form to indicate whether or not they wish to take part in an interview
- A FREEPOST envelope

Study packs were sent to eligible women via the post.

Inclusion Criteria

- Female
- Known to be at high risk of developing breast cancer and have attended a family history clinic to discuss this risk
- Had been offered a risk reducing mastectomy as part of their options for risk reduction (even if they subsequently chose screening)
- Able to speak and write in English
- Able to give informed consent in the opinion of their clinician

Exclusion Criteria

- Not having previously participated in the interview phase of this study
- Inability to give informed consent
- Terminally ill
- Inability to speak and write English
- Significant cognitive impairment or history of severe mental health disorder (if this was known to impact on their decision making)
- Recent cancer diagnosis (to avoid causing distress)

Women who consented to taking part in the focus group were all contacted to find convenient times to arrange a focus group meeting. The meeting day and time that allowed most women to participate was selected. The focus group took place in a dedicated meeting room within the University of Sheffield, with clear signs to the room from inside and outside the building. Informed, written consent was taken at the start of the meeting and the purpose of the study re-explained. A digital dictaphone was used to record the focus group.

Travelling expenses were reimbursed and refreshments made available. Participants were not paid for their time.

The focus group was conducted by two researchers who worked closely together and were familiar with the technique generally (Krueger 2002) and specifically within the context of this study. One (EM) facilitated the meeting, whilst the other (JH) took an observer role, however as discussion developed, her role became that of a participant. Given the small numbers involved, the facilitator was able to take notes to aide later transcription and analysis. Several copies of both questionnaires (one designed for women who have had surgery and one for women undergoing screening) were printed. Seats were arranged in a loose circle around a central table.

A meeting schedule was developed based on the questionnaires containing specific questions from the study team but without prescribing the order in which topics were discussed. This prompt sheet is included in appendix 7. The recognised technique advocated by Richard Krueger of Minnesota was used to guide the preparations for the meeting (Krueger 2002).

The focus group commenced with introductions, refreshments and a review of the study information sheet and the consent process. The questionnaires were then assessed, starting with the screening questionnaire, then moving onto the surgery version. Global comments were invited before moving onto reviewing the individual questions. Dominant participants were encouraged to expand upon their answers and quieter participants were encouraged to engage and contribute their thoughts. Areas that had been raised by the steering group on previous review of the draft questionnaires were raised at the appropriate time, going through the questionnaires, loosely from start to finish. The facilitator intervened as little as possible to encourage free discussion, guiding the topic and summarising where appropriate.

The audio-recording of the two-hour meeting was transcribed verbatim by the focus group facilitator and checked against the recording for accuracy. Notes were added where necessary to add clarity. The transcript was then analysed and points of unequivocal

agreement noted, points of discussion noted and points where the meeting had disagreed noted.

5.4.3 Results

The focus group meeting took place on Wednesday 25th May 2011 in the evening. Four (of five expected) women at increased risk of familial breast cancer attended. All four had had risk reducing surgery. Two of the four had undergone enhanced screening programmes prior to their surgery. Two women had been diagnosed with cancer and two had undergone purely risk reducing surgery. All had undergone breast reconstruction although the actual reconstructive techniques varied. The participants' ages ranged from 41-47.

A long sample of the focus group transcript is included in appendix 10. During the focus group, where participants had unanimously agreed on a point, a plan was made to change the questionnaires accordingly. Issues that had seemed contentious were discussed and where appropriate, planned changes made to the questionnaires. Where the conclusion remained unclear, issues were taken back to the study team. Examples of changes made to the questionnaire are presented below in table 5.5.3 with representative quotes.

Table 5-5-3 - Focus group example table

Change to questionnaire(s)	Quotes
<p>Question 9.6 wording changed from 'did you feel guilty?' to 'did you feel a sense of guilt?'</p>	<p>1 – I think 9.6 did you feel guilty about having your operation performed, is possibly erm, grammatically could change to 'did you feel a sense of guilt'</p> <p>E – yes</p> <p>1 – so that guilt is a terribly strong, it's not always a black and white yes I'm guilty, no I'm not, but a sense of guilt</p>
<p>Remove image of flowers from final page</p>	<p>yeah, I know it's like flowers to say thank you, but really, it also means like somebody died</p>
<p>Remove some numerical questions about risk and rephrase others</p>	<p>3 – it looks a bit daunting</p> <p>E – yeah</p> <p>4 – knowing that people sometimes freeze when they see numbers in boxes and percentages and tables and things like that maybe a bit more spread out or something</p> <p>1 – that page 6 does look very dry</p>
<p>Change from sending the questionnaire to sending a letter of invitation and then the questionnaire to those who wish to participate</p>	<p>2 – that's the other option, if it was really they could just think, oh I'm not ready, or maybe there could be some options or would the letter say, you know we would appreciate this, if you feel in any way you are not ready to do this, please don't do it</p> <p>4 – yeah, at the beginning like when you sent that out last week, that pretty much said it</p> <p>General agreement</p> <p>2 – we are aware this may not be the appropriate time for you</p> <p>Yeah</p> <p>2 – in your emotional state, or something like that, it's just not,</p> <p>1 – doesn't affect you</p> <p>General talking by everyone</p> <p>3 – maybe you could send them a letter and say would you like the pack that, er</p> <p>2 – yeah, an initial letter</p> <p>General yes</p>

	<p><i>E – yes, that’s another way of doing it, so if we have a general response that you’re happy to have a questionnaire sent to you</i></p> <p><i>2 – yeah,</i></p> <p><i>General yeah</i></p> <p><i>2 - and then you’re avoiding the people who it might upset because they didn’t know what it was they start reading it and then it affects them and they haven’t had any pre-warning</i></p>
<p>Remove Hospital Anxiety and Depression Scale</p>	<p><i>1 – section 10, could do with some qualification if it’s to remain in there, i.e. in it’s most simple way, is there anything else going on in your life that is causing you to feel the way you feel, but I’m not entirely sure that’s appropriate</i></p> <p><i>E – mmm. It’s going to be difficult to</i></p> <p><i>1 – put a list at the bottom of your relationships that have broken down recently (laughs gently)</i></p> <p><i>E – you’re thinking it perhaps doesn’t add so much?</i></p> <p><i>3 – I think you take it out</i></p>
<p>Change study title from ‘outcomes’ to ‘study of’...</p>	<p><i>1 – outcomes, I think is a very scientific word and isn’t erm, I understand exactly what it means but it seems very impersonal and if you’re asking me for my opinion because you value it, I think I would prefer you to call it something other than outcomes. I am not an outcome.</i></p> <p><i>General agreement</i></p>

5.4.4 Discussion

The participating women formed a self-selected group, being generally well informed and at ease expressing their opinions. Due to the small numbers involved, the participants’ experiences and backgrounds did not fully represent the range encountered by women at increased risk of familial breast cancer. Attempts were made to include as diverse a range of participants as possible but this was limited by which women wanted to be involved and, less so, when they were available.

The intention of holding a focus group had been to review the questionnaire from the point of view of the women who would be receiving it, looking at it both generally and specifically focussing on the individual questions. The discussion covered all of the intended topics, guided by the facilitator when necessary. The different backgrounds and experiences of the women participating led to sometimes quite different opinions being expressed (see transcript). Whilst it was necessary to occasionally steer the discussion back towards a specific question, this was not always the case and frequently these occasions led to interesting insights into the way in which questions could be interpreted by different people. This led to several questions being rephrased subsequently or different options being added to the response options. There were also questions where a Likert scale was changed to a yes-no response, based upon the feelings of the focus group.

An advantage of involving women who had been interviewed as an earlier part of the study was that they had insight into the study and the background to the questionnaires. This was most noticeable when topics were raised that had been discussed in the interviews but which had been omitted from the questionnaires, for example the impact of increased ovarian cancer risk, which applies to some but not all women at increased risk of familial breast cancer. The group (all of whom were at increased risk of ovarian cancer in addition to breast cancer) felt strongly that their answers reflected their experience holistically and that they could not attribute their experiences to breast related experiences alone. Their view was that, to add context, the questionnaire needed to know about ovarian risk and management as this was likely to impact on women's answers. During the initial questionnaire development phase, it was felt that ovarian cancer risk was a separate issue and could be reasonably left out from the questionnaire in order to reduce length. The focus group view was that it was better to have a meaningful, longer questionnaire and that they would prefer to include this section. This was an interesting finding and demonstrated participants' insight into how their experiences related to the answers they would give. This had not been as apparent in the interviews in phase one of the study and the process of discussion added significantly to our understanding of the way in which questionnaires would be answered.

The overall aim to validate the questionnaires by reviewing them with a focus group of proposed recipients was successful. The changes made to the questionnaires were a result

of improved understanding of how the questionnaires could be interpreted and how this would impact on answers. The original aim had been to hold two focus groups, one looking at the questionnaire designed for women undergoing screening, the second looking at the questionnaire designed for women who had had surgery to remove their breasts. One major weakness of the focus group was the fact that all of the participants were *BRCA1/2* mutation carriers and that all had had surgery. Whilst two had previously undergone a period of screening from choice, only one had had MRI breast screening and her decision to have surgery had been unrelated to her experiences with screening, which were generally positive. To add validity to the screening questionnaire especially, it would have been desirable to have some women without recognised gene mutations and some who were still in a screening programme. Time constraints for the project and the lack of positive responses from women engaged in screening meant that holding a further focus group was not possible.

5.5 The finalised questionnaires (see appendix 11)

The questionnaires were edited following the focus group transcript analysis to the following format:

An introduction, explaining the questionnaire and how to contact the study team

1. Background information: demographics, cancer history, breast surgery history
2. Family history: tabular history of cancers in family, genetic test details
3. Risk perception and impact: awareness of their actual risk and how it impacts on their life
4. Feelings at time of risk diagnosis: including support needs
5. Their role as an advisor for others
6. Risk management options they were offered
7. Screening experiences and views
8. Surgical views: relating to the decision to have surgery or not, timing, what was important in choosing the type of operation
9. Surgical experience (if appropriate): details of procedures, outcomes, body image, guilt, avoidance
10. Risk of ovarian cancer (if appropriate)
11. Intimate relationships: whether they have changed and how
12. Free text box for comments

5.5.1 Finalised questionnaire psychometrics

Reliability

Some issues were explored using two (or more) questions to allow assessment of internal reliability, although this was kept to a minimum as the questionnaire was already lengthy and any requirement that reduced acceptability (in terms of time required to complete the tool) was felt sufficiently deleterious as to be ultimately unhelpful.

Test-retest assessment was not possible in the pilot phase due to the limited number of participants and was not feasible in the ultimate questionnaire administration as the tool was then fully anonymised.

Validity

Face and content validity were assessed by the focus group and changes made accordingly. Images were changed to reflect the fact that familial breast cancer is not a terminal diagnosis. Questions were added to reflect the fact that an increased risk of breast cancer is often paired with an increased risk of ovarian cancer and the two interact in a complex manner, making it hard to tease apart why a response may be greater or lesser than expected without knowledge of this risk and risk modifying decisions.

Construct validity (the ability of the questionnaire to answer the questions being asked) was assessed by both the process of focus group discussion analysis and by the expert reference group and changes made to the heading titles, to the questionnaire title and to the order of questions.

There were no similar tools available to allow measurement of criterion validity.

Acceptability

The length of the questionnaire was reduced by removing the HADS tool, which was not felt to add much given the aims of the questionnaire. The title was changed in light of comments from the focus group who felt that 'outcomes' was inappropriate as we were asking them to report their own experiences which were not final outcomes but more an ongoing experience. The wording of some questions was changed to alter the focus or frame of the question to make it more acceptable. Time was taken to ensure the introductory explanatory sections sufficiently prepared participants for the following questions and to permit skipping anything that participants did not wish to answer. Due to the very personal nature of some questions, the manner in which questionnaires were administered was significantly altered to reduce the risk of distress, by first sending a letter asking for consent to send the subsequent questionnaire.

5.6 Summary

Chapter 5 has outlined the process that underpinned the questionnaire design and validation. Chapter 6 will describe the results obtained from the questionnaire phase of study. This is followed by the overarching discussion.

6 Chapter six - Questionnaire administration and analysis

6.1 Abstract

6.1.1 Introduction

The questionnaire study aimed to quantify themes identified by the interviews and to explore the impact that enhanced MRI screening had made on women making decisions on risk management. Questionnaires that were designed, refined, piloted and validated as described in chapter 6, were sent to a cohort of women, including half engaged in breast screening and half who had undergone risk reducing mastectomy for family risk.

6.1.2 Research Design

A bespoke questionnaire was designed and psychometrically evaluated and refined based on literature review, and expert reference group and a patient focus group to ensure its validity (described in section 6). Following iterative development a 2 stage invitation process was used to minimise the risk of psychological distress with an initial invitation to take part, followed by send out of the questionnaire itself to positive responders. Following ethics and R and D approval, the initial invitation to take part was sent to a cohort of women identified from regional Trust databases of women at high familial risk of breast cancer who had either been offered RRS or enhanced surveillance. Questionnaires were sent out between 2012 and 2013. Women responding positively were then sent the full validated questionnaire. Data were analysed using Microsoft Excel and SPSS Statistics.

6.1.3 Results

Of 157 women invited to participate in the questionnaire study, 51 responded favourably and were sent the full questionnaires (32%). 36 completed questionnaires were returned, 17 from women who had had risk reducing breast surgery, 19 from women undergoing breast screening for familial risk (53%). Median age of screening women was 40, (range 30-51), median age of RRM women was 47 (range 26-69). 21/36 (58%) were *BRCA* or other similar risk gene carriers. 7/36 (19%) had a personal history of cancer. All 36 (100%) were satisfied with their risk management decision, whether they elected for surgery or screening. 3/15 (20%) women who had RRM and reconstruction wished they had had a different operation (either with reconstruction or with a different form of reconstruction). Strength of feeling on discovery of risk correlated with a decision to choose RRM ($p=0.004$).

6.1.4 Conclusion

High levels of decision satisfaction were evident in all participants. A minority of those who chose surgery, if given the benefit of hindsight, would have changed their choice of procedure. Cancer related anxiety was highest in the groups undergoing screening and in those without a recognised gene mutation (compared to those who chose surgery and those with a gene mutation). Women who reacted strongly to their discovery of risk were more likely to choose risk reducing surgery. Access to support was viewed variably. Outcomes from surgery were also variable.

6.2 Introduction

As has been previously shown RMDM is complex and multifaceted with some women electing RRS and others enhanced surveillance. The psychological outcomes from this decision may vary widely with some women suffering ongoing anxiety related to perceived cancer risk and whilst awaiting results of screening tests. For others the intervention has a long term impact to reduce cancer anxiety, albeit at the cost of altered body image and potential adverse surgical outcomes. The following section has explored these issues using a bespoke validated questionnaire on a larger cohort of high risk women in a single UK health region.

The questionnaire was designed from a review of the existing literature and from semi-structured interviews with women at increased risk that guided the design of two bespoke questionnaires (section 6). The questionnaire phase of the study aimed to quantify themes identified in the interviews, establishing how common the issues discussed were in the high-risk community in a single UK health region and to look for associations between RMDM and outcomes.

6.3 Aims and objectives

The overall aim of the questionnaire was to assess the psychosocial outcomes for women living with an increased risk of developing familial breast cancer. There are many elements that the literature reviews and interviews highlighted as being of importance and for each of these areas outcomes are being measured specifically.

- Impact of personal history – e.g. of cancer or gene mutation upon RMDM
- Living at risk, especially
 - o Children and how they impact upon RMDM
 - o Risk perception (and conversely, perceived efficacy of RMS options)
- Risk management decision making and factors impacting upon this
- Screening
 - o Explore the 'wait for results anxiety' described in literature
 - o An active choice or a bridge to surgery, and why, thoughts about RMSs
- Surgery
 - o Impact upon normal activities
 - o Impact upon relationships

- How reconstruction affects outcomes

A secondary aim of the questionnaires is to gain understanding that can be used to better prepare women making risk management decisions in the future.

6.4 Study population

Women answering the questionnaires did so with a variety of backgrounds relevant to how they answered the questions. Some may have witnessed close family members dying of cancer whilst some may not. They may or may not have a personal history of breast cancer. Screening experience (mammography and or MRI) varied according to when women encountered their risk and decided upon management. Age is a key factor for some women in how they choose to manage risk as is family and these factors were included to allow comparisons to be drawn. The impact of their risk management strategy is also likely to have a significant effect on outcomes and for this reason data were collected on all of these variables. The questionnaire was piloted in a small population based in a single hospital before being sent to a larger regional cohort.

6.5 Research Design

6.5.1 Questionnaire design

See chapter 5 for more detail on the questionnaire design process.

Two questionnaires have been designed, one for women who have had risk reducing breast surgery, and one for those undergoing MRI breast screening. Initial attempts to make one questionnaire were awkward and excessively lengthy so they were divided accordingly. The questionnaires are broadly similar and are divided into sections:

- An introduction, explaining the questionnaire and how to contact the study team
- Background information: demographics, cancer history, breast surgery history
- Family history: tabular history of cancers in family, genetic test details
- Risk perception: awareness of their actual risk and how it impacts on their life
- Feelings at time of risk diagnosis: including support needs
- Their role as an advisor for other

- Risk management options they were offered
- Screening experiences and views
- Surgical views: relating to the decision to have surgery or not, timing, what was important in choosing the type of operation
- Surgical experience (if appropriate): details of procedures, outcomes, body image, guilt, avoidance
- Risk of ovarian cancer (if appropriate)
- Intimate relationships: whether they have changed and how
- Free text box for comments

6.5.2 Research governance

The study was approved by the tertiary Teaching Hospitals Research Governance Unit and was awarded Ethical Approval for the initial study and for the second round of questionnaire invitations (Abridged protocols and ethics approval letters are included in appendices 1 and 5). Further ethical consent has been granted to allow an extension of the questionnaire study to be expanded across the region based on the results from the initial study in Sheffield. Wider recruitment is ongoing and is not included in this body of work.

Local research and development approval was sought and a copy of the letter of approval is included in appendix 5.

6.5.3 Study protocol

The abridged (to avoid duplication of content) study protocol, invitation letters to participants, study information pack and consent forms are included in the appendices. Below is a summary of the questionnaire protocol.

Two questionnaires, one for screening women and one for women who have had surgery were designed using data collected in the previous linked study (semi-structured interviews, followed by focus group validation to ensure content and face validity for the patient group concerned and to ensure that the questions are unlikely to cause offense). They will be used to quantify the main issues raised by these groups of patients. The format is based on a

Likert type design to gauge the strength of agreement or disagreement with a range of statements relating to issues such as 'The preventative mastectomy has reduced your anxiety about developing breast cancer', (response options will range from strongly agree to strongly disagree).

Recruitment

The tertiary centre Familial Breast Cancer Database was utilised to select eligible patients by the chief investigator. A letter of invitation, study pack, study reply form, consent form and freepost envelope were sent out to eligible women. Women who consent to being sent the questionnaire were then sent the questionnaire along with a freepost envelope. Prior to sending an invitation, checks were made to ensure the patient was still alive.

Data Analysis

Once the questionnaire was completed, each question was analysed separately and in some cases grouped with questions which focused on a similar theme. The answers to the questions were correlated with demographic data as well as data about breast cancer risk and details about the women's chosen method of coping with her increased risk of developing breast cancer.

Data Management

All data was handled, computerised and stored in accordance with the Data Protection Act 1998. All data collected have been pseudo anonymised and databases were password protected with appropriate data security in accordance with the Data Protection Act.

6.5.3.1 Inclusion and exclusion criteria

Inclusion criteria for the questionnaire:

- Female
- Known to be at high risk of developing breast cancer and have attended a family history clinic to discuss this risk

- Have been offered or undergone risk reducing mastectomy
- Able to speak and write in English
- Able to give informed consent in the opinion of their clinician

Exclusion criteria:

- Inability to give informed consent
- Terminally ill
- Inability to speak and write English
- Significant cognitive impairment or history of severe mental health disorder (if this was known to impact on their decision making)
- Recent cancer diagnosis

6.5.3.2 Case identification

The tertiary centre database of women at increased familial risk was used to identify cases. All women included in this database had given permission to be contacted for research purposes. Women undergoing screening were identified from a departmental list of women being screened due to increased familial risk. (This has subsequently been taken over by NHSBSP.)

6.6 Recruitment

157 women were sent invitation letters, identified from the tertiary teaching hospital family history database and from the list of women undergoing screening due to increased familial risk. A power calculation, calculated retrospectively, determined that from a population of 157, 60 women were required to provide a 95% confidence level with a +/- 10% confidence interval. If the confidence interval is increased to +/- 15%, the number required reduces to 34 (Creative-Research-Systems 2017).

6.7 Data handling and statistics

Returned questionnaires were initially transcribed into a Microsoft Access database. Where appropriate, data were then transferred into both Microsoft Excel and SPSS for statistical

analyses. The majority of the questionnaire produced purely descriptive data and percentages, interquartile ranges and medians were used. The vast majority of data were categorical, with non-parametric distribution of data and statistical tests were selected accordingly. Where association between a demographic and a view were being assessed, Fisher's exact tests were used. Where comparison was drawn between, for example, screening and surgery women, Mann Whitney U test was used.

6.8 Response rate

Of the 157 women invited to the questionnaire phase of the study, 51 completed and returned the consent form required for a questionnaire to be posted (overall response rate 32.5%). As soon as a consent form was received, the relevant questionnaire was sent

36 questionnaires were returned (response rate from initial responders 70.5%, overall response rate 23%), 17 from women who had had risk reducing breast surgery and 19 from women undergoing screening due to familial risk.

6.9 Completeness of returned questionnaires

The surgery questionnaire contained 45 stem questions giving a total of 765 answers in 17 questionnaires. Of these, only 13 were left blank i.e 98.3% of questions were completed. Screening questionnaires had 34 stem questions giving a total of 646 answers in 19 questionnaires. Of these, 12 were left blank: i.e. 98.1% of questions were completed.

Where questionnaires were completed incompletely (the questionnaire instructions do allow participants to leave blank sections that are either not applicable or where the participant wishes to move on to a different topic for whatever reason), the answers that were completed were included in the analysis. Where the total number of answers is not the same as the total number of completed questionnaires, the total number for comparison is included.

6.10 Questionnaire interval consistency

Cronbach's alpha was calculated for topics that contained several questions along a similar theme. Where the same questions were asked in both the screening and surgical questionnaire, a combined score is quoted. Other areas that are specific to each questionnaire pertain only to that questionnaire – see table 6.6.1.

Cronbach's alpha scores greater than 0.7 indicate acceptable reliability. Greater than 0.8 is good and greater than 0.9 considered excellent (Kline 2000). One possible explanation for the lower result in the surgical questionnaire looking at screening views (0.596) is the choice of questions. Women were asked if they felt confident that screening would detect problems early, about interval cancer concern and about false negatives. Whilst the screening group were consistent in their feelings about the efficacy of screening, the surgical group were seemingly not and the low score for internal consistency for this group likely reflects this.

Table 6-6-1 Cronbach's alpha

Topic	Source	Cronbach's alpha
Cancer related anxiety	Combined screening and surgery questionnaires	0.871
	Screening alone	0.794
	Surgery alone	0.900
Screening efficacy	Combined screening and surgery questionnaires	0.768
	Surgery questionnaires	0.596
	Screening questionnaires	0.818
Threat of cancer as a reason for choosing surgery	Surgery questionnaires	0.846
Surgical appearance outcomes	Surgery questionnaires	0.906
Screening appearance questions	Screening questionnaires	0.728
Surgery is unnecessary	Screening questionnaires	0.871

6.11 Findings

6.11.1 Demographics

Table 6-6-2 Demographics of questionnaire participants

	Screening n=19	Surgery n=17
Age (years)	Median 40, Range 30-51	Median 47, Range 29-69
Gene mutation	6 (32%) had gene mutations <ul style="list-style-type: none"> • 1 <i>BRCA1</i> • 4 <i>BRCA2</i> • 1 unstated mutation 13 had no proven mutation (or had not been tested)	15 (88%) had gene mutations <ul style="list-style-type: none"> • 5 <i>BRCA1</i> • 9 <i>BRCA2</i> • 1 AT 2 had no proven mutation
Previous breast cancer	1 had a previous breast cancer, 18 had not	6 had a previous breast cancer, 11 had not
Partners	16 were either married or in a relationship at the time of RMDM 1 was divorced 2 were single	16 were either married or in a relationship at the time of RMDM 1 was divorced
Children	14 had children, 5 did not Children aged from 1-20 years	15 had children, 2 did not Children aged ranged from 2-48 years

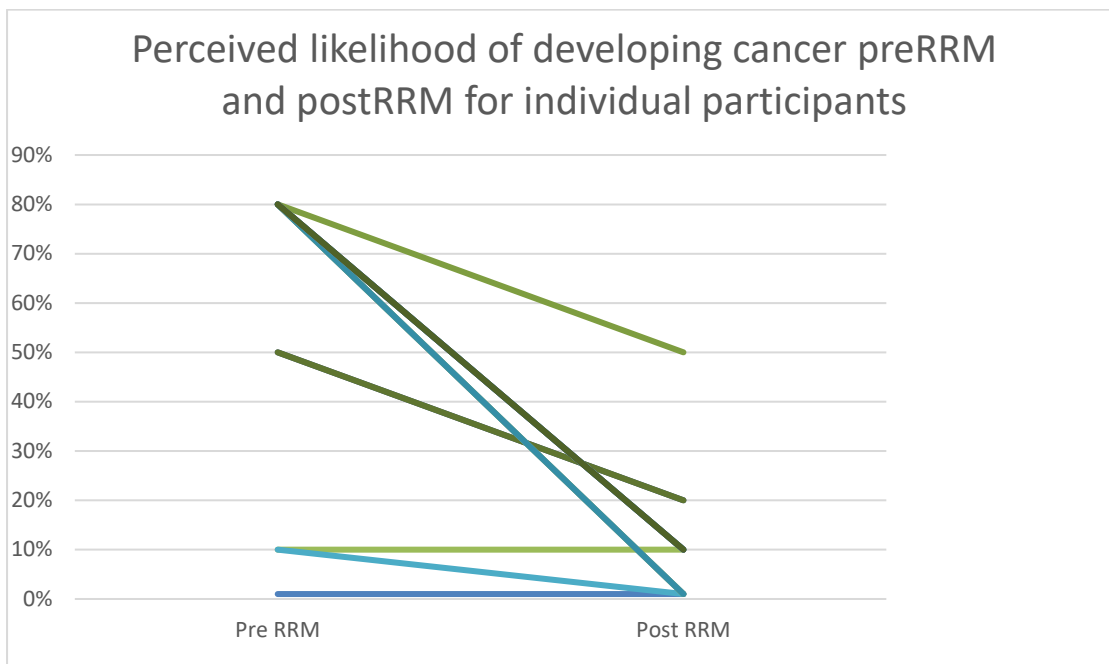
6.11.2 Risk perception

Women who had undergone risk reducing mastectomy were asked to recall their perceived risk of developing cancer from before their operation and to compare that with their perceived risk of cancer after surgery – see table 6.6.3 and figure 6.1. Interestingly, of the women who felt that their risk of cancer was 80-90% before surgery, for some it dropped to <1% post RRM, whilst others still rated it as 50%. Also interesting were the two women who felt that their risk of developing cancer was unlikely (<1%) pre-surgery and unchanged by RRM. Clearly in the main however, the perception of risk was reduced after RRM.

Table 6-6-3 Perceived cancer risk pre and post RRM

Case	Perceived risk before RRM	Perceived risk after RRM
1	<1%	<1%
2	10%	10%
3	10%	<1%
4	50%	20%
5	50%	20%
6	80-90%	<1%
7	80-90%	10%
8	80-90%	<1%
9	80-90%	10%
10	80-90%	10%
11	80-90%	50%
12	80-90%	<1%
13	80-90%	10%
14	80-90%	10%
15	80-90%	Left blank
16	80-90%	10%
17	80-90%	10%

Figure 6-1 Change in risk perception after surgery (each line represents one participant)

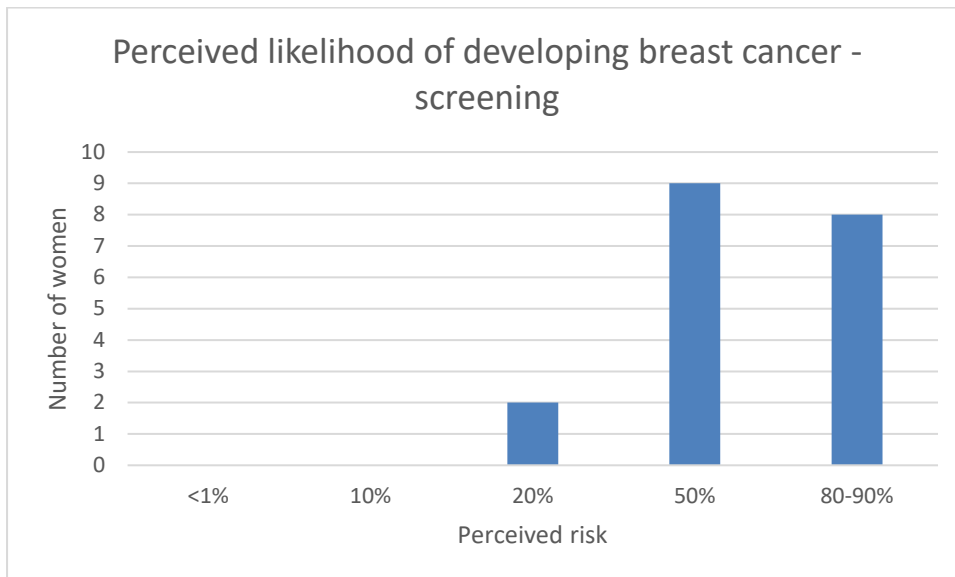


There was no significant relationship between gene positivity and pre-operative perception of risk ($p=0.34$)

Women undergoing breast screening estimated their risk of actually developing cancer as being slightly lower than those who had undergone surgery (see figure 6.2), with a median of 50% as opposed to 80-90% for the RRM group. This may reflect the fact that women in the screening group contained fewer gene mutations and will have been given risk estimates that are accordingly lower, or it may reflect a difference in risk perception or both.

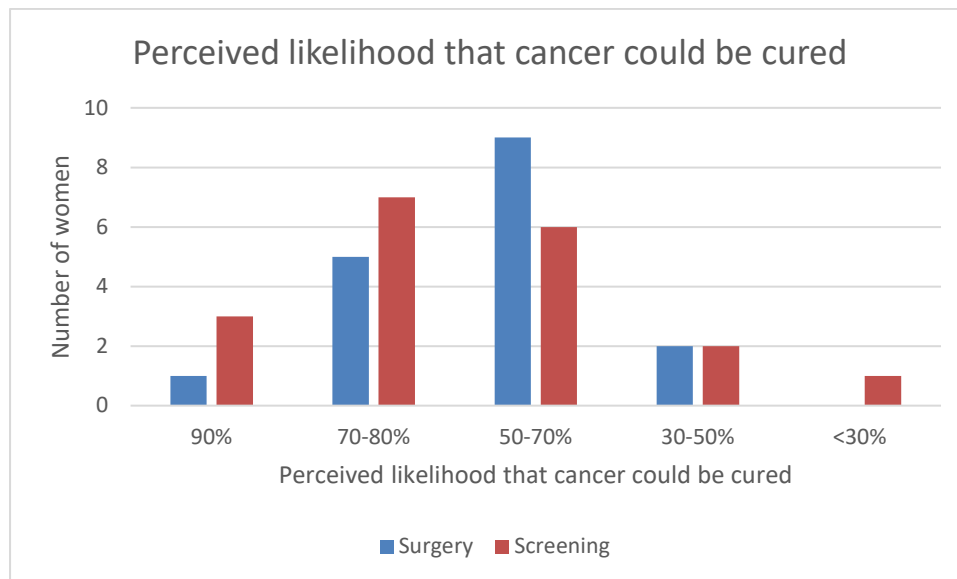
Women with a gene mutation (n=20) had a median risk perception of 80-90% (pre-surgery or screening). Women without a gene mutation had a median risk perception of 50% , which was significantly less ($p=0.027$), and probably appropriate given the information the women will have been given. Post RRM, those without a gene only numbered 2, and they both felt their risk was <1%. Post RRM those with a gene mutation had a variety of views about their ameliorated risk, between <1% to still 50%, the median was 10% ongoing risk of cancer, which is probably approximately correct.

Figure 6-2 Perceived cancer risk - screening



Given that cancer related anxiety is a frequently quoted reason that women choose risk reducing surgery, women were also asked to indicate how likely they thought they would be to survive cancer if it did develop, see figure 6.3.

Figure 6-3 Perceived cancer cure



No significant difference was apparent in perception of cancer cure between women who chose screening and those who chose surgery ($p=0.34$). Women with a gene mutation were slightly more optimistic about the chances of cancer being cured, with a median “likely to be cured” 70-80% chance of cure (range “very likely” 90% to “low chance of cure” 35-50%) than those without a gene mutation, for whom the median was “moderate chance of cure” 50-70% (range from “very likely” to “unlikely to be cured” <30% chance), this was not statistically significant. To give context the median 5 year survival for a woman with breast cancer in the UK is presently ~70-80% so most of these women had been accurately advised and retained this knowledge well.

6.11.3 Effects of living at risk

Cancer related anxiety was assessed asking women to focus on how they had felt over the week prior to completing the questionnaire. Screening and surgery findings largely mirrored each other (see figures 6.4 and 6.5), with few women in either group finding cancer related anxiety interfered with daily activities but with a third of both groups finding the frequency that they worried about cancer being somewhat or a lot (as opposed to a little or not a lot). There was no significant difference in the reported cancer related anxiety between surgery and screening groups ($p=0.174$) – see figure 6.6. Women with gene mutations and without gene mutations were also broadly similar, with no statistically significant differences ($p=0.226$) but a trend towards higher reported anxiety apparent in the data (see figures 6.7, 6.8 and 6.9).

Figure 6-4 Cancer related anxiety RRM

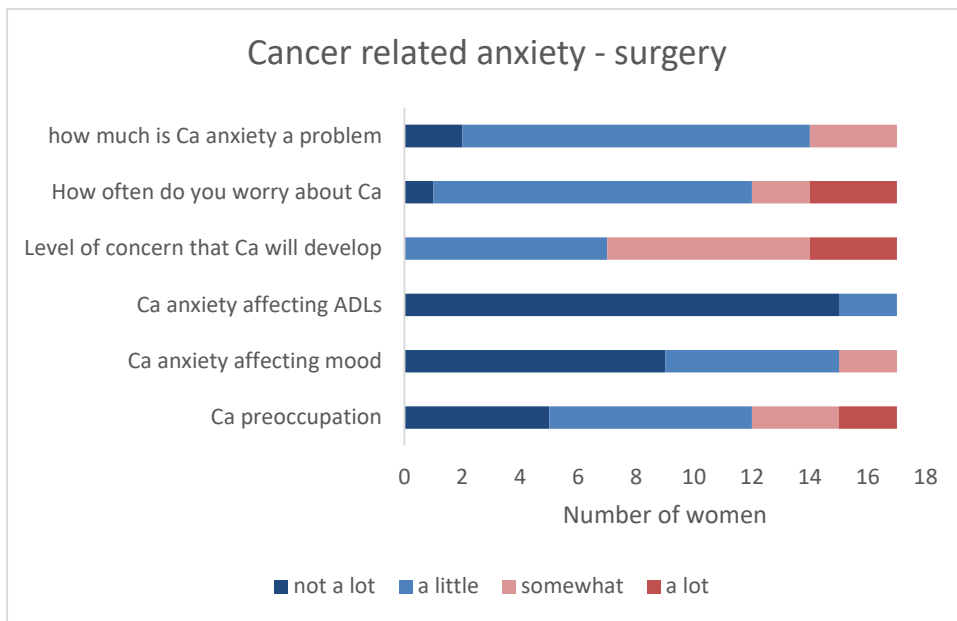


Figure 6-5 Cancer related anxiety - screening

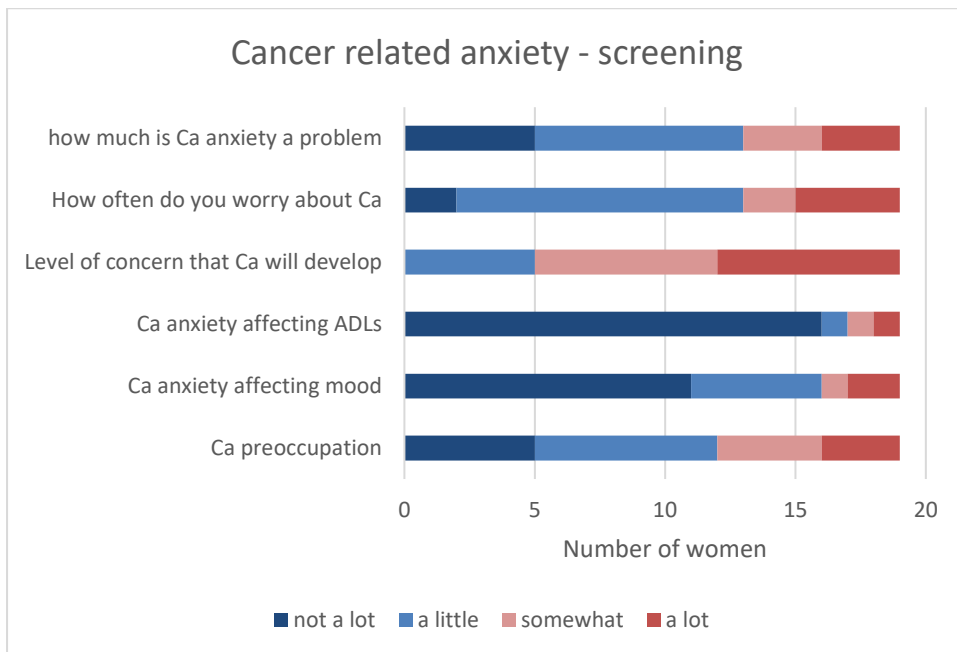


Figure 6-6 Comparison of Cancer related anxiety screening and surgery

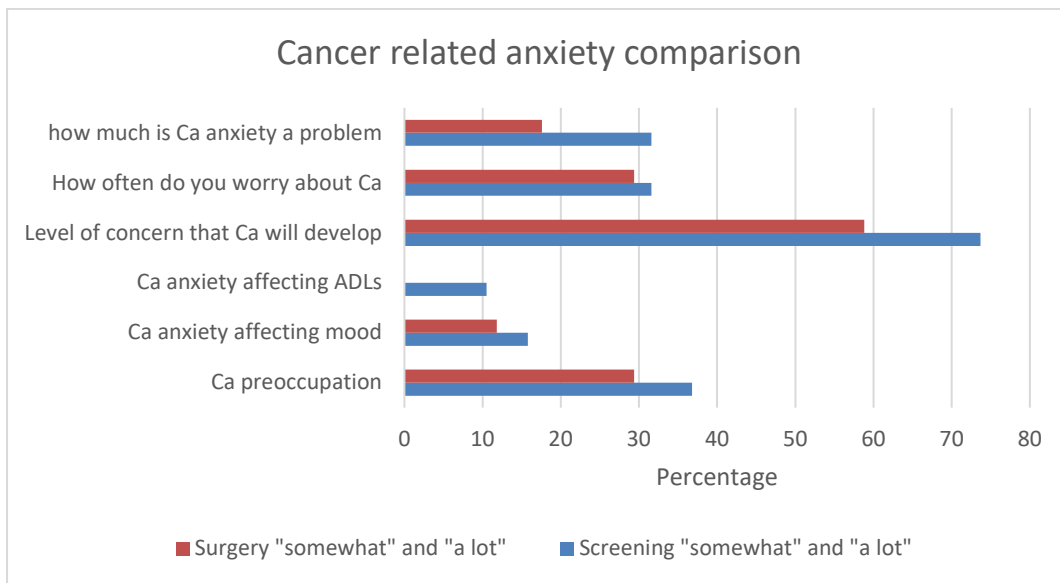


Figure 6-7 Cancer related anxiety – no known gene

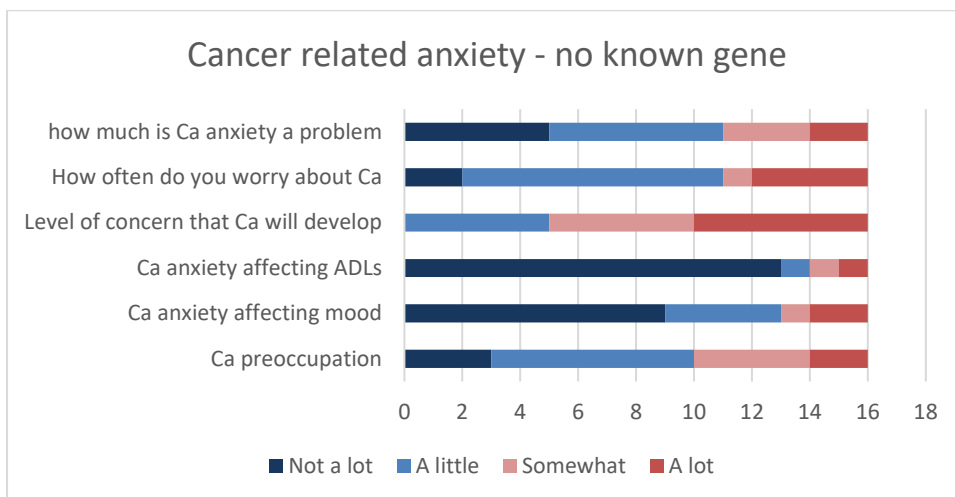


Figure 6-8 Cancer related anxiety - gene positive

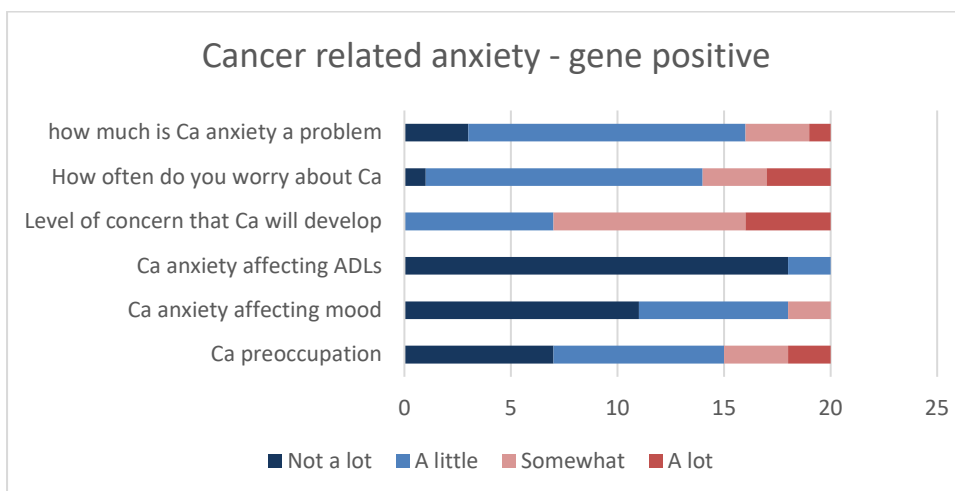
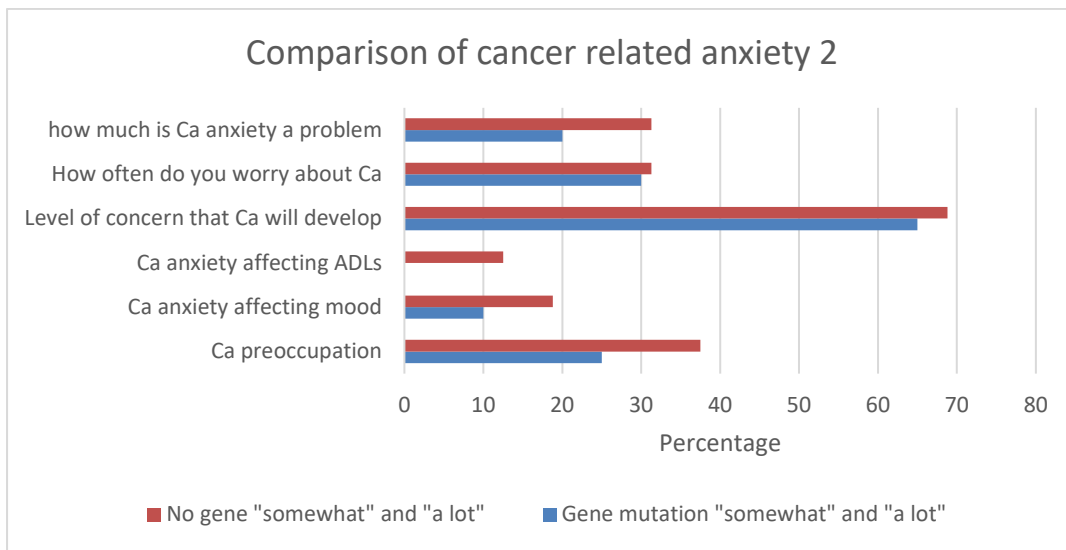


Figure 6-9 Comparison of cancer related anxiety gene and no gene



Where the groups diverge more were the recalled reactions to discovering their risk, see figures 6.10 to 6.15. A greater proportion of the surgery group recalled strong feelings of fear, panic, shock etc. than the women who went on to choose screening ($p=0.004$). Similarly, the women with positive gene tests described stronger feelings ($p=0.0001$). This strength of feeling, which did not manifest in the questions about cancer related anxiety is a possible factor leading some women to choose surgery over screening. In all groups, some feelings seemed more common than others:

- Guilt (that they might pass on their risk to their children)
- Fear
- Lack of control
- Upset
- Need for information

Figure 6-10 Risk discovery (surgery)

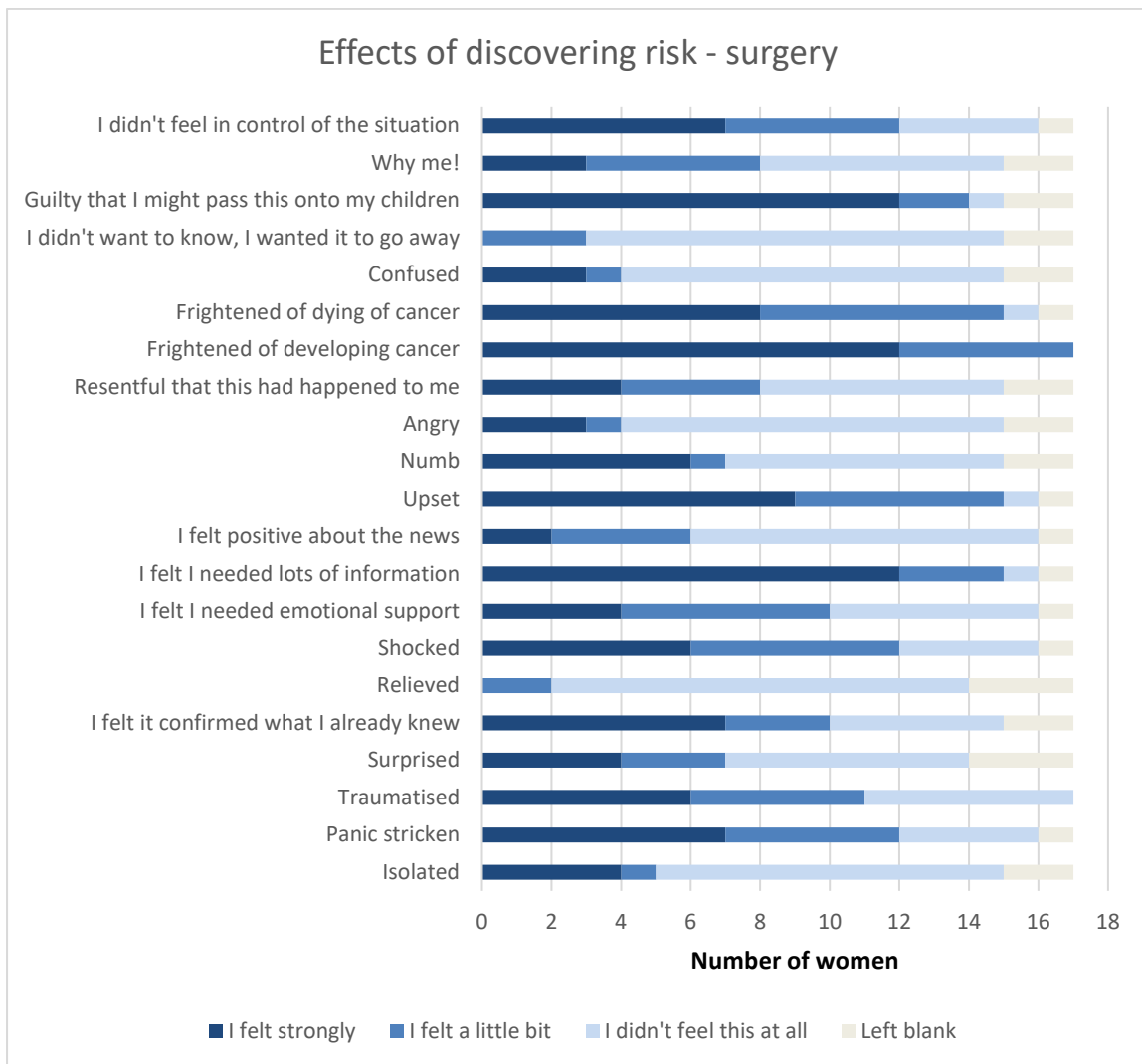


Figure 6-11 I felt it: Surgery vs screening (Numbers = questions in 6.12)

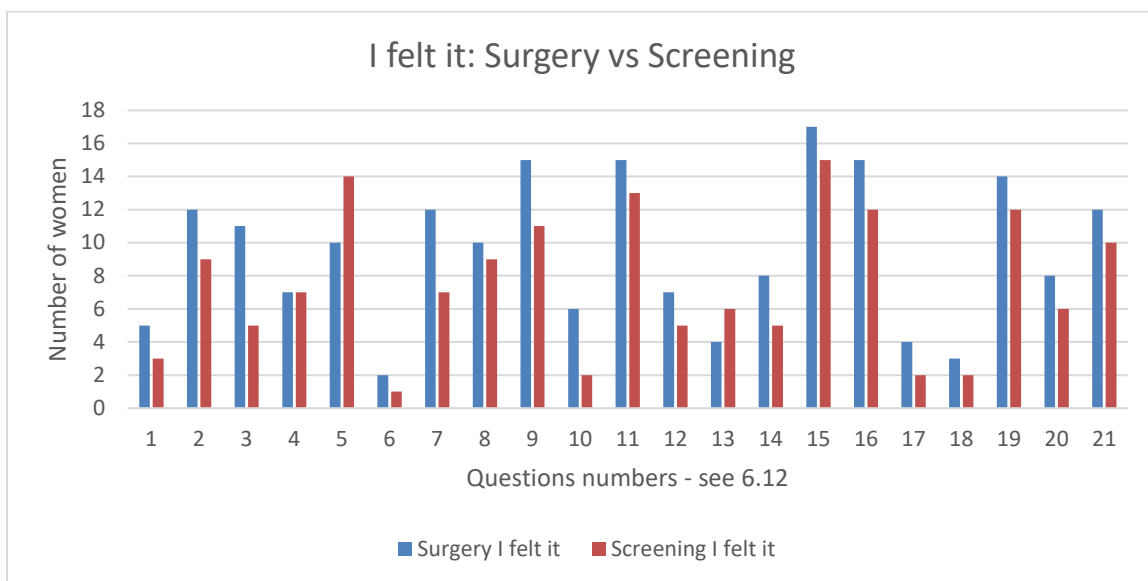


Figure 6-12 Risk discovery (screening)

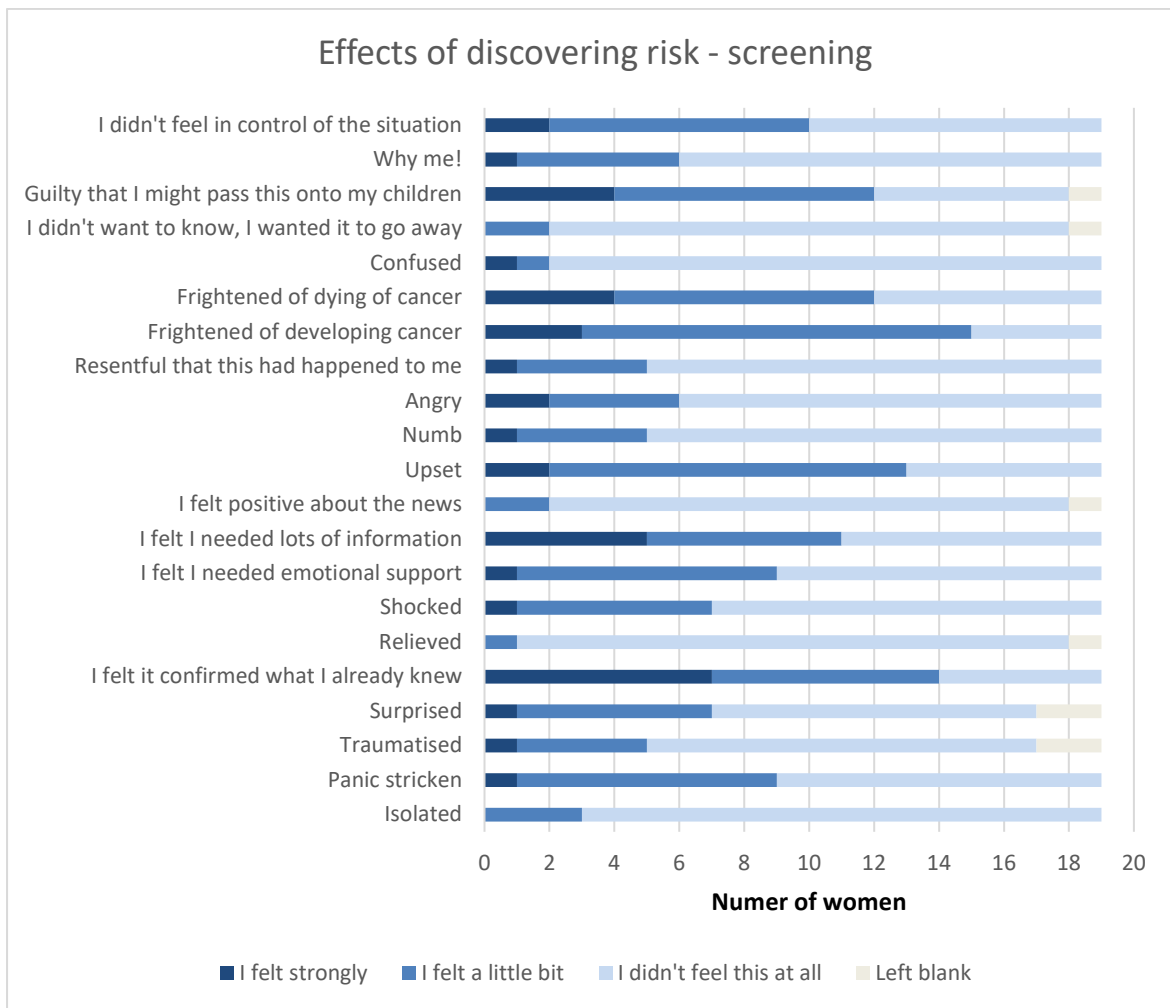


Figure 6-13 Effect of discovering risk - gene positive

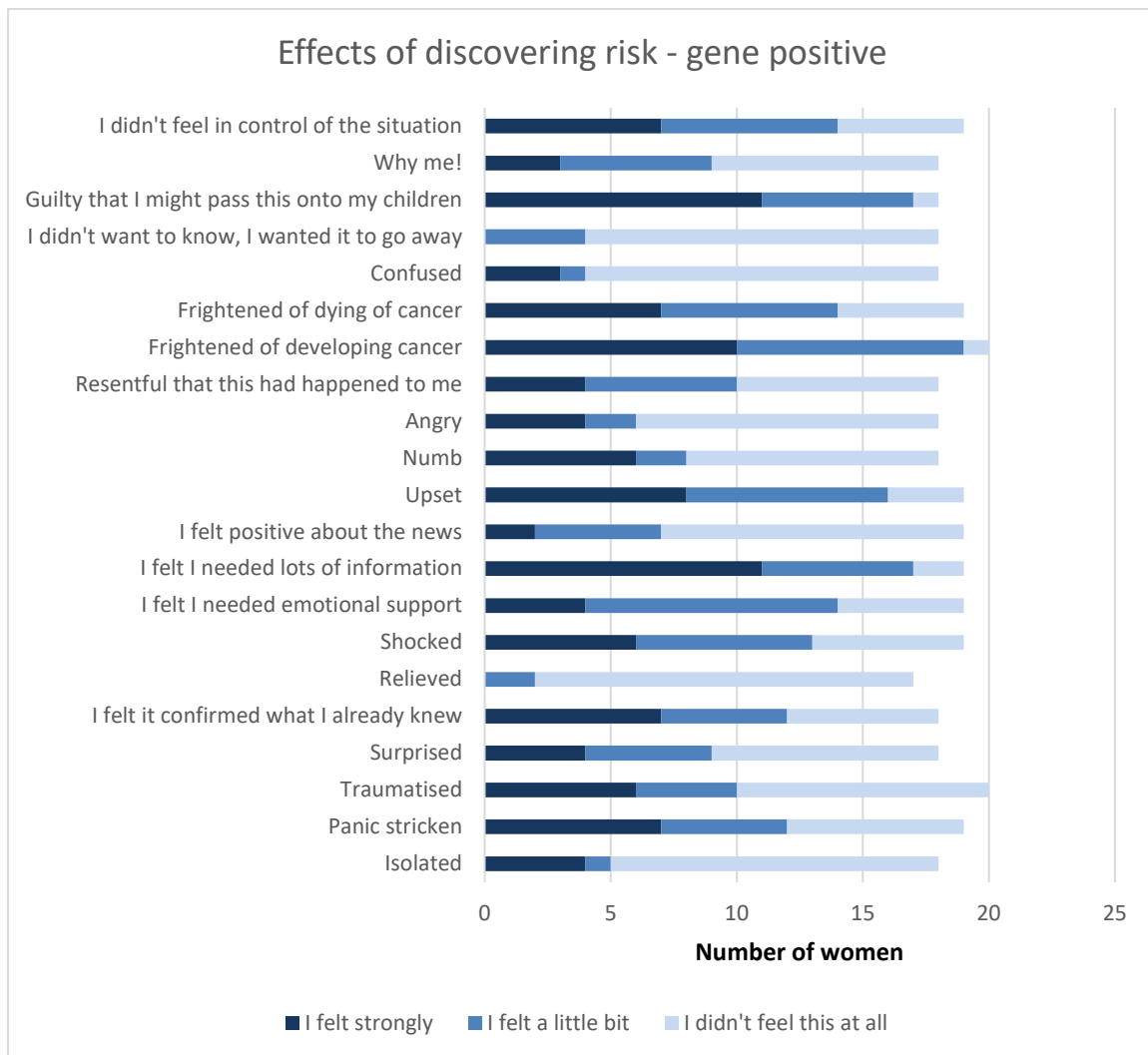


Figure 6-14 I felt it: Gene positive vs No gene (Numbers = the questions in 6.15)

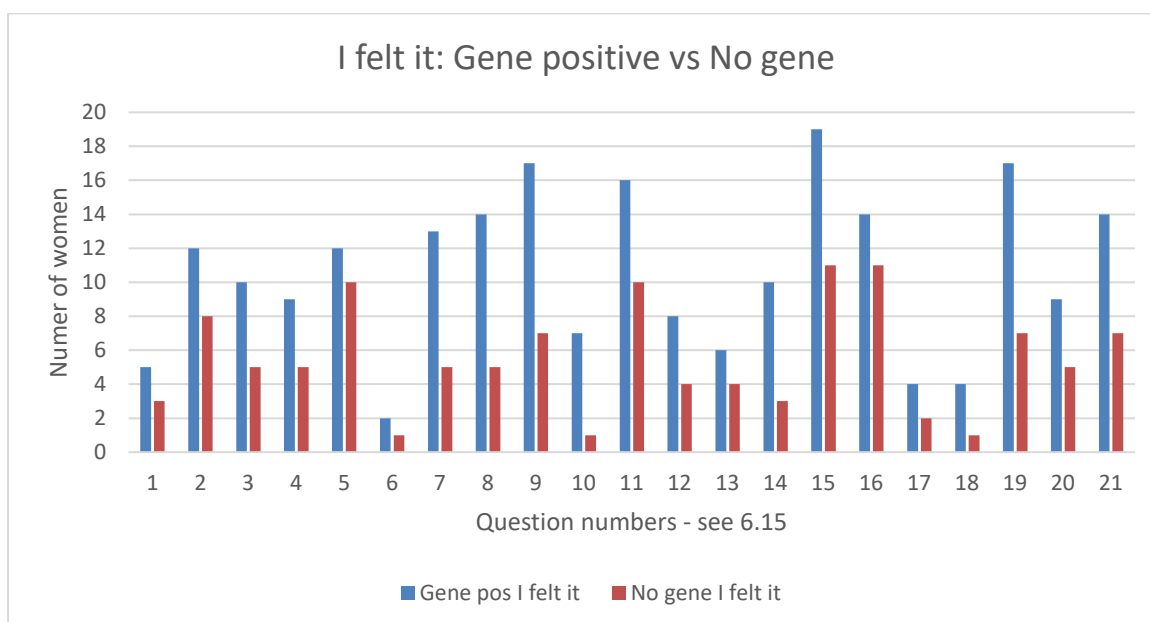
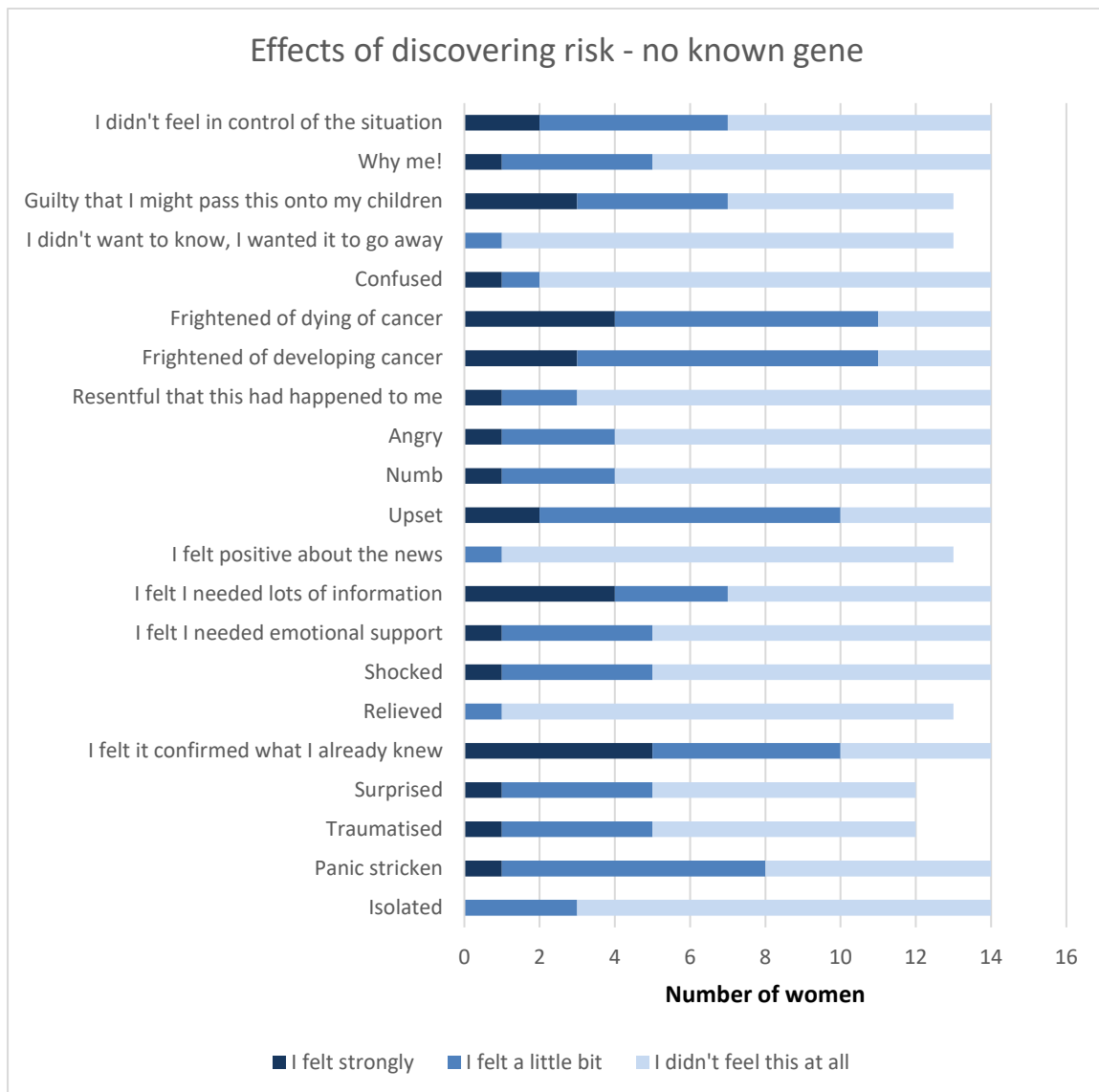


Figure 6-15 Effect of discovering risk – no known gene



6.11.4 Sources of support

Sources of support differed between women who chose surgery and those who opted for screening, see table 6.6.19.

Table 6-6-4 Main sources of support

Surgery	Screening	Gene positive	No known gene
Clinic doctors (100%)	Family (78.9%)	Genetic nurses (95%)	Family (81.3%)
Genetic nurses and clinic nurses (94.1%)	Nurses in clinic (73.7%)	Clinic doctors (95%)	Clinic nurses (75%)
Partners (82.4%)	Partners (57.9%)	Clinic nurses (94.7%)	Friends (60%)
Family (70.6%)	Genetic nurses and clinic doctors, leaflets and friends (all 52.6%)	Partners (85%)	GP (56.3%)

The main outlier in the 'support' analysis are the women without a gene mutation, who seemed to derive little support from healthcare professionals (the exception being clinic nurses) in comparison to the other groups (see figures 6.16 and 6.17).

The role that nurses, both in genetic clinics and in breast clinics play in providing support should not be underestimated, similarly the role that partners and family play in providing support around the time of risk management decision making is clearly significant to women. Written information, be it leaflets, online or in books, was not regarded as very helpful by many. Whether this reflects the quality of information available or the way in which women interact with it cannot be determined from these data, but would be an interesting area for further research, especially as there are already studies looking to develop written material to help women reach a decision with which they are satisfied.

Figure 6-16 Sources of support (surgery)

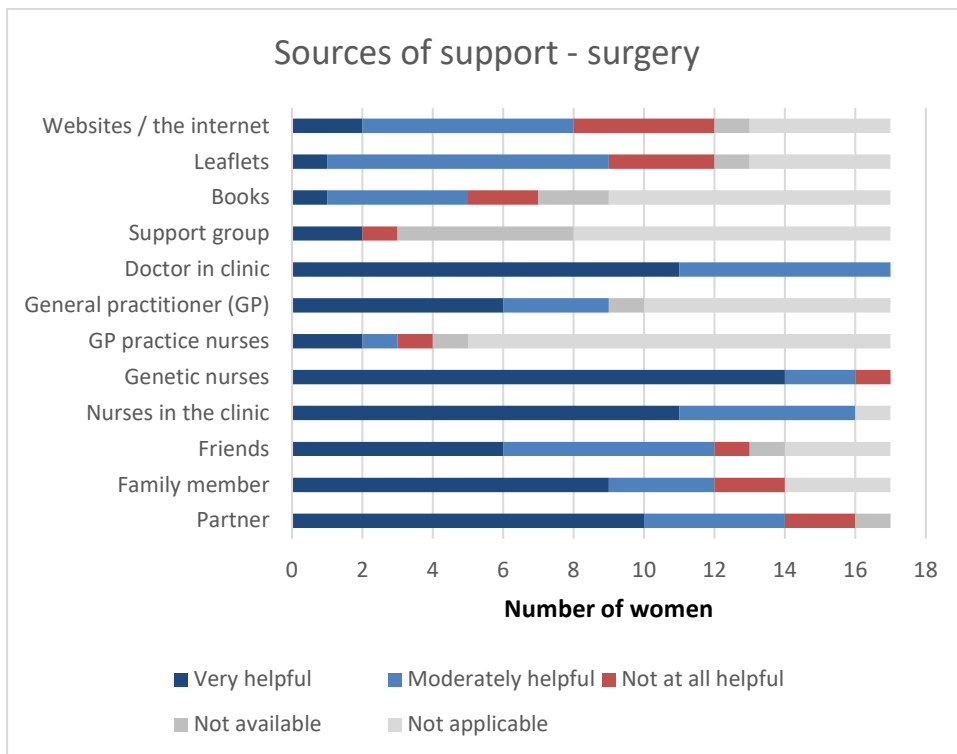
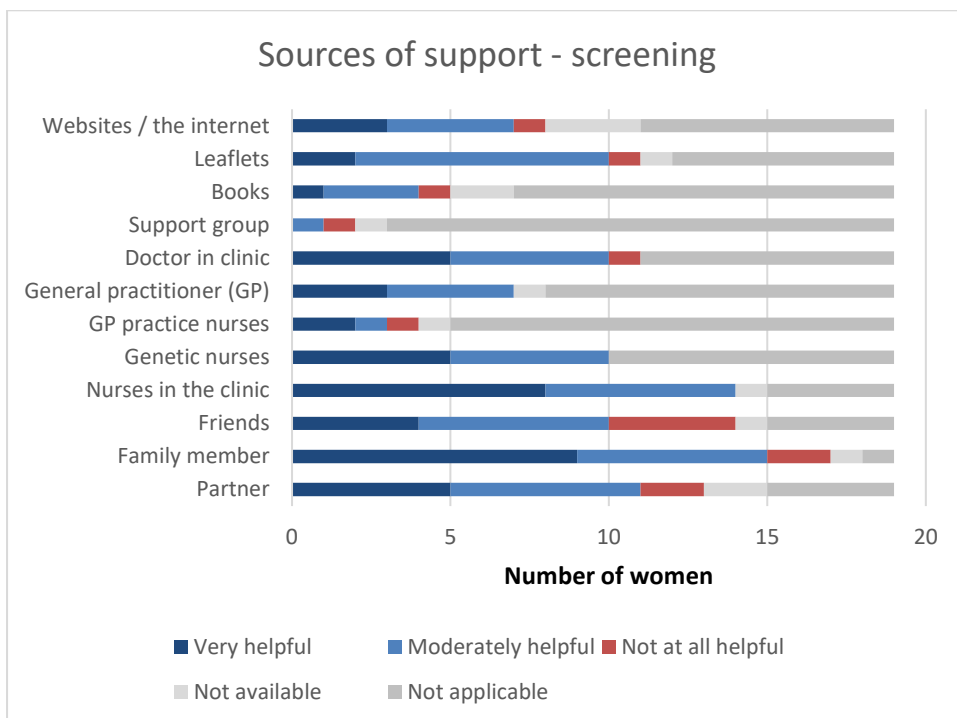


Figure 6-17 Sources of support (screening)



2 of the 17 women who had surgery had contact with support groups, with 10 of the remaining 15 expressing a desire to have access to a support group – see table 6.6.22. In the

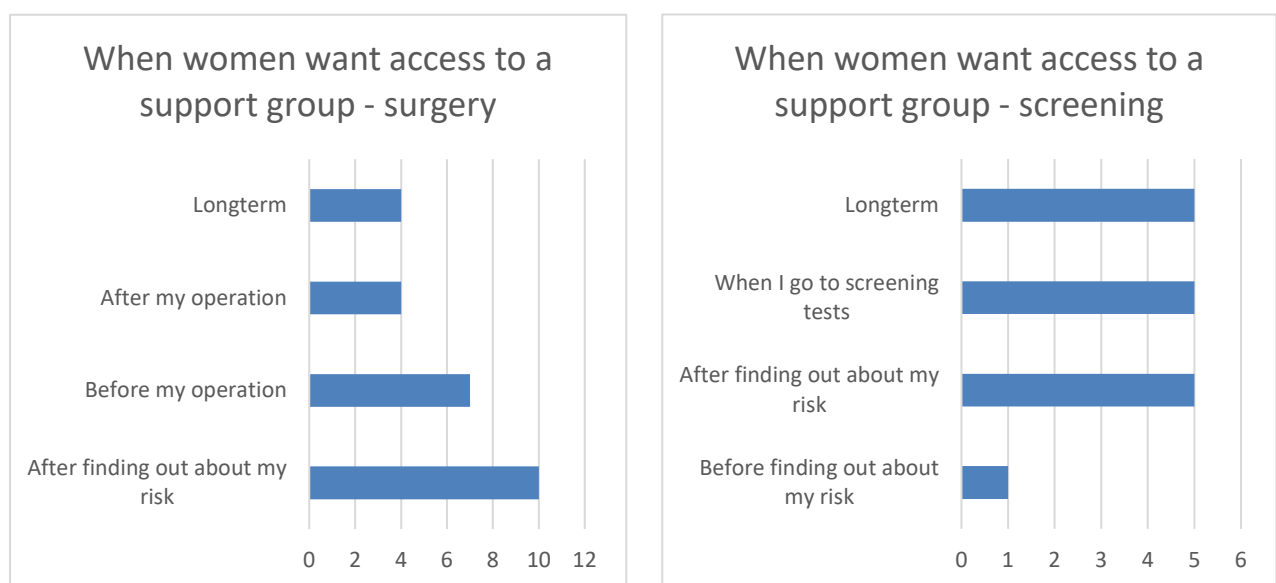
screening group, 1/19 had contact with a support group, with 6 of the remaining 18 wanting to have had access. 5 of 16 women without a gene mutation wanted access to a support group, whereas 13 of 20 with a gene mutation wanted support group access. In short, women with a gene mutation and those who chose surgery had a greater (unmet) demand for support groups, with a significant minority not wanting to engage in this facility.

Table 6-6-5 Demand for support groups

	All women n=36	Surgery n=17	Screening n=19	Gene positive n=21	No known gene n=15
Had SG access	8.3%	11.8%	5.3%	15%	0%
Wanted SG access but did not find it	44.5%	58.8%	31.6%	55%	31.3%
Did not want SG access	47.2%	29.4%	63.1%	35%	68.7%

Women who had undergone surgery preferred to have access to a support group upfront when they were making decisions about surgery and going through the process of surgery, perhaps unsurprisingly. Women in a screening programme appeared to want support group access in the long-term, likely reflecting their ongoing risk. See figure 6.18.

Figure 6-18 Support group timing



When asked about their views on the support available in the surgical group, most women felt there was either good support or just enough (80% of all participants expressing an opinion) – see figure 6.19. When this is examined in more depth, the provision of support pre-op was generally felt to be better (86.7% good or just enough) than that available post operation (73% good or just enough). 93% of the screening group felt that support available was good or just enough (see figure 6.20). 82.4% of women with a gene mutation and 91.7% of women without thought support was good or just enough (see figure 6.21).

Figure 6-19 Provision of support around surgery

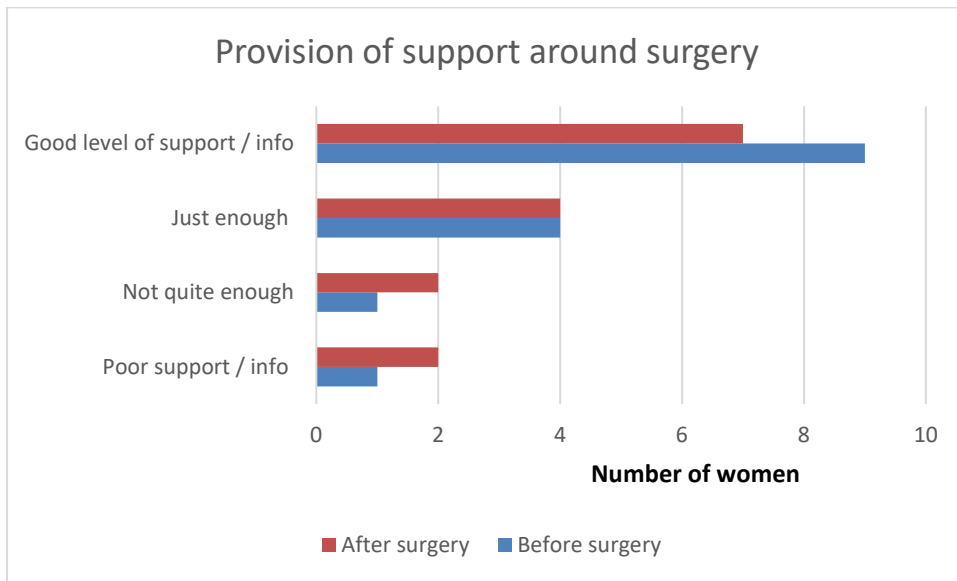


Figure 6-20 Provision of support for screening women

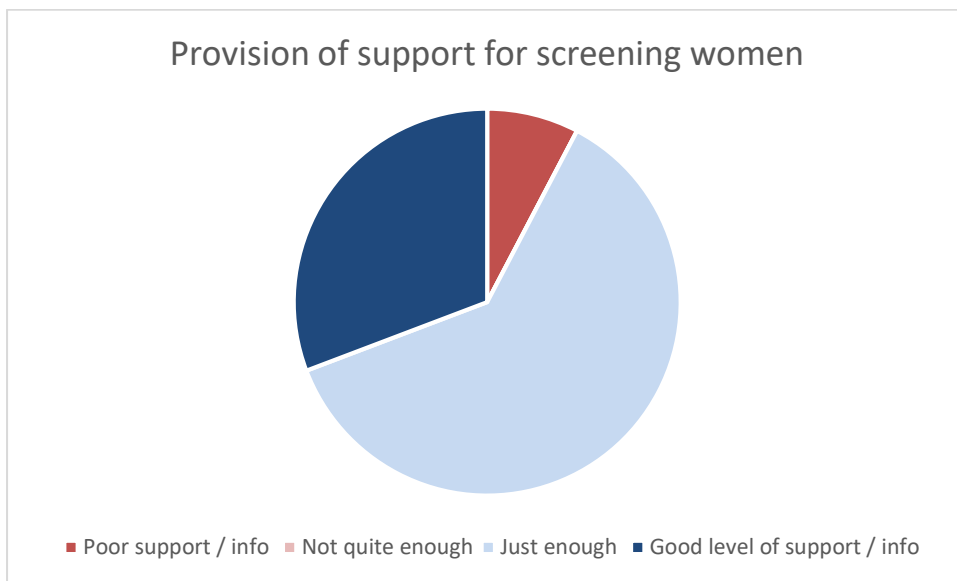
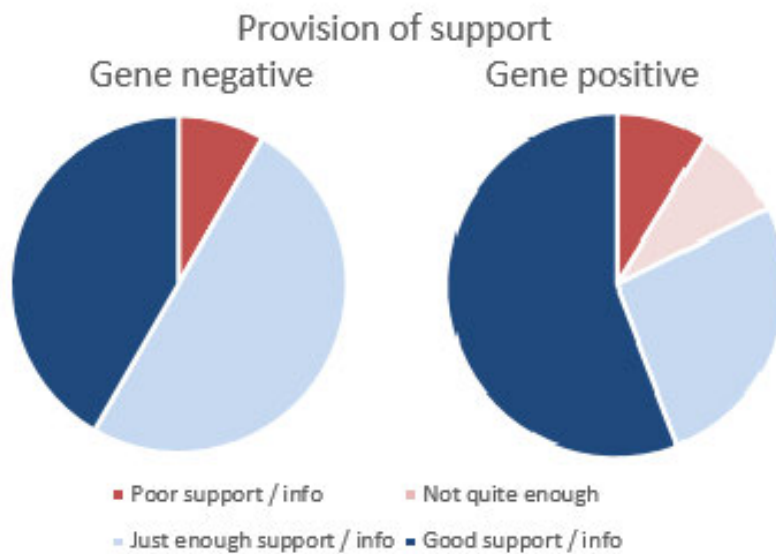


Figure 6-21 Provision of support - gene status



With a proportion of women in the interviews describing the supportive role of family and friends, the questionnaire included questions about how comfortable women felt discussing their risk with other people – see figures 6.22 and 6.23. The overwhelming majority of both groups feel comfortable discussing their risk. A small number in both groups preferred not to or did not discuss their risk at all. Notably, discussing risk with children had a greater proportion of women preferring to avoid discussion (34%) although there was no significant difference between those in the surgical or screening groups ($p=0.46$) and with similarly mixed results in the gene and no gene groups.

Figure 6-22 Comfort discussing risk - surgery

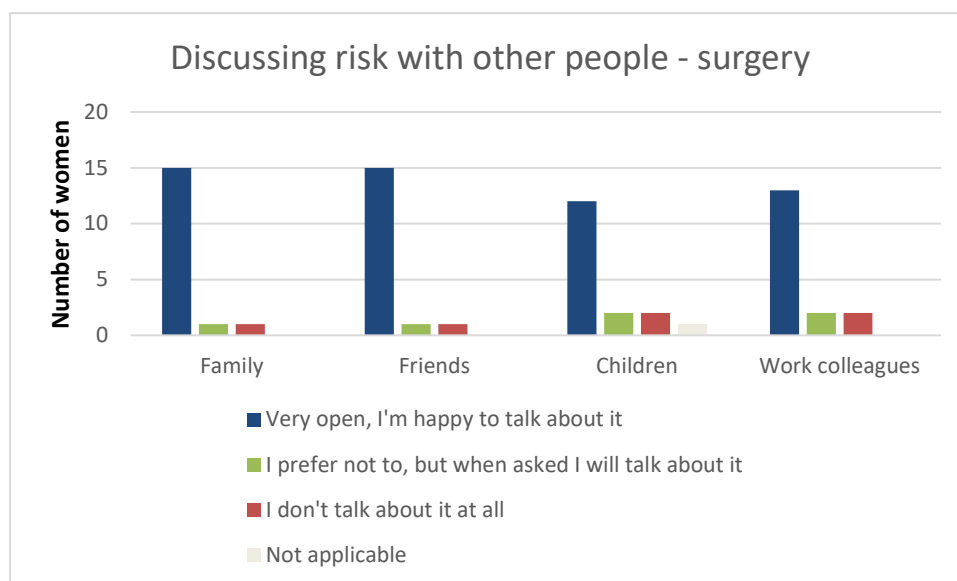
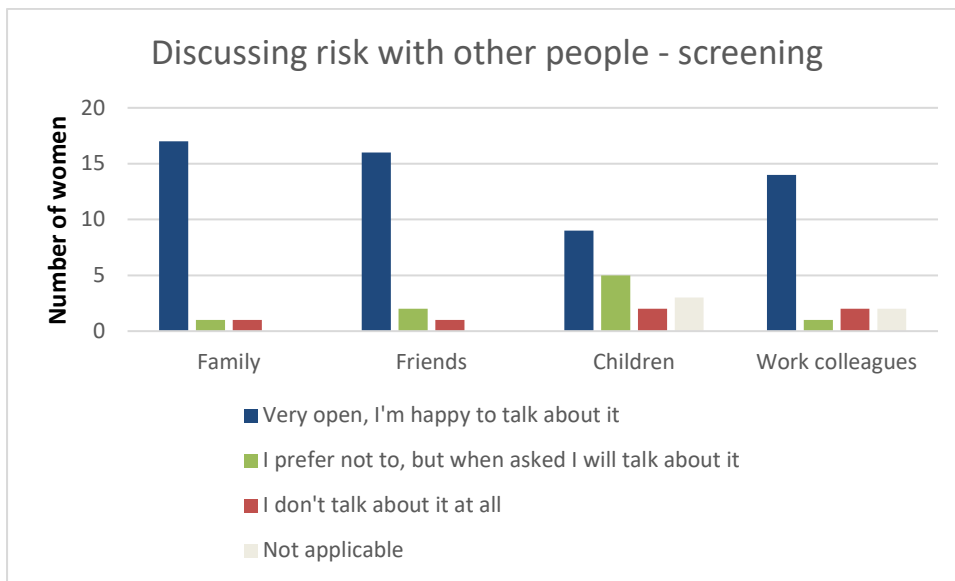
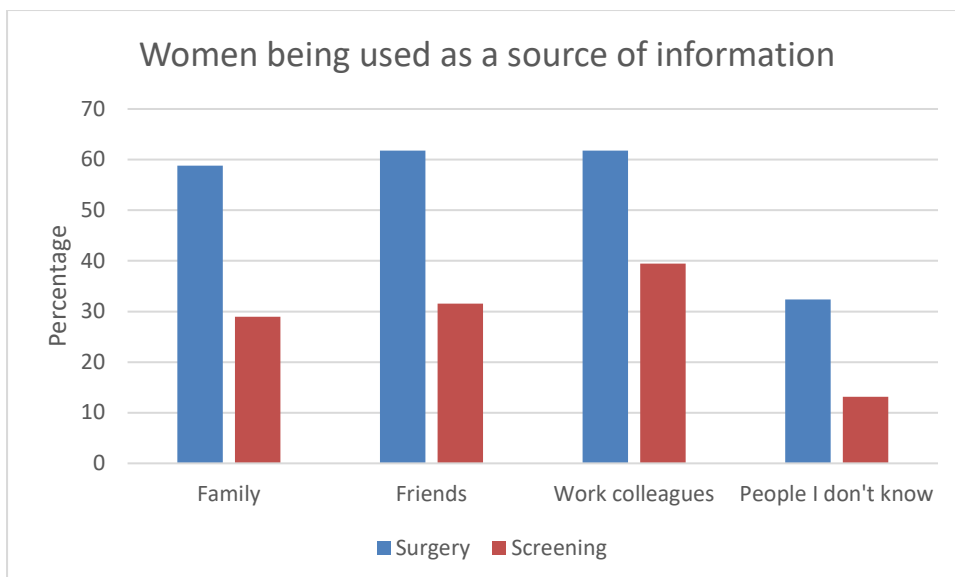


Figure 6-23 Comfort discussing risk - screening



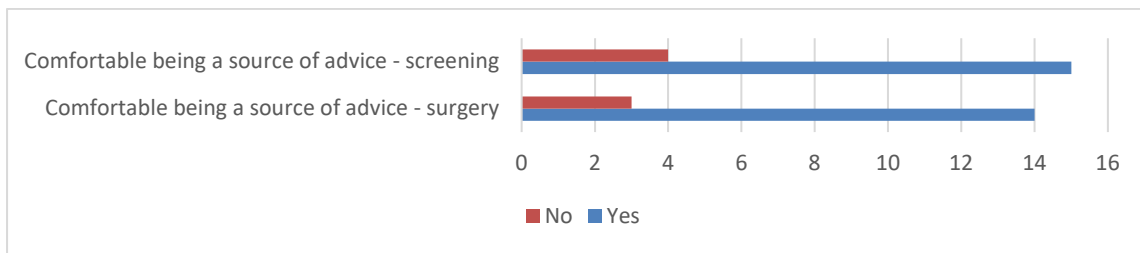
Women known to be at increased risk are frequently used as a source of information about both familial risk and breast cancer in general, from family and friends to strangers, with no significant difference ($p=0.81$) between the surgical and screening groups in terms of women's views about this phenomenon – see figure 6.24.

Figure 6-24 Women as a source of info for others



Women were asked if they felt comfortable being used as a source of information for others. 81% were comfortable with no difference between surgery and screening women (see figure 6.25), 75% of gene positive and gene negative women also felt comfortable as advisors of others.

Figure 6-25 Views of being a source of info for others

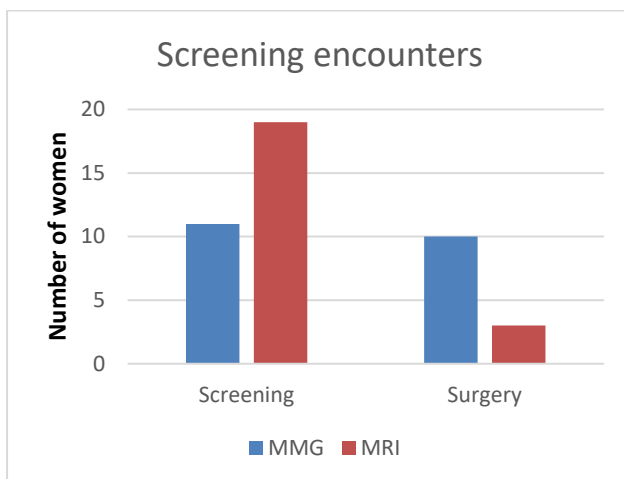


6.11.5 Risk management decision

Screening

Views and experiences were obtained about screening and surgery with an aim to better understand the risk management decision process.

Figure 6-26 Previous screening encounters



Clearly the women undergoing screening as their choice in risk management strategy have had greater exposure to screening encounters – see figure 6.26. Their experience with MRI in particular, is vastly different (x6 greater) to that of the surgical group.

Perhaps unsurprisingly, the women who chose surgery expressed greater concern about the possibility that screening could miss cancer (66.67% vs 42.1%) or that interval cancers could develop (84.6% vs 47.1%) (non-significant findings $p=0.43$) (see figures 6.27 and 6.28). The screening group appeared to be more optimistic about the likelihood that any cancer detected would be at an early stage than the surgical group, although again, this was not a significant difference ($p=0.13$).

Figure 6-27 Views of screening and tabulated key

Table 7-29 Key to table

K	I found getting time off work to go for screening difficult
J	I found the time required for screening tests to be problematic
I	I found the screening tests inconvenient
H	I found the screening tests painful
G	I found the screening tests acceptable
F	I found the wait for results acceptable
E	I felt anxious when waiting for screening results
D	I felt anxious when attending for screening tests
C	I worried that screening might miss something
B	I worried that cancer might develop in the time between screening tests
A	I felt confident that screening will identify any problems in my breast at an early stage

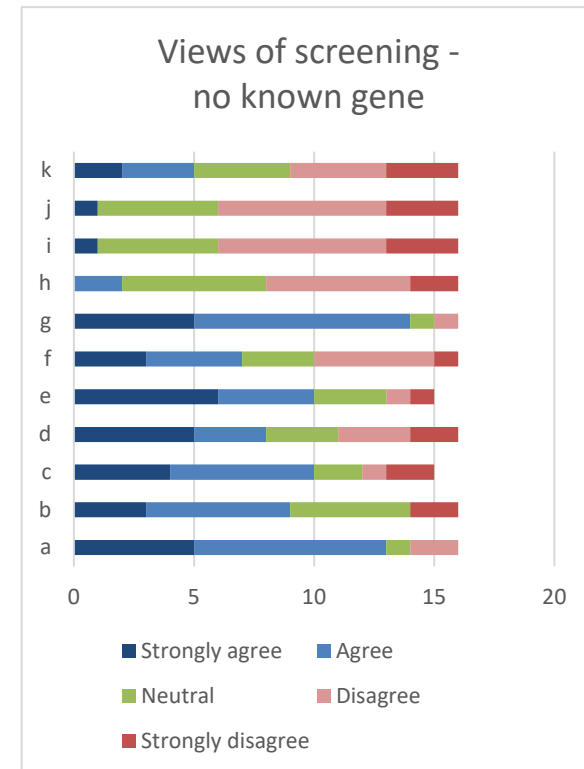
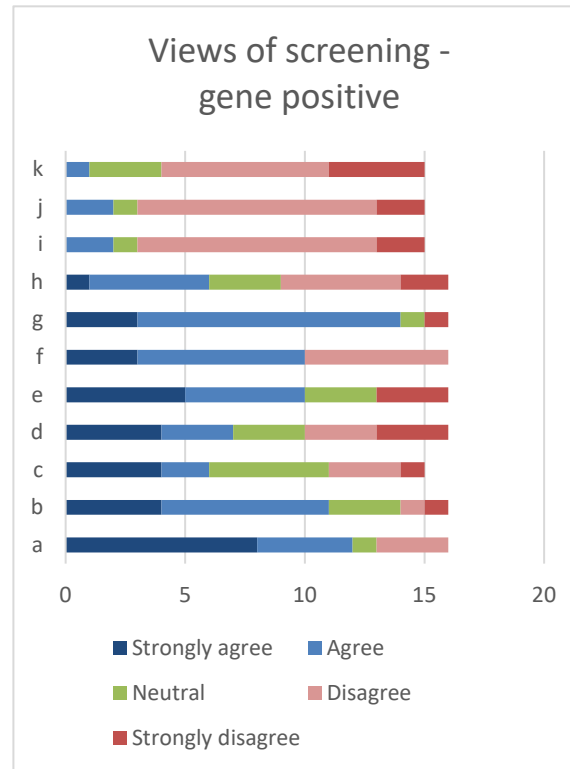
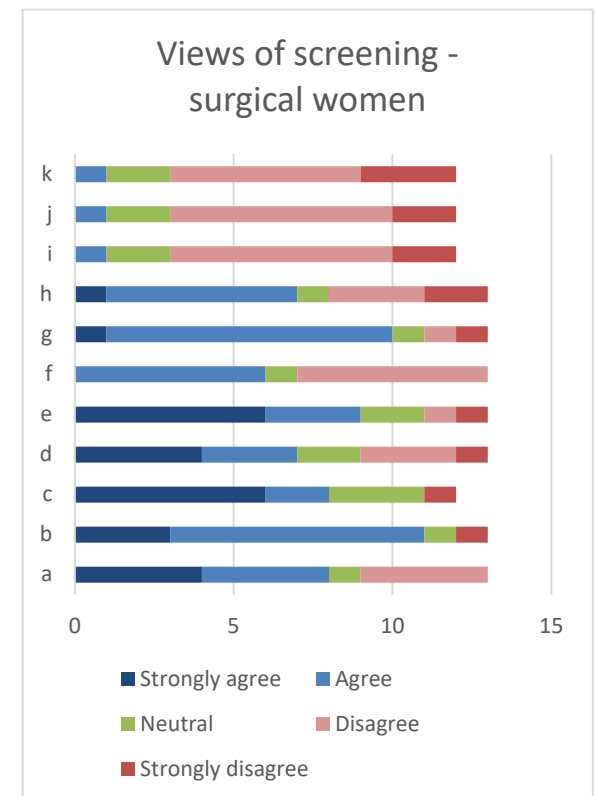
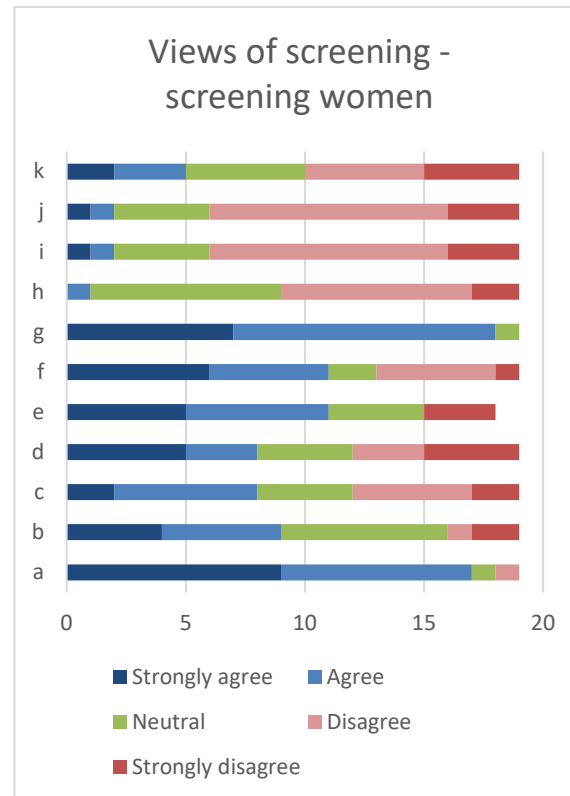


Figure 6-28 Views of screening and tabulated key

Table 7-29 Key to table

K	I found getting time off work to go for screening difficult
J	I found the time required for screening tests to be problematic
I	I found the screening tests inconvenient
H	I found the screening tests painful
G	I found the screening tests acceptable
F	I found the wait for results acceptable
E	I felt anxious when waiting for screening results
D	I felt anxious when attending for screening tests
C	I worried that screening might miss something
B	I worried that cancer might develop in the time between screening tests
A	I felt confident that screening will identify any problems in my breast at an early stage



2 of 16 (12.5%) women who had risk reducing surgery experienced a recall during screening before having their surgery. 4 of 19 (21%) women engaged in a screening programme at the time of the questionnaire had experienced a screening recall.

All women who chose screening over surgery felt they had made the right decision. 13 of 19 women in the screening group regularly self examined their breasts. Only 8 of 19 in the screening group recalled being offered risk reducing breast surgery. This may reflect their lower level of risk such that RRS was not appropriate or their own lack of interest in the option such that it was not further explored by counsellors.

Surgery

Reasons why women chose to have RRM are outlined in figure 6.29. Cancer related anxiety, a desire for control and to be there for children and lack of confidence in screening were the statements most commonly agreed with by participants. One free text comment added that this woman had surgery “to make my daughters and sister, all of whom are *BRCA1+* take it seriously”. 14 of 15 women with children stated positively that they chose surgery to be there for their children in the future. A greater number of women without children chose screening, although with small numbers it is not possible to attribute this as causative. There were no differences between women with a gene mutation and those with no known gene in these views.

Figure 6-29 Reasons for choosing surgery

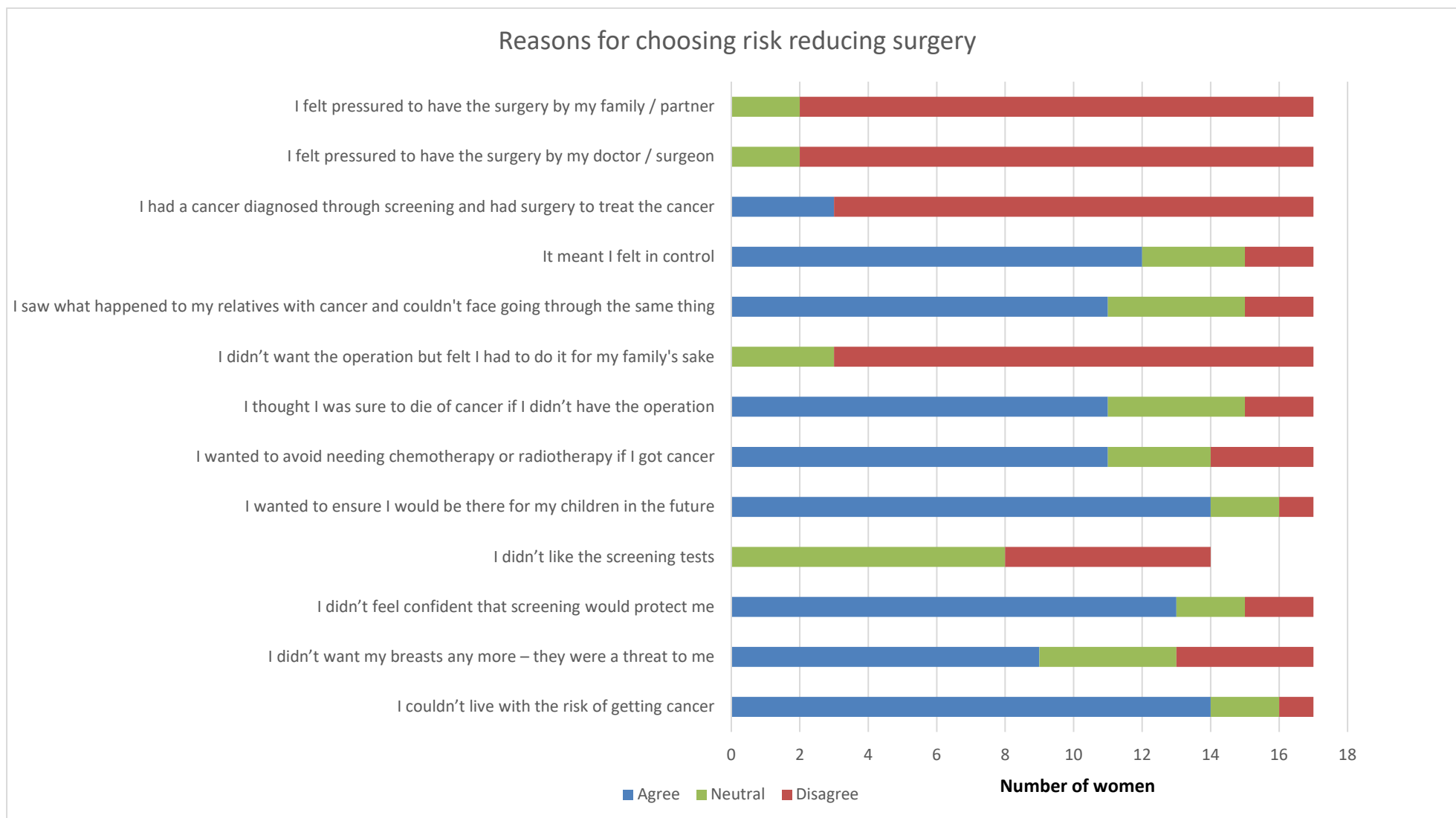
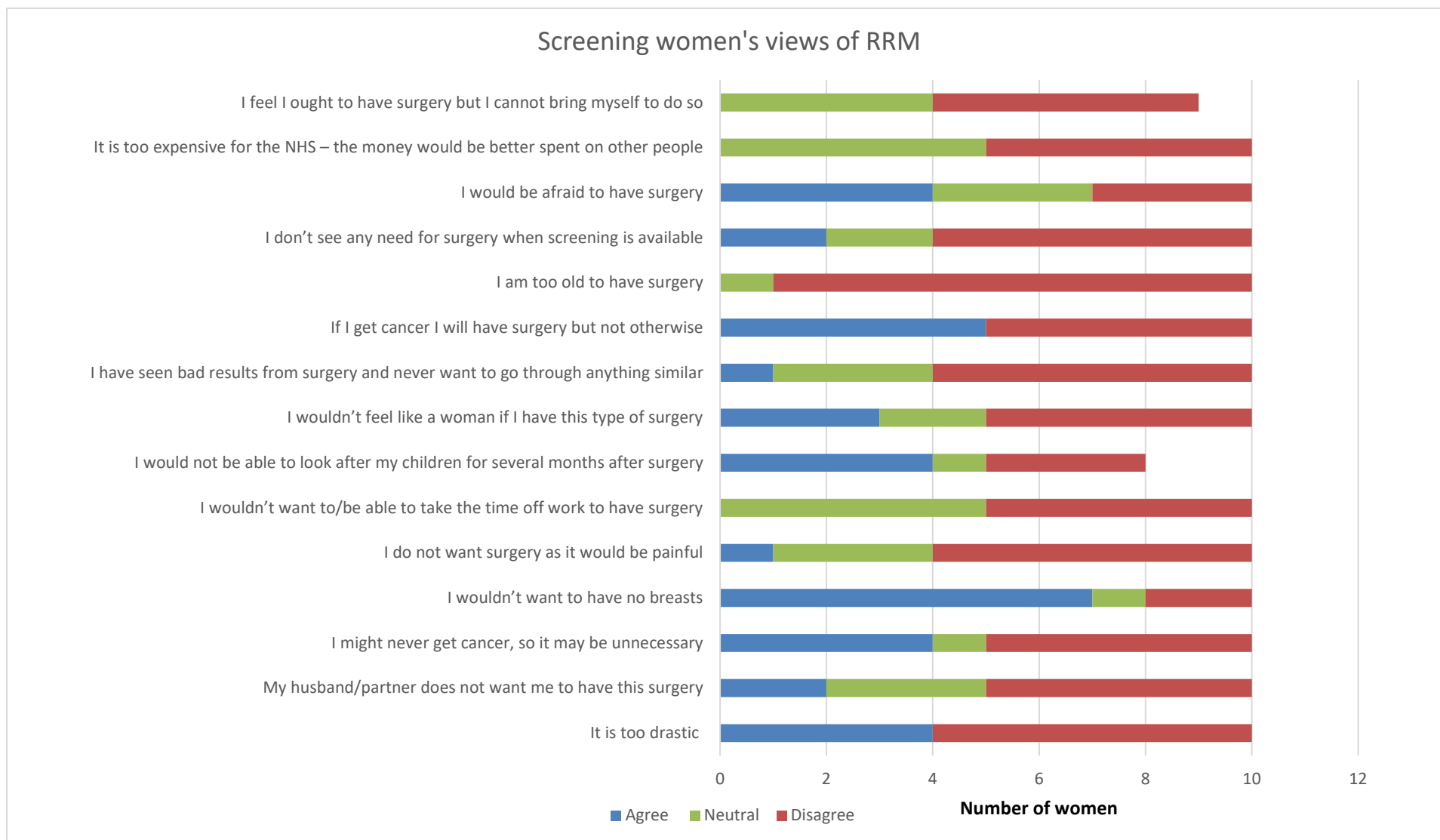


Figure 6-30 Reasons for not wanting RRM



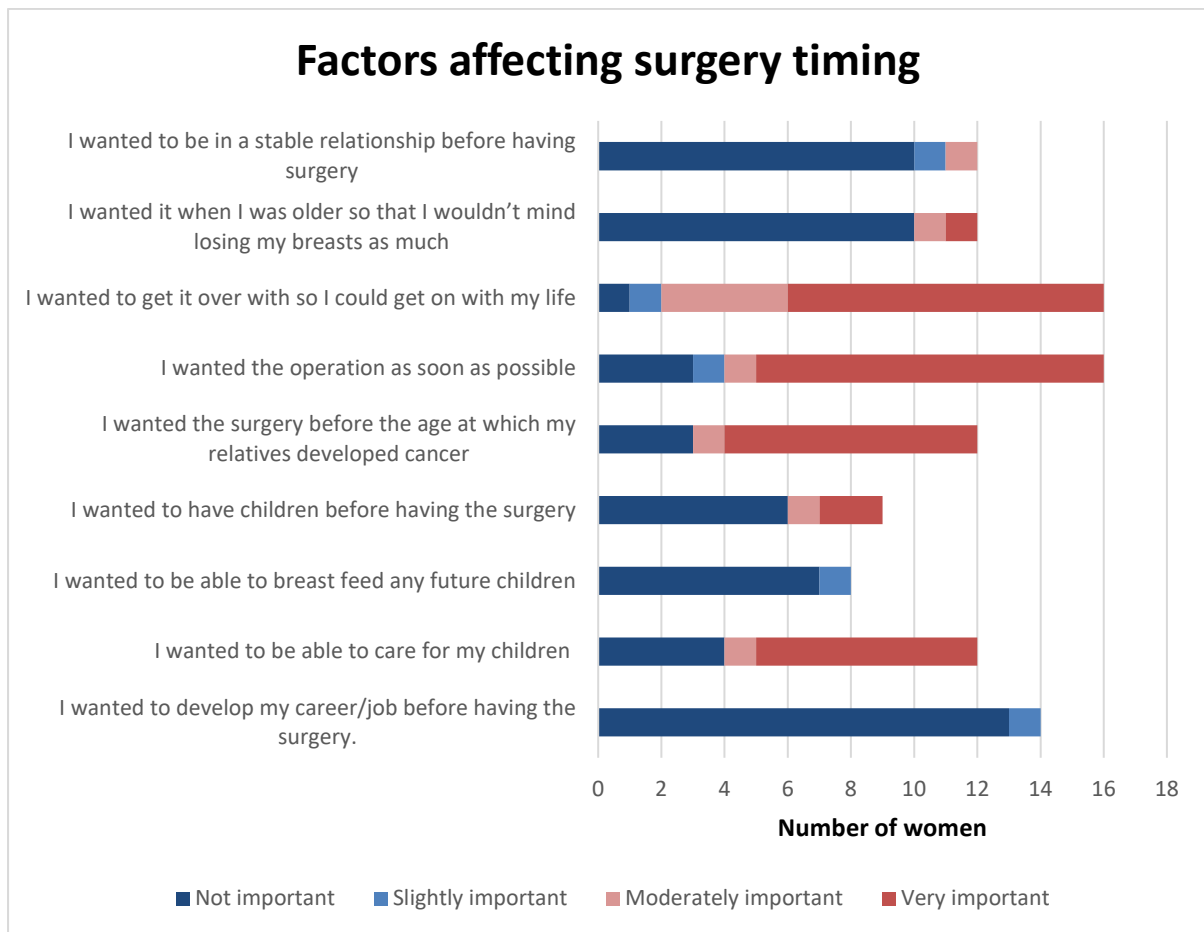
Women undergoing screening who recalled having been offered surgery (n=8) were asked why they did not want surgery – see figure 6.30. The most commonly agreed with statements included “I wouldn’t want to have no breasts”, and “If I get cancer I will have surgery but not otherwise”. Body image concerns, wanting to avoid “drastic” and potentially unnecessary surgery and childcare commitments were also agreed with as reasons.

3 women had firm plans to have risk reducing surgery in the future. All 3 (of 3) wanted to delay surgery to be able to care for either existing or planned children, 1 wanted to delay until after she had had children, 2 delayed surgery until nearer an age at which their relatives developed cancer and 1 wanted to delay due until she was older so she wouldn’t mind losing her breasts as much.

Of the 9 women who were contemplating surgery in the future, 7 definitely wanted reconstruction, 1 may want reconstruction and 1 was unsure.

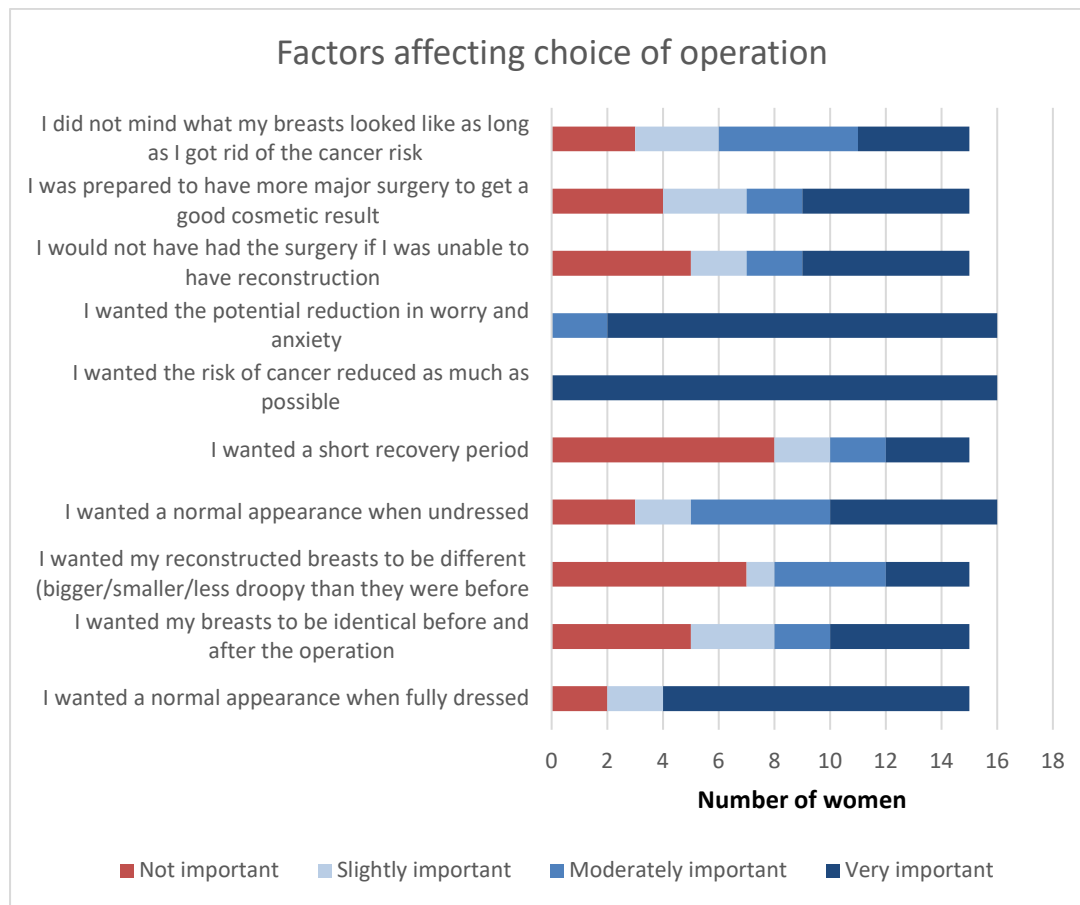
Figure 6.31 looks at the factors that influenced women’s decisions to undergo risk reducing surgery. A majority of women wanted surgery as soon as possible (62.5%) and so that they could get on with life (87.5%). Most wanted it before the age at which their relatives developed cancer and several timed surgery to fit around childcare. Of note, career, breastfeeding intentions and a desire to be in a stable relationship were not seen as reasons to delay. One woman added in a free-text box “I had very lumpy breast and I could not tell when a new lump appeared, I didn’t want to make a fuss all the time”.

Figure 6-31 Factors affecting surgery timing



In terms of the actual procedure that women chose to have done, all 16 felt it was very important that the risk of cancer be reduced as much as possible. They also all wanted a reduction in worry and anxiety. 86.7% felt it was very important to have a normal appearance when dressed. Other possible factors had a more mixed reaction, for example, “I do not mind what my breasts look like as long as I got rid of the cancer risk” was ‘not important’ to some and ‘very important’ to others. See figure 6.32.

Figure 6-32 Factors affecting surgery choices



6.11.6 Experience of surgery

Operations happened between 1994 and 2011 (median 2007). Women aged between 24 and 65 years when they had risk reducing breast surgery (median 38 years). 11 had mastectomy and immediate breast reconstruction, 5 had mastectomy and delayed reconstruction and 1 had mastectomy alone. 8 had implant alone techniques, 5 had LD alone and 4 had LD with implant techniques. 6 out of 17 (35.3%) required revisional surgery. 11 (64.7%) would have undergone RRM without reconstruction but 6 (35.3%) would not have had RRM without reconstruction.

10 (58.8%) reported no complications – see figure 6.33 (although 3 of these 10 ticked the seroma complication box in a later question), 7 (41.2%) reported having complications (x8 seroma, x2 haematoma, x2 infection requiring antibiotics, x1 pain, x1 implant rupture and x2 capsule contracture)

Figure 6-33 Complications experienced

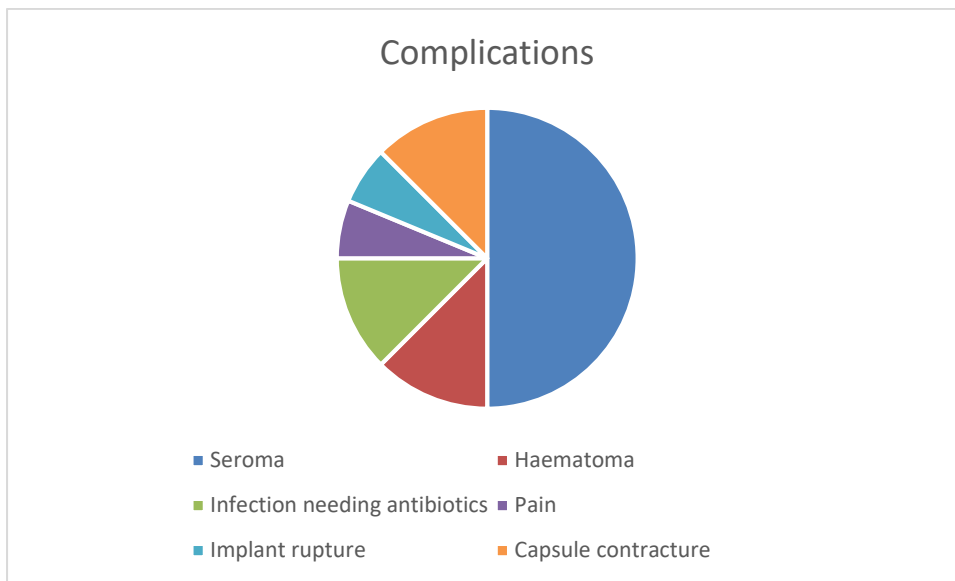
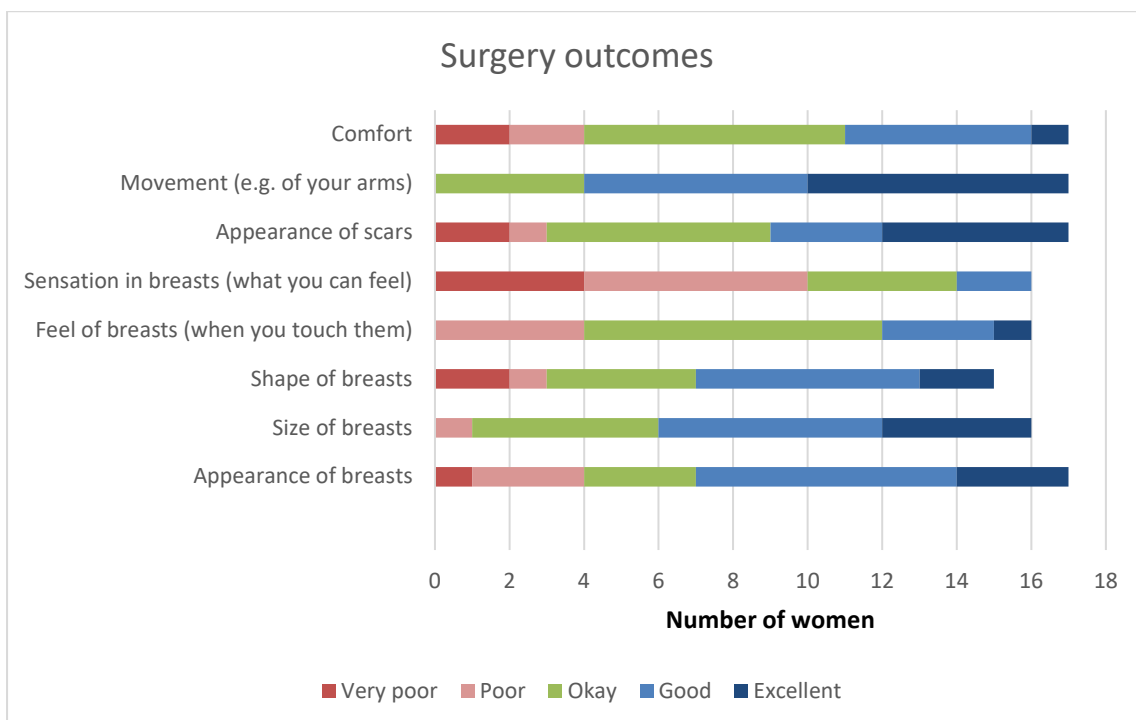


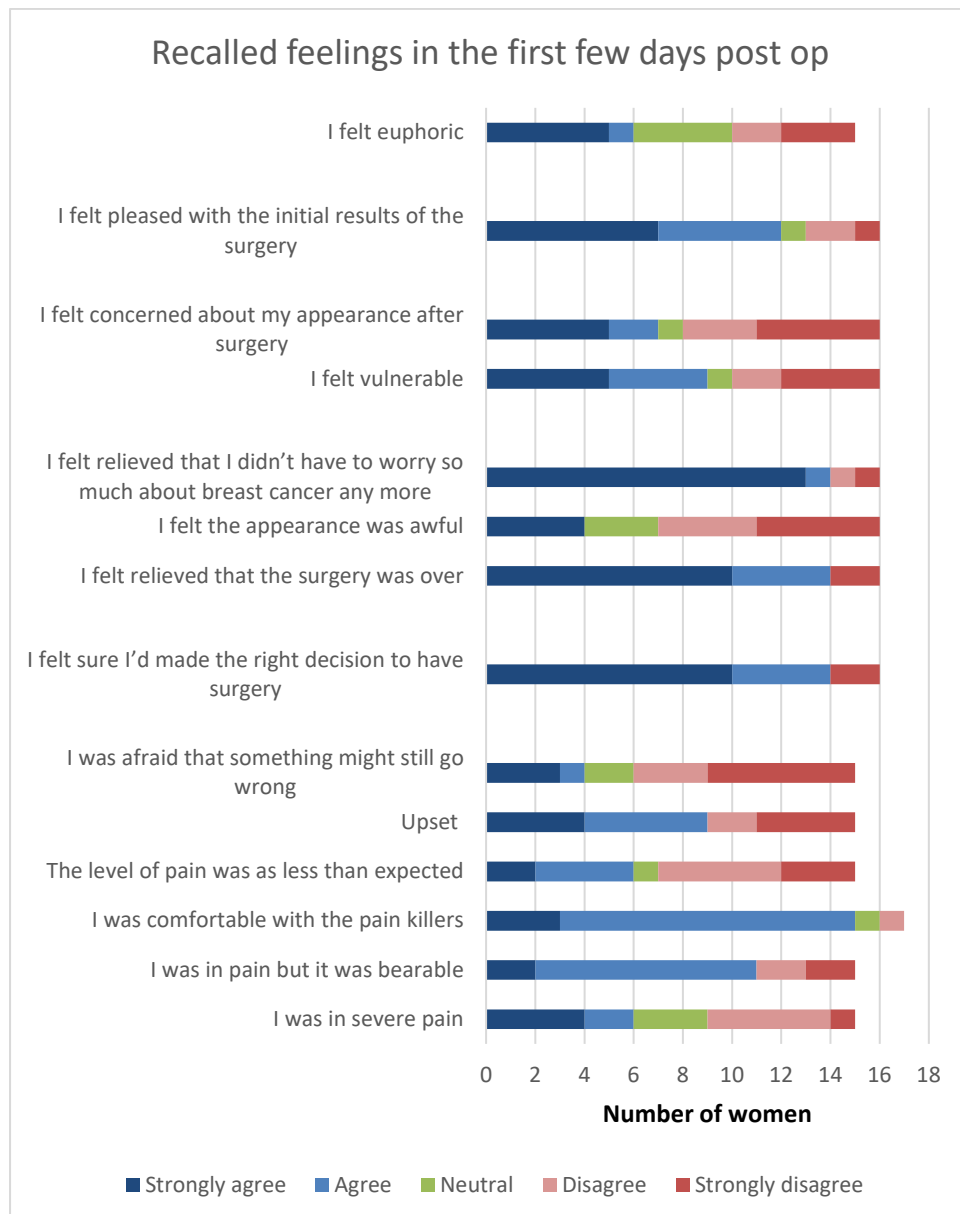
Figure 6-34 Surgery outcomes



77.9% of women rated the outcomes either okay, good or excellent. 22.1% rated a result as poor or very poor. Sensation was poor in the majority (62.5%) and feel, comfort and appearance also had 24% rating them as either poor or very poor. See figure 6.34.

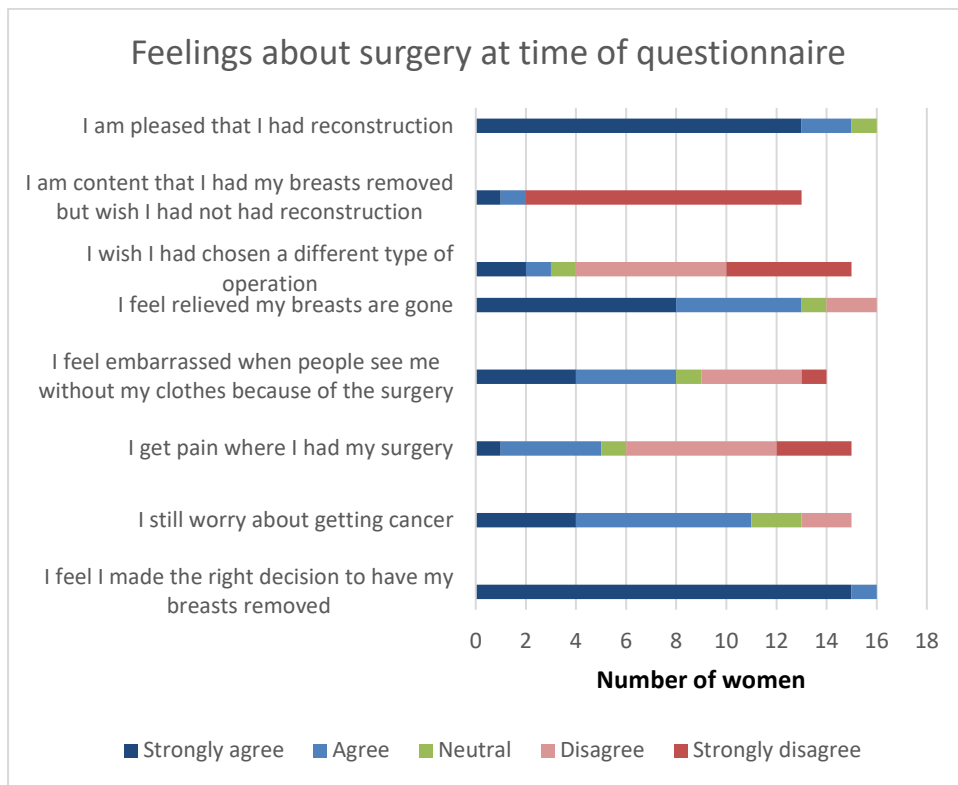
9 of 16 (56.3%) women felt their reconstructed breasts were not their own.

Figure 6-35 - Recalled feelings early post-op



Women were asked to recall their feelings in their first few post-operative days – see figure 6.35. Clearly this introduces recall bias but these views were so strongly held in the focus group and interviews, that it was felt worthy of further exploration. Again, views were very mixed. Most felt relieved that surgery was over. 14 of 16 felt sure that surgery had been the right decision for them. In the main, pain was not a major issue, although 6 of 15 recalled severe pain. These views were compared with women’s views of surgery at the time of the questionnaire (see figure 6.36).

Figure 6-36 Feelings about RRM at time of QN



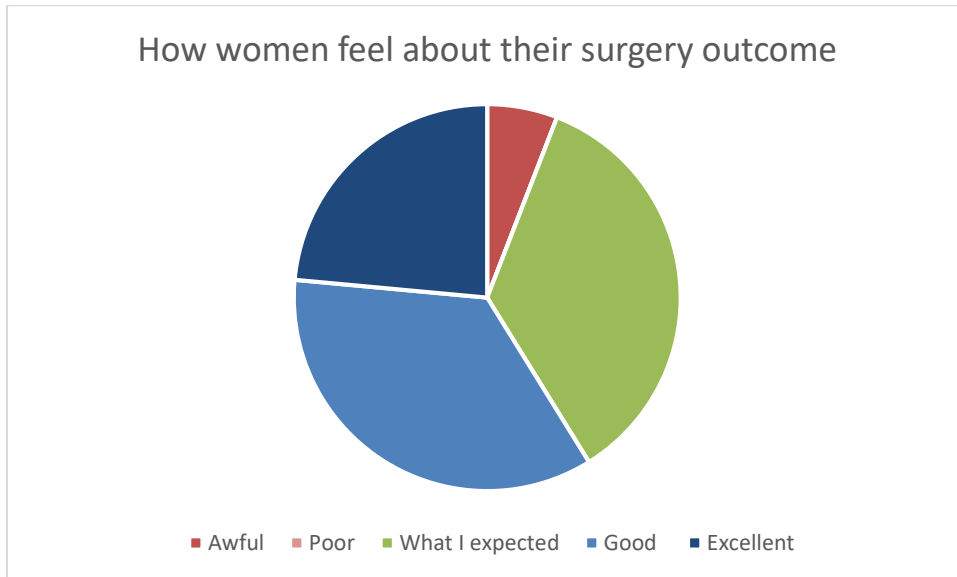
All bar one was pleased that they had reconstruction. Most (80%) did not feel they should have chosen a different procedure. 4 women thought recovery was quicker than they had expected, 4 thought it was longer than they expected and 8 felt it was what they had expected.

3 of 17 felt a sense of guilt about having had risk reducing breast surgery, all 3 agreed that they did not feel as deserving as patients who had cancer. In a free text box, one woman added that she felt guilty about having *BRCA1* and surviving cancer-free. Another added “*I cried when the nurse took the dressings off and she actually said to me ‘why are you crying? You chose to have your breasts off. Others here didn’t have a choice!’ I was devastated and ashamed*”.

None of the women had changed their job or their lifestyle as a result of surgery.

Overall post RRM outcomes were rated as either good or excellent by 59% with 35% feeling it was what they had expected. 6% felt it was awful. This is summarised in figure 6.37.

Figure 6-37 RRM overall outcome



6.11.7 Body image

Figure 6-38 Body image in screening women

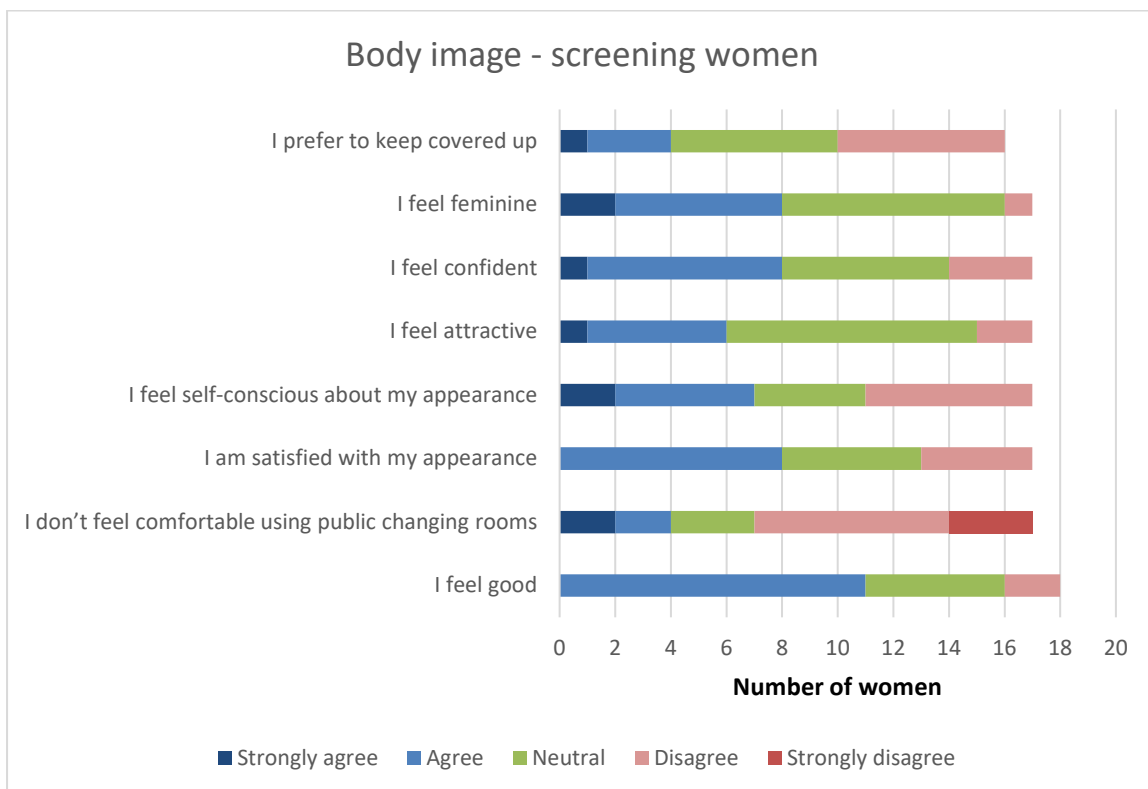
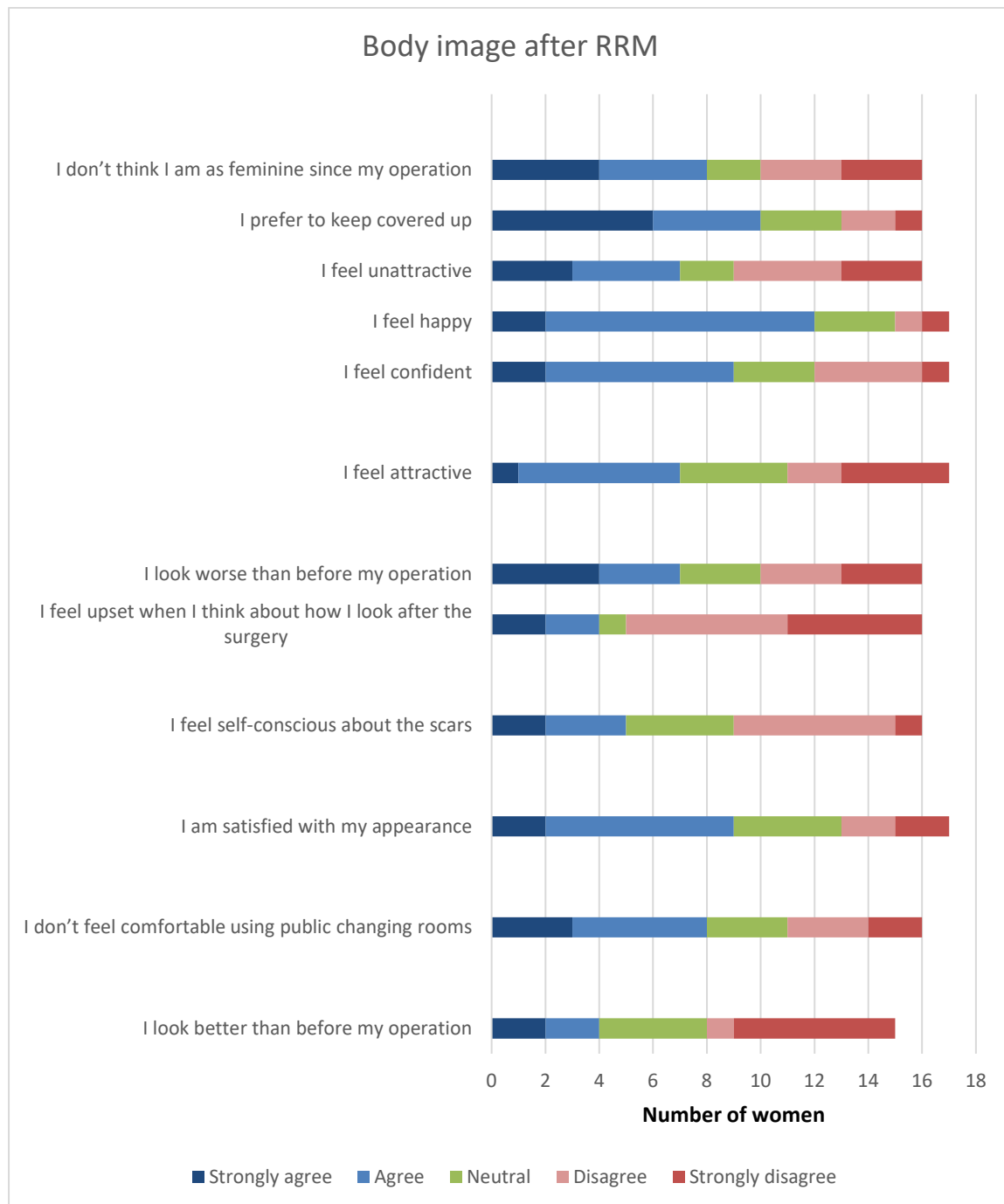


Figure 6-39 Body image after RRM



Results from the body image questions were varied – see figures 6.38 and 6.39. Post operatively, some women were very positive about the result of surgery whilst others suffered in terms of body image. Half of the responding women felt less feminine since surgery and 43.7% felt unattractive (although there are no pre-operative results to correlate this with). 6 of 17 women avoid looking at their breasts after RRM and 5 of 17 also avoid touching them. In the screening group, 1 woman avoids looking at her breasts and 2 avoid touching them. A free-text comment added “I was pleased that my husband was pleased”.

6.11.8 Relationships

Of the 16 women who were in a relationship at the time of surgery, 8 felt it had changed since surgery, 8 felt it had not changed. Of those who felt it had changed,

- 5 felt closer to their partner, none felt more distant
- 5 felt their physical relationship had changed in bad way, none felt it had improved
- 3 felt emotionally their relationship was better, 2 felt it was worse
- No partnerships had broken down since surgery

8 felt sexual activity had changed since surgery, 9 felt it had not

- 6 felt they had less interest in sex, 2 felt they had more interest
- 3 felt their partner had less interest, 1 felt their partner had more interest and 11 felt that their partner's interest in sex was unchanged

Screening - Of those who are or were in a relationship at the time they discovered their risk, 1 felt their relationship had changed (more distant and physically worse in a bad way) but 12 felt it had not changed. Of the 15 who were sexually active, none felt it had changed since finding out about their increased risk. None felt their partner's attitude to sex had changed either.

6.11.9 Decision satisfaction

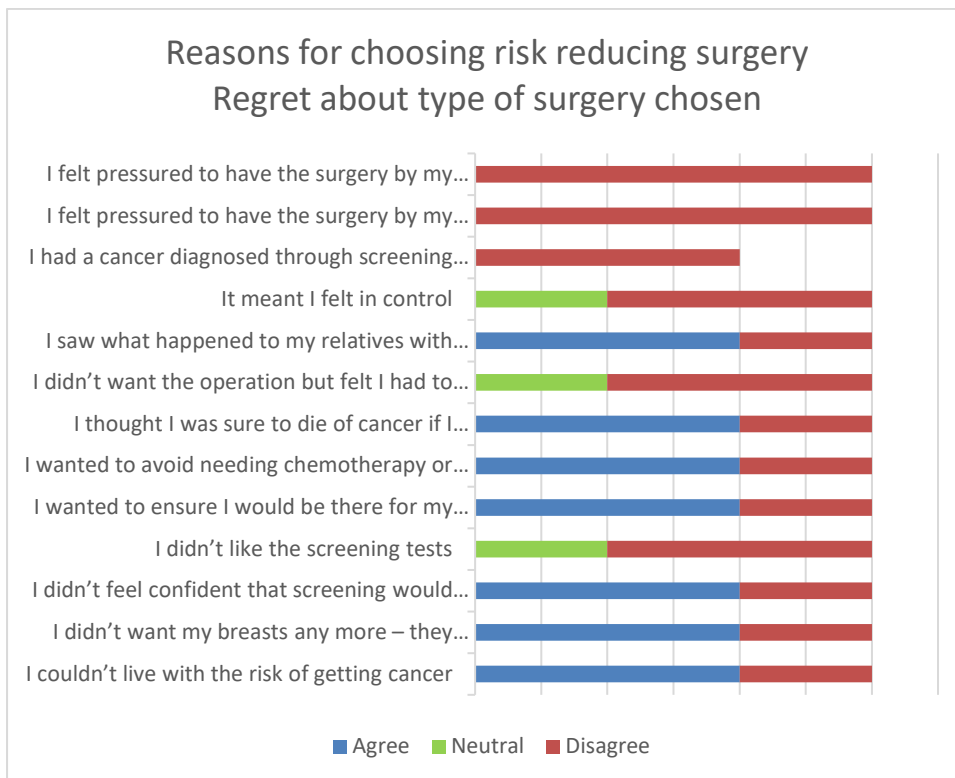
100% of women who chose screening felt satisfied that it was the right decision. 100% of women who had risk reducing surgery and who answered the question (one left it blank) either agreed or strongly agreed with "I feel I made the right decision to have my breasts removed". 15 of the 16 women (93.75%) strongly agreed. 11 of 15 (73.3%) disagreed or strongly disagreed with "I wish I had chosen a different type of operation", although 3 of 15 agreed with this (20%). 2 strongly agreed and agreed respectively with "I am content that I had my breasts removed but wish that I had not had reconstruction" (13 strongly disagreed with this).

The women who would have chosen a different operation or foregone reconstruction numbered 3. These women's questionnaires have been reviewed in greater depth to try to understand this outcome, see also figures 6.40 and 6.41.

- Age at time of questionnaire – 43, 51 and 60, ages at diagnosis of increased risk and time of RMDM – not stated. Age at surgery – 34, 46 and one was not stated.
- One had had previous breast cancer.
- All 3 were *BRCA* gene carriers.
- All 3 had children, ages ranging from 10 to 41 years.
- 1 had simple mastectomy without reconstruction. 2 had mastectomy and immediate reconstruction with LD flap and implant technique.
- 2 had complications (seroma, haematoma, capsular contracture), 1 needed revisional surgery. 1 had no complications or revisional procedures.
- All 3 rated their risk of breast cancer pre-surgery as 80-90%. Post-RRM risk of breast cancer was rated as <1%, 10% and 50%.
- Pre-RRM support was rated as just enough by 2 and as good by 1. Post-RRM support was rated as poor, not quite enough and just enough respectively.
- Appearance, shape, feel and sensation all scored poorly in questions about surgical outcome. All 3 felt their breasts were not their own.
- 2 felt recovery took longer than they had expected (one left this blank)
- 2 of 3 felt guilty about having had surgery due to the impact on their family, feeling like a burden and being less deserving than patients with cancer.
- All felt they looked worse post-RRM and all preferred to keep covered up. 2 of 3 either agreed or were neutral about feeling happy and confident.

The woman who had simple mastectomy without reconstruction commented in a free-text box *“I wanted reconstruction but they wouldn't because I'm overweight. I wish I'd insisted”*.

Figure 6-40 Reasons for surgery - regret

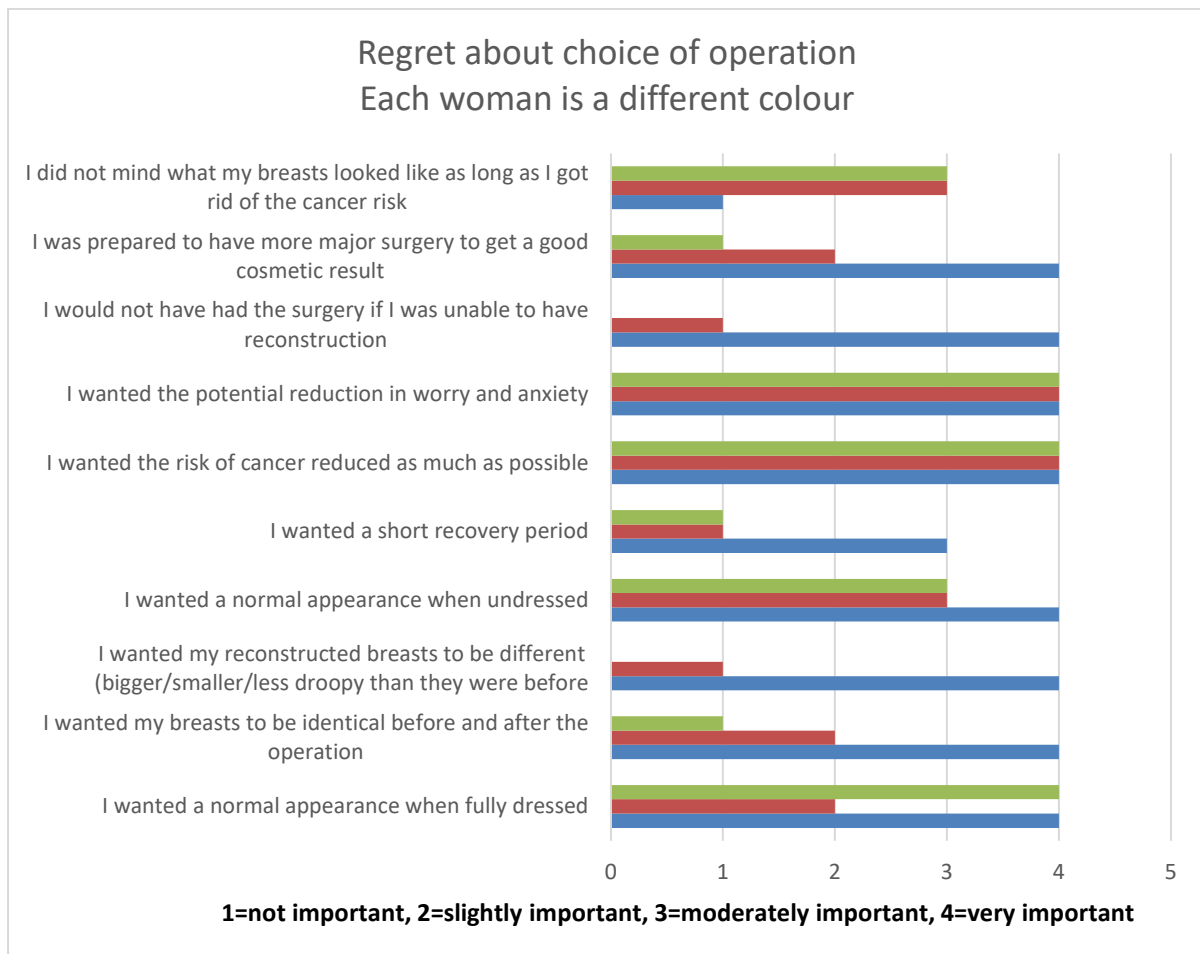


Factors women felt were important in the timing of their surgery were also reviewed for the three women who expressed regret. 1 of 3 wanted surgery as soon as possible but 2 felt this was not important. Factors influencing the choice of operation was interesting. 1 of the 3 women felt it was very important that:

- She had a normal appearance dressed and undressed
- Her breasts looked identical before and after surgery.
- That her reconstructed breasts looked different (e.g. less droopy, smaller, bigger) – *(this clearly contradicts the previous question)*

In addition she wanted to reduce her risk and worry / anxiety, which were also rated as very important. In this case, it seems likely that her expectations of surgery were unrealistic, which likely impacted upon her feeling the outcome was not as good as she had expected. The other two women were more balanced in what they hoped to achieve with surgery.

Figure 6-41 Regret about surgical choice



In summary, all women who participated were satisfied that their risk management decision had been the correct decision for them. 20% would have chosen a different type of operation and 2 of 15 would have preferred, in hindsight, to have simple mastectomy without reconstruction.

6.12 Discussion

6.12.1 Risk discovery and risk management decision making

Discovery of risk and risk management decision making appear to be, for most women, events that they wish to move beyond. For some women, managing their risk by electing to undergo bilateral mastectomy is an effective way to feel their risk has been addressed; for others enrolling in a high frequency surveillance programme provides this risk amelioration, allowing them, in the main, to accept their situation and move on with life. There was a non-significant trend, however, in women who chose screening to have greater cancer related

anxiety and interference than those who had undergone risk reducing surgery, which is in keeping with published work (Hatcher, Fallowfield et al. 2001, Lodder, Frets et al. 2002, Geiger, Nekhlyudov et al. 2007).

A desire for normality was apparent throughout many of the themes explored in the questionnaires. Discovery of risk can perhaps be compared to a period of illness, from which women wish to 'recover'. Their choice of risk management strategy needs to match their desire for metaphorical recovery and this will be determined by women individually, based on priorities, circumstances and perceptions that will usually be opaque to observers, be they family, friends or healthcare professionals.

6.12.2 Risk management strategies

Women's views of screening and surgery were very varied. Interestingly, in spite of a high number having been recalled (21%), all women who had chosen screening, felt it had been the correct decision. (Published recall rates for MRI high risk surveillance (per 100 scans) are between 8-17 (Kriege, Brekelmans et al. 2004, Warner, Plewes et al. 2004, Kuhl, Schrading et al. 2005, Leach, Boggis et al. 2005, Lehman, Blume et al. 2005). The views of surgery expressed by the screening group suggest that screening is not being treated as a bridge to surgery by many, but that it is an active choice that better matches their tolerance of risk and desire for risk amelioration. In keeping with published studies, those with gene mutations were more likely to choose surgery (Garcia, Lyon et al. 2014) reflecting the uncertainty of risk in those without a known mutation. It may also be true that healthcare professionals may have recommended screening over surgery for this group.

The majority of women who chose surgery felt that screening wouldn't protect them. All those who chose surgery felt it was important to reduce the risk of cancer *and* to reduce cancer related anxiety. Most wanted to look normal when dressed, some wanted to look normal undressed too. Managing expectations, particularly pertinent to immediate breast reconstruction, is an important part of the risk management decision making counselling process. Without adequate information, women risk feeling disappointed by their choice.

6.12.3 Outcomes

There were some who reported negative views of appearance, confidence and femininity following surgery but they were in a small minority and of proportions broadly similar to those published in the National Mastectomy Breast Reconstruction Audit (NMBRA) which measured treatment outcomes for women having mastectomy with or without reconstruction (Jeevan, Cromwell et al. 2014). This is also in keeping with published work by (Frost, Schaid et al. 2000, Hopwood, Lee et al. 2000, McGaughey 2006). Many were 'neutral' when asked to rate these outcomes, which is hard to interpret, but could be assumed to mean 'no change'. 4 of 17 who rated the post-surgical appearance of their breasts as poor and (the same 4 women) their overall appearance as poor, aged 43, 50, 51 and 54, clustering around the median age of questionnaire participants. Franzoi demonstrated that body image is often reported as poorer with advancing age (Franzoi and Koehler 1998). In this series, the older questionnaire participants did not rate their appearance as any worse than the younger group.

Relationship change was common in the risk reducing surgery group, reported by half of those in a relationship. Changes were mixed, some felt closer, some more distant and some felt their physical relationship had suffered. Only 1 of the screening women in a relationship felt things had changed. The changes reported in the surgical group could reflect simple post-operative recovery times, which particularly for bilateral mastectomy and IBR, are not quick, but are likely to also capture the longer term sequelae of RRM, including body image, confidence and femininity changes that can impact on relationships.

That all responders reported feeling their RMD had been the right one for them is reassuring. The small number of surgical women who were dissatisfied with their choice of procedure (but not choice of RMS) were analysed in more depth and at least in one case, poor correlation between expectation and result can account for this outcome. The fact that none of the screening cohort had had a cancer diagnosed (partly due to the design of the study, those who have cancer often choose bilateral surgery and so would move into the RRM group) is a limitation of this study. It would be very interesting to know if women who choose screening and who have cancer detected remain satisfied with their RMS decision and this remains an area in need of further work.

6.12.4 Support

The process of risk management decision making is clearly complex and highly individualised and most women value support. A consistent finding on discovery of risk was the desire for information and most women rated the nurses in genetic and breast clinics as being a significant source of support, likely (although neither explored nor proven in this study) because they are skilled at providing this information in a manner than women can understand, remember and use to make decisions. Half of all the women surveyed wanted access to a support group, although this was closer to 60% in women who were gene positive or who chose risk reducing surgery than in the no gene mutation and screening groups (~30%). This is perhaps unsurprising given the irreversibility and magnitude of consequences for those choosing an operation. The fact that women are making a choice to essentially disfigure themselves is highly unusual both within medicine and society as a whole and the need for extra support is clear.

These data demonstrate the need for high quality information that is, ideally, tailored to the individual. Women deciding on surgery need to know the likely outcome of their individual RRM and-or reconstruction and be provided with realistic expectations, in order that they can make a truly informed decision with which they remain satisfied in the long-term.

Healthcare professionals need to appreciate the impact of living at familial risk and be sensitive to the differences between these women and those who are being treated for cancer. Women at increased familial risk can choose to put themselves and their families through the ordeal of surgery and then have to live with the consequences, in the full knowledge that they may never have developed cancer. Guilt was relatively common when discussing the impact of familial risk on children. It was less common in relation to surgery but should perhaps be explored with women in pre-operative counselling in order that it can be addressed.

6.12.5 Limitations

There are a number of limitations to this study. The fact that data were collected retrospectively is clearly going to introduce recall bias, particularly for questions such as, "How did you feel immediately after your operation?". Some questions are hard to interpret

without a baseline 'norm' to act as a comparator, for example, the impact of living at risk topic that was explored with a series of questions about cancer related anxiety and how it interferes with life and daily activities.

Comparing groups, be it surgery vs. screening, or gene positive vs. no gene mutation adds further potential error. The risk of cancer and personal experiences are likely to differ between these groups. One does not act as a control for the other and neither are they groups that are matched in any way.

The wording of the questions may have also introduced error. Both the expert reference group and the focus group were involved in selecting terminology for Likert scale questions. One example of where phrasing could be considered ambiguous is "not a lot, a little, somewhat, a lot". What some women describe as "a little" may be "not a lot" to some and "somewhat" to others. The order could also be considered confusing, particularly if "somewhat" and "a little" are viewed as hard to discriminate between.

A question was missed from the screening questionnaire that should, with hindsight, have been included, exploring the impact of recall. This would have provided a greater understanding of how, in challenging times, screening women balance the ongoing risk of cancer against the risks and benefits that are associated with risk reducing surgery. Similarly the questionnaire did not explore chemoprophylaxis. This, however, was not inadvertent. At the time of the questionnaire it was not routinely available although it would be interesting in future work to look at women's views of this modality of risk reduction and to see how it impacts on choices of other RMSs.

The response rate was disappointing and introduces weakness to the study. Had there been greater numbers, more confidence could be had in the subgroup analyses, for example the 'gene positive' group that included just two screening women. Due to the small numbers, comparisons between, for example immediate breast reconstruction and delayed were not undertaken.

Attempts to understand *why* women hold the views they hold and *why* they make the risk management choices they do are not possible from this study alone. These data quantify, as they set out to do, the views that are held and some of the circumstances and experiences that may influence these views. They do not allow derivation of future women's views, nor will they provide any mechanism to extrapolate what is likely to lead to a good outcome for an individual facing RMD choices. The degree of heterogeneity in the questionnaire findings demonstrates that women can share seemingly similar circumstances and experiences of a RMS and still hold very dichotomous views.

The following chapter will explore the accumulated data from each of the phases of this study, drawing the phases together to create an overarching discussion of the findings.

7. Chapter seven – Discussion

The aim of this study was to establish the psychosocial outcomes for women and partners of women at increased familial breast cancer risk when undergoing either enhanced screening or risk reducing surgery. Objectives included:

- Establishing the impact of living at increased risk for women and their partners
- Exploring views toward risk management options in women and their partners
- Exploring the decision making process and factors affecting decisions
- Identifying the psychosocial outcomes for women at increased familial breast cancer risk
- Quantifying the outcomes identified in the qualitative study with a wider cohort of women

Mixed methods were used to meet these aims and objectives, incorporating the strengths of the different techniques and, by including some duplication, further strengthening the findings. Another advantage of mixed methods is the reduced likelihood that a small methodological weakness in one component will significantly impair the overall results.

The following techniques were employed in this study:

- Narrative exploration of existing literature relating to familial breast cancer risk
- Systematic review of the psychosocial outcomes for women undergoing enhanced screening and risk reducing mastectomy
- A qualitative study using semi-structured interviews with women and (separately) with their partners to establish the impact of living at increased familial breast cancer risk and to explore views and experiences of the different risk management strategies
- Questionnaire design utilising experience of the expert reference group
- Focus group assessment and validation of the novel questionnaire tool
- Questionnaire study using the bespoke, validated tool

7.1 The results

The three data gathering components to this study: the systematic reviews; the interviews and the questionnaires, have been analysed separately in their respective chapters (3,4 and 6). The findings from these phases of the study were then pooled and a process not dissimilar to framework analysis conducted to amalgamate the findings, developing five “metathemes”:

1. A desire for normality
2. High reported satisfaction with choices
3. A desire for information and/or support
4. The individuality of women
5. Cancer related anxiety

7.1.1 A desire for normality

The interviews found the discovery of risk could be compared to a period of illness, from which women and their partners wish (them) to ‘recover’ albeit potentially accommodating significant change, be that a long-term cancer-related-anxiety or post-surgical body image concerns. This finding was similar to a process of ‘acceptance’ described in the systematic reviews, a necessary step that allowed women to ‘move on’ (Lloyd, Watson et al. 2000, Lodder, Frets et al. 2002). Choice of risk management strategy needs to match women’s desire for metaphorical recovery and this will be determined by women individually, based on priorities, circumstances and perceptions that will usually be opaque to observers, be they family, friends or healthcare professionals. The simple desire for normality was also evident in interviews, with some women stating this directly whilst others described the acceptance process identified above.

Women also clearly described a desire for a normal appearance both in interviews and in the questionnaire findings, and for some this was sufficient deterrent to surgery that they felt screening was the only reasonable option. Others would sacrifice this desire for a normal body appearance for the reduction in risk that surgery offered, and in some cases this trade off resulted in poor body image and dissatisfaction with reconstructive surgery. A motivating factor driving some women to choose RRM is the idea that it more rapidly addresses the

problem, which was demonstrated in the interviews, questionnaires and also in previous research (Lloyd, Watson et al. 2000, Lodder, Frets et al. 2002).

7.1.2 High reported satisfaction with choices

Both in this study and common within published studies was a high level of decision satisfaction (Josephson, Wickman et al. 2000, Lloyd, Watson et al. 2000, Lodder, Frets et al. 2002, Metcalfe, Esplen et al. 2004, Geiger, Nekhlyudov et al. 2007, Rolnick, Altschuler et al. 2007). The questionnaires and interviews identified a minority of women who had undergone RRM and reconstruction who would, if given the benefit of hindsight, have selected different reconstructive procedures. This is also in keeping with published work, demonstrating high levels of risk management decision satisfaction but lower levels of reconstruction satisfaction (Frost, Schaid et al. 2000, Heiniger, Butow et al. 2015).

The National Mastectomy and Breast Reconstruction Audit found that women with immediate breast reconstruction were less satisfied than those with delayed reconstruction and hypothesised that this was because IBR women substituted a normal, albeit often diseased breast for an insensate, firm, different shaped reconstruction, as opposed to DBR women who substitute a mastectomy scar for a reconstructed breast (Jeevan, Cromwell et al. 2014). This is taken a step further in women who have RRM and IBR, who substitute normal, un-diseased breasts for reconstructed breasts, perhaps going some way to explain this phenomenon. The interviews found that women who were less satisfied had usually experienced complications *and* poor aesthetic outcome, with similar findings in the questionnaire with an additional finding of insufficient post-operative support. The systematic review found that elevated anxiety and / or poor baseline body image correlated with reduced satisfaction and poor perceived cosmetic result, which are views that can be explored before RRM and support provided accordingly.

An important distinction should be drawn that whilst women are, in the main, satisfied with their risk management strategy, and a majority are not significantly distressed in the long-term, they are not all un-distressed.

7.1.3 A desire for information and/or support

The need for clear, tailored information was described by the systematic reviews. Women who over-estimate their risk were identified as a sub-group at increased risk of a poor psychosocial outcome. Correcting women's risk perception with accurate information is both possible and desirable to reduce the likelihood of long-term dissatisfaction and distress. In interviews, the topic of support groups was discussed and women seemed to identify these groups as being able to provide them with first-hand accounts of what to expect and how to prepare themselves accordingly, in short, support groups would be a source of desirable information.

Social support was demonstrated in the systematic reviews to improve psychosocial outcomes (Metcalfe, Esplen et al. 2005, den Heijer, Seynaeve et al. 2012). Interviews and questionnaires highlighted the high degree of support received from nurses in both genetic and breast clinics. The questionnaires also highlighted women's desire for information and how support is required throughout the journey, particularly following surgery, when it is not always readily available.

Partner interviews identified the impact that the support needs of women place upon them. Partners rarely requested support but frequently expressed frustration at having to balance their existing responsibilities, for example work, with the additional burden of caring for their partner without support. Both women and partners described the distress they felt watching their partner come to terms with their risk and the impact of their chosen risk management strategy. The impact upon relationships and particularly sexual relationships can be significant especially after RRM, with reported (and observed) reduction in femininity and body confidence (Frost, Schaid et al. 2000, Hopwood, Lee et al. 2000, Metcalfe, Esplen et al. 2005, McGaughey 2006, den Heijer, Seynaeve et al. 2012).

A key finding from the narrative review was the need for tailored information to guide women in making an informed decision on risk management, with access to improved information seeming to consistently improve outcomes (Armstrong, Weber et al. 2005). Recognising women at increased risk of psychosocial distress and intervening to reduce

distress are also highlighted as areas upon which to focus further work. The systematic reviews identified groups of women at such increased risk: see table 7.1. Of note, both groups include three identical risks: young age, over-estimation of risk and high baseline anxiety / distress. It would seem entirely possible that women presenting to a family history clinic could be screened for these risk factors early in their journey of risk discovery and subsequent management. Findings from the questionnaire add to this list of women at increased risk of an adverse psychosocial outcome women with unrealistic expectations of their risk management strategy

Table 7-0-1 Women at risk of psychosocial distress

Enhanced screening risk groups	Risk reducing surgery risk groups
Age under 40	Younger women
Over estimating risk of cancer	Over-estimators of breast cancer risk, both at baseline and following RRM
High baseline anxiety	High cancer-related anxiety / distress at baseline
Having relatives actively undergoing treatment for cancer	Women without access to good social support
Breast self-examination weekly	Poor body image scores at baseline
	Women who have surgical complications

Methods of reducing distress include:

- Information aimed at improving accuracy of risk perception
 - iPrevent is one such tool that aims to address the difficulties in conveying risk (Collins, Bickerstaffe et al. 2016) to patients, some of whom present with an assumed cancer inevitability.
 - Counselling can, depending on the skills and knowledge (both generic and individualised to the patient) of the counsellor, similarly adjust risk perception (Goodwin 2000).
- Information aimed at providing greater understanding of the possible and likely consequences of the risk management strategies
 - Visual information, especially photos, are particularly desirable

- Support groups, whilst not of interest to every woman at increased risk, are frequently noted by their absence by those who would choose to engage (Lloyd, Watson et al. 2000, Bebbington Hatcher and Fallowfield 2003, Rolnick, Altschuler et al. 2007)
- Targeted counselling may help with difficulties that are unpredictable and unpleasant, for example:
 - Women recalled from surveillance for additional tests
 - Women who experience surgical complications, for example loss of an implant
 - Women who have immediate family members diagnosed with cancer

It is imperative that adequate resources are allocated to allow delivery of a high-quality family history service and where possible, to develop decision support information and support networks locally. Probably even more important, the role of a supportive partner should not be underestimated and efforts should be made to facilitate their involvement, where possible and desirable to both parties and to provide support to both partners.

7.1.4 The individuality of women

Conducting and subsequently analysing the interviews incontrovertibly presented the individuality of this (and perhaps any) group of women. It is impossible for a clinician, in a short space of time, to fully appreciate let alone understand the complex myriad of experiences, circumstances, aims, perceptions and preconceptions of their patient. It is, however, possible for a patient to be guided to consider these factors and how they influence their risk management choices. This individuality was equally evident from the questionnaire analysis both in terms of the decision-making process and the women's recounted experiences. The systematic reviews found that a minority suffer long-term distress and that this group can be identified in advance using a set of red-flags including risk overestimation, poor social support and high baseline cancer-related-anxiety (amongst other factors). To explore all of these concepts with patients requires careful counselling and is likely to impact favourably on psychosocial outcomes for individual women.

7.1.5 Cancer related anxiety

Cancer related anxiety was found to be common in the systematic reviews, the interviews and questionnaires, also in keeping with other previously published work (Lloyd, Watson et al. 2000, Lodder, Frets et al. 2001, Foster, Evans et al. 2002, Bebbington Hatcher and

Fallowfield 2003, van Oostrom, Meijers-Heijboer et al. 2003, Metcalfe, Esplen et al. 2005, Heiniger, Butow et al. 2015). Women cited fear of cancer as a frequent motivator to choose surgical management, alongside a desire to 'be there for children' in the future, both concordant with previous work (Goodwin 2000). Interviews found that although RRM involves a mutilating procedure for which there are well documented adverse outcomes (see chapter 3.1), it is, for the majority of women who undergo RRM, an acceptable cost for reducing the distress they experience of living at risk. Whether women who choose screening derive any similar benefit is unclear

Other findings that merit further discussion are outlined below.

Women's (recalled) reaction to being told they were at increased familial risk seemed to predict, in the questionnaire study, the subsequent risk management decision. Women who reacted more strongly, (for example strong feelings of fear, panic and shock) were more likely to choose risk reducing surgery than screening. High levels of distress upon discovery of risk were not correlated to high cancer related anxiety and whilst some studies found that cancer related anxiety was more common in women who chose surgery (Lodder, Frets et al. 2002, Heiniger, Butow et al. 2015, Portnoy, Loud et al. 2015), others, including this study, found it to be more common in women who chose surveillance (Hatcher, Fallowfield et al. 2001). This strength of feeling correlating with decision management has not been reported before and was established by using information gathered in interviews to guide questionnaire development, allowing exploration of phenomena that widely used validated tools may not have captured.

This impact of living at increased familial breast cancer risk clearly affects the woman herself, but this study has shown how the effects are much broader. The role of partners and the impact upon them has been explored very little (Mauer 2015). Interviews with partners identified the supportive role that they play in both risk management decision making and in supporting their partner through the consequences of that decision. Where women chose reconstruction, partners appeared to feel this was either exclusively or predominantly for her own benefit and they were often ambivalent about reconstruction.

There is no evidence to demonstrate a reduction in cancer-related anxiety or distress within screening women (Valdimarsdottir 1995, Drossaert, Boer et al. 1996, Spiegel, Esplen et al. 2011, Bredart, Kop et al. 2012). One study did find better generic health-related quality of life compared to reference data (Rijnsburger, Essink-Bot et al. 2004), but this was likely reflecting women's backgrounds (noted to have better health status than women from the general population) more than an effect of surveillance, for which psychosocial outcomes remain much less clear.

7.2 Limitations of this study

Heterogeneity of familial risk introduces significant difficulties to meaningful interpretation of existing evidence. Studies vary widely in their interpretation of familial risk. Some use the presence of a single family member with breast cancer as a surrogate marker of increased risk, whereas others require evidence of a positive gene mutation. These two definitions fall at opposite ends of a broad spectrum of familial risk. Definition-related issues are not limited to level of risk: 'screening' can include triennial mammography in the 5-6th decades or annual MRI scans from the age of 30 years, combined with annual mammography; 'gene mutation' is vague and almost entirely meaningless without associated risk levels and even terms like 'anxiety' vary significantly in terms of extent and impact. A further common problem encountered was recall bias, which in some studies spanned decades. These common issues should be borne in mind when comparing the results of this study with previously published work.

Participation in the partners' interview study was very limited. The study protocol restricted recruitment to partners of women who had already participated, and directly agreed to their partner being invited. Were this partner study to be repeated, a different, open recruitment strategy would likely improve participation and also reflect the views of a broader sample of partners. It is possible that a study of views of partners will struggle with recruitment regardless of methodology, if women's partners simply do not want to discuss their situation and views.

A further limitation of this study was the use of a *denovo* questionnaire. Previously non-validated tools have been shown to over-estimate satisfaction (Ware and Hays 1988). Whilst

significant time (both researcher and focus group participant's) and expertise have been spent validating this tool, it is possible that interpretation will improve with greater use. Limited response rates were disappointing and to some extent, restricted questionnaire analysis. The study protocol, discussed in depth at the focus group, felt that participants needed to consent to being sent a questionnaire with potentially emotive and highly personal questions. This two stage recruitment strategy is likely to have reduced the response rate considerably.

7.3 Clinical relevance of findings

This study adds to existing literature by measuring psychosocial outcomes at a time when options for risk management have recently changed. MRI surveillance is now widely available and represents a valid and effective risk management strategy, that for some women, better matches their desire for risk amelioration and their tolerance of the additional (i.e. not-risk-reducing) adverse effects of the different risk management strategies. This study also adds the views of partners, which have rarely been explored and particularly not since the addition of MRI surveillance.

7.4 Future work

Using the findings from this study, further work should focus on the development of tools aimed at reducing distress associated with risk management. This could take various forms:

1. Tools designed to identify women at increased risk of poor outcome
2. Tools designed to provide better information for women and their families
3. An education package for healthcare professionals designed to allow improved understanding of the needs of the woman (and her family) at increased familial breast cancer risk

Further research into the psychosocial impact of chemoprophylaxis in women at increased familial risk would add considerably to our understanding of the risk management options available at present. Similarly, the impact of cancer diagnosis on women who chose surveillance needs to be assessed, both in terms of decision satisfaction and psychosocial outcomes.

Healthcare professionals involved in assessing risk, informing women of their risk management options and guiding women through the actual process should explore all options available locally to facilitate a fully informed decision and well supported journey. This is particularly pertinent in an era of significant resource limitation, with units offering risk reducing surgery without, for example, the benefit of access to a psychologist. The findings from this study could be used to develop a tool to identify women likely to benefit from additional support to reduce the risk of what could be considered a predictably poor outcome, an example being a very young woman who considerably over-estimates her risk and who has little or no social support and pre-existing body-image dis-satisfaction. How that support is delivered clearly raises further resource issues for units to consider but these do need to be considered in order that an acceptable standard of care is provided for women at increased familial risk. By developing such a tool, risk could be stratified and scarce resources more appropriately targeted.

7.5 Conclusion

Women at increased risk of familial breast cancer are a diverse group. This study has provided an appreciation of the journey that they and their families face, the factors that women consider when making choices about how to manage their breast cancer risk and the outcomes they experience. Generally psychosocial outcomes are acceptable to women with high levels of decision satisfaction, but for a minority, risk reducing measures result in long-term psychosocial morbidity. The more common causes of distress include adverse body image changes, generalised and cancer-specific anxiety and distress. Recognising women at increased risk of adverse effects relating to their choice of risk management strategy may allow targeted support to enable women to better understand *and* manage their risk with a reduction in associated psychosocial distress.

Psychosocial outcomes in women at increased familial breast cancer risk

MD THESIS

VOLUME 2

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Appendices

1. Abridged study protocol

Psychosocial and Physical Outcomes in Women at Increased Familial Breast Cancer Risk

Protocol Version 5.1

12.09.2011

STH15485

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Study Synopsis

Breast cancer is the most common cancer affecting women in the UK, affecting over 40 000 women per year and causing the deaths of 13 000 (Cancer Research UK 2009). Whilst 70% of all cases are sporadic, i.e. not due to an underlying genetic predisposition, 25% are thought to have an inheritable component to their aetiology and a further 5% are thought to be due to carriage of one of the powerful breast cancer genes, including *BRCA1*, *BRCA2* and much less commonly, the Li-Fraumeni syndrome (TP53 gene mutation), Ataxia Telangiectasia and Cowden's syndrome. Such women are at a massively elevated risk of developing breast cancer compared to the normal population, with up to an 85% risk of developing the disease by age 70. In addition, the age at which the cancer occurs in these gene carriers is, on average, 20 years earlier than in women who develop sporadic cancer. The disease may therefore affect women in their 20's, 30's and 40's, when concerns about survival, body image, career, child care and fertility may be even more significant. Predictive testing of at-risk women is now possible, enabling at-risk individuals to take pro-active steps to reduce their risk of developing or dying from the disease. Strategies may include earlier or more frequent screening (with mammograms or MRIs) or prophylactic surgery to remove the ovaries or breasts before cancer develops.

Limited qualitative research is available that specifically explores the attitudes of women in the United Kingdom who are known to be at high risk of developing breast cancer and their decisions regarding coping with this risk. In particular little is known about the needs and satisfaction of the sub-groups known to have *BRCA1*, *BRCA2* or TP53 mutations.

This study will focus on the psychosocial and physical aspects of coping with an increased risk of developing breast cancer. Different ways of managing this increased risk will be explored. Factors affecting how women choose how to manage the increased risk including cancer-related anxiety, body image, physical disability and close relationships will also be discussed. The impact or potential impact of prophylactic mastectomy will be considered with particular reference to the issue of body image and its association with surgical procedure type and outcome, issues of regret relating to surgery and discussion as to whether the relative risk reduction achieved by the surgery has reduced their cancer-related anxiety.

A mixed methodology will be used to address these issues. Phase 1 of the study will comprise a systematic review of the literature to gain insight into some of the relevant issues that face these women such as cancer-related anxiety, close personal relationships, body image, physical well-being and quality of life.

Phase 2 will comprise qualitative, in depth interviews with purposively selected women who have undergone or have considered undergoing prophylactic mastectomy because of their genetic risk until saturation of themes in framework analysis is achieved.

Phase 3 will comprise a questionnaire study. The content of the questionnaire will be derived from the themes raised in the interview study. We anticipate that these questions will relate to regret or satisfaction with choice of risk management, the basis of any regrets, cancer anxiety, issues relating to family and personal relationships and physical issues including side effects from surgery and body image.

The Sheffield Familial Breast Cancer Service database will be used to identify eligible women. This database contains details of all women who have been seen by the service for the past 6 years for the purpose of case management, service evaluation and to enable women to be contacted if new risk reduction strategies become available, (for example, MRI screening which obtained funding approval by NICE 2 years ago: the database enabled us to contact all eligible women in retrospect and offer them this service). Women who have either had relevant gene mutations identified or who have had prophylactic surgery will be identified and contacted by letter inviting them to take part in the interview and/or the questionnaire study.

Phase 4 will comprise interviews with women's partners. We will identify these individuals when making contact with their affected partner. These interviews will focus on the initial decision making, (whether they approved or not, whether they were involved or not), the outcome, whether the decision has impacted on the relationship in a negative or positive way, their fears about the development of cancer in their partner and whether these have been allayed by regular screening or surgery. Finally we will determine whether they regret the initial decisions and why. We hope by these means to gain a comprehensive insight into the needs of this patient group for physical and psychological support before, during and after such profoundly life changing decisions.

Background

As per chapters 1 and 3

Aims and objectives

As per chapter 2

Study design

As per chapter 2

Systematic review of the literature

As per chapter 3

Qualitative, in depth, patient interviews

As per chapter 5

Eligibility Criteria

As per chapter 7

Recruitment strategy

The Sheffield Teaching Hospitals NHS Foundation Trust Familial Breast Cancer Service maintains a database of all cases seen for the past 6 years for the purpose of case management, service evaluation and audit. Data is recorded about breast cancer risk category, gene carriage status, attendance at regular breast screening and any decisions regarding prophylactic surgery. The lead clinician for the familial breast cancer service, Ms Lynda Wyld, will identify potentially suitable women, who will be contacted, either by letter or when they attend their follow up clinic, (most women who have undergone prophylactic mastectomy or who are gene carriers remain under annual review). They will be asked if they would be interested in taking part in the study and given an information pack to read.

The information pack will contain the following:

An Introductory Letter from the research study team outlining the study and inviting participation

A Study Information Sheet explaining the study

A Study Reply Form to indicate whether or not they wish to take part in an interview

A FREEPOST envelope

Upon receipt of a Study Reply Form indicating a positive preference for participation in an interview, participants will be contacted by telephone to arrange a convenient time and place for an interview to take place. Interviews will preferably be held in the Academic Unit of Surgical Oncology at the Royal Hallamshire Hospital and participants will be reimbursed for their travelling expenses when they attend and offered refreshments during the interview. A telephone interview may be offered for some women for whom travelling is difficult or they will be offered a home interview by one of the research team. A letter will be mailed confirming the interview date.

Data Analysis

The interviews will be digitally recorded and transcribed verbatim. A digital Dictaphone is available for this purpose, (including an adapter to allow telephone conversation recording). Transcript analysis will follow the National Centre for Social Research 'Framework analysis' approach to identify recurrent themes (Ritchie and Spencer 2003). This technique has successfully been applied to other studies undertaken within the Academic Unit of Surgical Oncology in which the study will be based (Wyld, Collins et al. 2005, Hussain, Wyld et al. 2007). Themes from these interviews will then be used to devise a more structured questionnaire which will help to quantify the findings of the qualitative phase on a wider population of women known to have a high risk of developing breast cancer in Yorkshire.

Women will also be asked if they would be prepared to allow their partner to be contacted for interview (phase 5 of the study). If so, an information pack, study reply form and FREEPOST envelope will be given to the women to pass to her partner to decide to take part as and when wished.

Questionnaire

As per chapters 6 and 7

Eligibility Criteria

As per chapter 7

Recruitment strategy

The Familial Breast Cancer Database, (details as above), will again be utilised to select eligible patients by Ms Wyld. A letter of invitation, study pack, study reply form, consent form and freepost envelope will be sent out to eligible women. Women who consent to being sent the questionnaire will be sent the questionnaire along with a freepost envelope.

Questionnaire Piloting and validation

As per chapter 6

Data Analysis

As per chapter 6

Views of partners

Background as per chapter 1

Eligibility Criteria

As per chapter 7

Recruitment strategy

Partners of women at increased risk will be identified by either approaching women (and their partners if present) in family history breast clinics or at the time of interviewing women at increased risk as part of this study and with consent from the woman at increased risk. Partners will be sent an information pack, study reply form and invited for interview. The pack will include:-
An Introductory Letter from the research study team outlining the study and inviting participation
A Study Information Sheet explaining the study
A Study Reply Form to indicate whether or not they wish to take part in an interview
A FREEPOST envelope

Analysis

As per chapter 7

Patient and public involvement in research

Patient and public involvement is an essential part of the proposed study. A consultation document issued by the DoH, 'Best Research for Best Health: A new National Health Research Strategy' (Department of Health 2005) and the Research Governance framework stressed the importance of increased public involvement in health research (Department of Health 2003). The UK Department of Health now requires Trusts holding NHS Research and Development Support Funding to demonstrate evidence of involving consumers in their research activity. Representation will be sought at all stages of the project including the development of the present project. The present study will involve the North Trent Cancer Research Network Consumer Research Panel and two service users with a keen interest in active involvement in the project. These individuals will be invited to join the study steering group. They have assisted with the study from the outset in particular in the development of study information sheets. They will also take a role in advising on how the research findings should be disseminated, how to reach users and help to ensure user

friendly appropriate language in newsletters, presentations etc. Travel costs and time to attend meetings will be reimbursed to all consumer members attending.

Dr Karen Collins has substantial expertise in patient and public involvement in health research (Collins and Ahmedzai 2005, Collins and Stevens 2006). She currently facilitates the North Trent Cancer Research Network Consumer Research Panel and is also an appointed Executive member of INVOLVE, a national advisory body responsible for providing information, advice and support to the Department of Health and other organisations on issues on patient and public involvement in health, social and public health research.

Activity	Time in months									
	3	6	9	12	15	18	21	24	27	30
Regulatory approval (Research Governance and Ethics) and literature review	■									
Prepare interview schedule for qualitative study (Phase 1)	■									
Commence interview recruitment and patient interviews		■								
Framework analysis of patient interviews		■	■							
Development and piloting of questionnaire (Phase 2)			■	■						
Recruitment for questionnaire study (including completion of questionnaire)				■	■	■				
Analysis of questionnaire data						■	■	■	■	■
Prepare interview schedule for qualitative study of health care workers and partners (Phases 4+5)				■	■	■				
Commence interview recruitment and interviews (Phases 4+5)					■	■	■			
Framework analysis of interviews					■	■	■	■		

Data management

All data will be handled, computerised and stored in accordance with the Data Protection Act 1998. A Site File of study documentation will be retained for a minimum of 15 years after study completion. All data collected will be pseudo anonymised and databases will be password protected in accordance with the Data Protection Act. Data will be stored in a locked room at the Royal Hallamshire Hospital, Sheffield, for as long as is necessary before being destroyed.

Ethics

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996. Informed written consent will be obtained from the patients prior to entry into the study. The right of a patient to refuse participation without giving reasons will be respected. The patient will remain free to withdraw at any time from the study without giving reasons and without prejudicing further treatment. The study will be submitted to and approved by a Research Ethics Committee prior to entering patients into the study. The Study team will provide the main Research Ethics Committee

with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation. The study will be conducted in accordance with the principles of GCP according to the EU Directive 2005/28/EC (Commission of the European Communities 2005).

Confidentiality

The study will collect patient data that may include some patient identifiers. All data collected will be pseudo anonymised and databases will be password protected in accordance with the Data Protection Act. A list of participant names will be stored separately from participant details. The study will comply with all aspects of the Data Protection Act 1998. Any information that would allow participant or clinicians to be identified will not be released into the public domain. If a participant withdraws consent for their data to be used then it will be confidentially destroyed.

Archiving

At the end of the study, data and the Study Site File will be securely archived for a minimum of 15 years. Following authorisation from the sponsors arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be confidentially destroyed.

Indemnity

This study will be sponsored by Sheffield Teaching Hospitals NHS Foundation Trust which therefore will be liable for negligent harm caused by the design of the study. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a research study, and the NHS remains liable for any negligence and other negligent harm to patients under this duty of care. However the risks associated with this study are minimal.

Study sponsorship

This study will be sponsored by Sheffield Teaching Hospitals NHS Foundation Trust.

Responsibilities and operational structure

The Chief Investigator (Ms Lynda Wyld) will have overall responsibility for all aspects of the study.

Funding

The day to day conduct of the study will be undertaken by Dr Sally Erskine, Academic Foundation Trainee, during her 4 month research placement and Ms Emma Surgey, Surgical Research Associate, over the following year. The necessary digital transcription machines are already available in the department. Stationary and Postage costs for the questionnaire phase will be supported by Ms Wyld out of her discretionary funds.

2. An example letter to participants

Printed on Hospital Headed note paper.

Dear [Insert name here]

We would like to invite you to participate in a research study. The study is being carried out by researchers from The University of Sheffield.

The study is called 'Psychosocial and Physical Outcomes in Women at Increased Familial Breast Cancer Risk'. We are trying to find out how women who have an increased breast cancer risk because of factors running in their family have coped with this risk. We are also interested in how their partners have been involved in and affected by these decisions. We hope that information from this study will help other women and their partners make choices about their own treatment in the future. We have contacted you with your partner's permission.

We have enclosed an information sheet for you to read and help you think about whether you would like to take part. Taking part or not is entirely up to you.

Whether you decide to take part or not, please complete the Study Reply Form and return it in the FREEPOST envelope provided. You do not need a stamp. If you decide not to take part, please tick the box beside 'No, I do not wish to take part in this study' and return the form to us. You do not need to fill in any other details on the form. The research team will not make any further contact with you about the study.

If you wish to take part in the study, then please tick 'Yes, I would like to take part in this study', fill in the contact details section on the Study Reply Form, and the consent form provided, and then return the form to us in the FREEPOST envelope provided. Once we receive the form, a member of our research team will contact you to arrange an interview at a time and place most convenient to you.

If you would like to find out more about the study before deciding whether or not to take part please contact the Principal Investigator, Ms Lynda Wyld, at the address above or by telephone on 0114 226 1229 or email l.wyld@sheffield.ac.uk

Yours sincerely

Miss Lynda Wyld

Senior Lecturer and Consultant Breast Surgeon

3. An example study information pack

Title: Psychosocial and Physical Outcomes in Women at Increased Familial Breast Cancer Risk

Invitation to participate in the study

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

The research team responsible for the study includes junior doctors who are completing the research as part of their training. They are supervised by consultants and experienced researchers.

What is the purpose of the study?

Some women may have an increased risk of developing breast cancer particularly if several members of their family have had breast cancer. They may be offered regular tests such as mammograms (x-rays of the breast) or MRI scans (magnetic scans) to help pick up any signs of cancer as soon as possible. They may be offered surgery to remove both breasts (prophylactic mastectomy or risk-reducing surgery) as this is may reduce the chance of them developing breast cancer.

Women who are thought to be at high risk may be offered genetic testing to see if they have a gene mutation which makes

them more likely to develop cancer in the future. Knowing whether or not they have a gene mutation may influence decisions about whether they would consider risk-reducing surgery or not.

Decisions about how to cope with an increased risk of breast cancer are very difficult, particularly if members of the family have been affected by the disease. They are often life-changing decisions. The purpose of the study is to understand why women make certain decisions about this risk and whether or not they are satisfied with their choices. This information may help women making such decisions in the future.

We would therefore like to interview a number of women about their views relating to their increased risk of developing breast cancer and how they have coped with this risk. ~~We have also included a short questionnaire asking about mood and general quality of life. This is to help us find out more about the choices made by individuals and the reasons behind their decisions.~~

We wish to interview approximately 25-30 patients during this study.

Why have you been invited to take part?

If you are a woman known to have an increased risk of developing breast cancer and have attended an out-patient breast cancer clinic at the Royal Hallamshire Hospital in Sheffield we are interested in interviewing you.

We would like to hear your views on coping with an increased risk of developing breast cancer and identify your preferences for managing this risk. We would like to discuss whether you

are satisfied with the decisions you made. Other topics which may be discussed during the interview include cancer-related anxiety and how this has changed over time, your family history and how this has affected your decisions, close personal relationships, body image, side effects from surgery (if relevant) and how the decisions you have made regarding coping with your increased risk of breast cancer affect/have affected your everyday life. We would also like to talk to you about the information and support you think women might need or want to help them make their decisions.

We know that close family members and in particular partners are also affected by these kinds of decisions. If you are comfortable, we will discuss these issues during the interview and may ask you whether you would be happy for your partner to be interviewed at a later date. Your partner will not be approached about this unless you have given us your permission during your interview. If you agree to your partner participating, you will be given information about the study to discuss with your partner.

We may also contact you at a later stage to ask if you would also complete a brief questionnaire about these issues.

Do you have to take part?

No. It is up to you to decide. Your taking part in this study is entirely voluntary. If you do not want to take part, you do not have to and you do not have to give a reason. If you decide to take part but later change your mind, you can withdraw from the study at any time and do not have to give a reason. No one will be upset if you do this and it would not affect any current or future standard of care or treatment you receive.

Whether you decide to take part or not is entirely up to you. If you decide not to take part in an interview, please tick the box beside 'No, I do not wish to take part in this study' and return the form to us in the FREEPOST envelope provided. You do not need to fill in any other details on the form and you will not be contacted again about this study.

What will happen to you if you take part?

If you wish to take part in the study, then please tick 'Yes, I would like to take part in this study'. Please fill in the short questionnaire, the contact details section on the Study Reply Form and the consent form provided, and then return them to us in the FREEPOST envelope provided. Once we receive the form, a member of our research team will contact you to arrange an interview at a time and place most convenient to you. The interview would usually take place in at the Royal Hallamshire Hospital, but can be conducted elsewhere if you would prefer. If taking part in an interview meant you had to travel to meet us, we would reimburse your travel costs. Interviews will take about an hour and will be conducted by an experienced researcher. This interview will be recorded with your consent. Recordings will be stored electronically and will only be available to the research staff working on the study. Your name and details will be stored separately from the interview recording and linked via a code number so you will not be identifiable. The recordings will be stored according to data protection laws, on a computer with a password kept in a locked room in the University. They will be kept for 2 years until the data has been processed, and then confidentially destroyed.

We would like to see how the issues discussed during your interview relate to your breast cancer risk and any treatment or

screening you have had for this. To do this, we would like to assess your breast cancer risk and any treatment or screening you have had for this. To do this, we would like to ask your permission for a member of the research team to access relevant sections of your medical notes to collect information about your investigation and management relating to your risk of breast cancer. We will only do this with your permission, if you tick the relevant box on the questionnaire, and all information will be dealt with in a completely confidential manner.

There may be opportunities to take part in the study at a later date, for example by completing a questionnaire. If you do not want to be interviewed but are interested in taking part in other parts of the study then please tick 'I do not want to be interviewed but am interested in participating in other parts of the study in the future', you will then be sent further information at a later date. You will only be contacted about participating in other parts of the study if you have agreed to this on the reply form.

If you agree, your GP will be informed that you are taking part in the study. They will not be told about any of your answers.

What are the possible risks and disadvantages of taking part?

There are no specific risks associated with taking part in this study but you may suffer some inconvenience in terms of the time taken to be interviewed. The interviews will take approximately an hour to conduct. You may find some of the questions difficult to answer. If you find any of the questions upsetting the interview can be stopped at your request at any

time. Specialist help and support is available should you feel any part of the study has upset or affected you in any way.

What are the possible benefits of taking part?

This research study will not directly benefit you, but what you tell us will give us a much better understanding of the views of and choices made by women at increased risk of developing breast cancer and should help us to provide better guidance for women facing similar decisions in the future.

Will your taking part in the study be kept confidential?

Yes. All information that is collected about you during the course of the research will be kept strictly confidential. Everyone who takes part in the study will be assigned a case number, and all of the data relating to each person will be held on a database and will only be linked to that code number, and not to your name or address so that you cannot be recognised. All interview documents will only be labelled with a code number and will be stored in a locked room in the University, which is only accessible to the research team. The records will be kept for 15 years after the finish of the study and then destroyed. Access to any information stored on computers will be protected with passwords and restricted to the researchers working on the study.

If you decide to withdraw from the study at any time this will have no effect on your medical care. You will not be asked for any further information. Any questionnaires or interviews that you have already completed will be kept confidential. The records will be kept for 15 years after the finish of the study and then destroyed.

What will happen to the results of the research study?

The results of the study will be presented at conferences and published in scientific journals, and will be made available to you if you wish. You will not be identifiable in any of the presented or published reports. Quotes from interviews may be used when presenting results; these will be fully anonymised so that you could not be identified. Please let us know if you would like to receive a copy of the research findings by ticking the box on the Study Reply Form. It may be several years before the study findings are ready.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, well-being and dignity. This study has been reviewed and given a favourable opinion by the Sheffield Research Ethics Committee.

What if you are harmed or unhappy about any aspect of the study?

As there are no specific risks associated with this study it is highly unlikely that you will be harmed. However some of the issues discussed may be difficult or emotional for you. You do not have to talk about any issues which you do not want to discuss. If you feel you have been upset by the interview and would like some extra support you will be offered follow up appointments with the clinical psychologist working for the family history breast cancer clinic or another clinical member of the team. If your score for the mood questionnaire indicates a high level of distress you will be advised of this. If you feel that this relates to your breast cancer risk you will be offered follow up appointments with the clinical psychologist working for the

family history breast cancer clinic or another clinical member of the team.

If you have any concerns or complaints about any aspect of the study please contact the Principal Investigator of the study in the first instance:

Ms Lynda Wyld (Senior Lecturer and Consultant Breast Surgeon), K Floor, Royal Hallamshire Hospital, Sheffield S10 2JF. Telephone 0114 226 1229.

If you remain unhappy and wish to complain formally, you can go through the NHS Complaints Procedure by contacting Dr Mike Richmond, Medical Director, Sheffield Teaching Hospitals NHS Foundation Trust, 8 Beech Hill Road, Sheffield, S10 2SB. Telephone: 0114 271 2178.

Who is organising the study?

The study is being run by the University of Sheffield.

Contact for further information

If you would like any further information, or have any questions concerning this study, please contact the Principal Investigator, Miss Lynda Wyld (Senior Lecturer and Consultant Surgeon), K Floor, Royal Hallamshire Hospital, Sheffield S10 2JF. Telephone 0114 2712510.

What do I need to do now?

Whether you decide to take part in this study or not, we would be grateful if you would complete the Study Reply Form accompanying this information leaflet and return it to us in the FREEPOST envelope provided. You do not need a stamp.

If you decide not to take part, please tick the box beside 'No, I do not wish to take part in this study' and return the form to us. You do not need to fill in any other details on the form.

If you wish to take part in the study, then please tick 'Yes, I would like to take part in this study', fill in the contact details section on the Study Reply Form, the short questionnaire and the consent form provided, and then return the form to us in the FREEPOST envelope provided.

Once we receive the form, a member of our research team will contact you to arrange an interview at a time and place most convenient to you. Feel free to call us with any queries you may have and/or talk the study over with anyone else.

Please keep this information leaflet for future reference.

**Thank you for reading this information sheet and for
taking an interest in the research study.**

4. An example consent form

Title: Psychosocial and Physical Outcomes in Women at Increased Familial Breast Cancer Risk

I confirm that I have read and understood the information leaflet dated 10th December 2009 (version 2.1) for the above study. I have had the opportunity to consider the information and ask questions and have had these answered satisfactorily.

Please initial box

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

--

I give permission for the interview to be audio recorded.

--

I understand that quotes from my interview may be used within written reports or publications and that any quotes would be completely anonymous and could not be linked to me in any way.

--

I give permission for my GP to be informed that I am taking part in the study.

--

I agree to take part in the above study



Name of Participant Date

Signature

Name of Person taking consent Date

Signature

When completed, 1 for participant, 1 for researcher site file

5. Letters confirming ethical approval and local research governance approval

Sheffield Research Ethics Committee

1st Floor Vickers Corridor

Northern General Hospital

Herries Road

Sheffield

S5 7AU

Telephone: 0114 271 4011

Facsimile: 0114 256 2469

08 October 2009

Ms Lynda Wyld

Senior Lecturer

Academic Unit of Surgical Oncology

University of Sheffield

Royal Hallamshire Hospital

S10 2JF

Dear Ms Wyld

Study Title: **Psychosocial and physical outcomes in women at increased familial breast cancer risk**

REC reference number: **09/H1308/121**

Protocol number: **1**

The Research Ethics Committee reviewed the above application at the meeting held on 05 October 2009. Thank you for attending to discuss the study.

Documents reviewed

The documents reviewed at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>	
Covering Letter		08 September 2009	
REC application		10 August 2009	
Investigator CV			
Participant Information Sheet: Patient interview	1	08 September 2009	
Participant Information Sheet: Questionnaire phase	1	08 September 2009	
Participant Information Sheet: Health Care professionals	1	08 September 2009	
Participant Information Sheet: Partners	1	08 September 2009	
Participant Consent Form: Patient interviews	1	08 September 2009	
Participant Consent Form: Consent for permission to contact partner	1	08 September 2009	
Participant Consent Form: Health Care professionals	1	08 September 2009	
GP/Consultant Information Sheets	1	08 September 2009	
Referees or other scientific critique report			
Interview Schedules/Topic Guides	patients V1	08 September 2009	
Patient invitation letter (interview)	1	08 September 2009	
Patient invitation letter (questionnaire - new patients)	1	08 September 2009	
Patient invitation letter (interview participants)	1	08 September 2009	
Reply form (questionnaires)	1	08 September 2009	
Study reply form (patient interviews)	1	08 September 2009	
Participant Consent Form: Partners	1	08 September 2009	
Letter of invitation to participant	Health Care Professionals V1	08 September 2009	
Study reply form - Health Care Professionals	1	08 September 2009	
Interview schedule - Health Care Professionals	1	08 September 2009	

Invitation letter - partners	1	08 September 2009	
Study reply form - partners	1	08 September 2009	
Interview schedule - partners	1	08 September 2009	
Protocol	1	08 September 2009	

Provisional opinion

Reviewing members felt that, on the whole this study did not raise any ethical issues and the researchers had submitted a very good application, all the documentation was very clear.

The Committee members noted the following:

Some clarity was needed on the number of questionnaires that would be required in phase III. There is a reference that the investigators may wish to contact participants at a later stage and it was queried whether they ought to be consented for this further contact. Members were concerned that their situation may change i.e. they may become ill or family circumstances may change and further contact in these instances may not be appropriate.

It was queried why it was necessary to inform the patient's GP that they were participating in the project. Concerns were expressed about the telephone interview and why this was felt to be necessary.

It appeared that women would be asked to consent if their partners could be approached to be interviewed. Members felt that this was perhaps not the best route; patients could be given a letter/invite to take to their partners. It was also noted that investigators wished to interview both the women and their partners; with a sample size of 25 this appeared to be 100% of the partners.

The following points were discussed and either clarified or points agreed:

- The sample size of partners appeared to be 100% take up. It was explained that this does not have to be the same patient/partner as some women may not have partners. It was not the intention to match.
- The missing questionnaires i.e. the QoL questionnaire, the Body Image Questionnaire and the HAD scale will be supplied. The questionnaire that will be

derived from phase I and Phase II will be submitted as, and when, it is complete. (The information sheet will also reference the number of questionnaires and how long it is expected to complete each one).

- The information sheets will be modified to reference that this is partly an educational study, and it will include how the tapes will be stored and when they will be destroyed. They will also be modified to include what will happen to the data if they decide to withdraw at some point. If relevant, some mention of direct quotes will be referenced.
- The subject of potential re-contact at some stage in the future was discussed and it was agreed that consent would be taken for this. The information sheets will be modified to reflect this change.
- It was explained that the rationale for informing the GPs of their patient's participation in the project is in case any issues, which may involve their GP at some point in the future, are uncovered during the interview. By informing them they are aware of the study and the possibility that their patient may contact them if problems arise. The committee accepted this view.
- The subject of the women consenting for their partner to be contacted was discussed. It was explained that this route had been specifically chosen so that they did not feel coerced into participating. Members felt that it would be preferable if the ladies could pass on some information to their partner.
- It was explained that the idea of the telephone interview was to provide minimal disruption for the patient. The telephone conversation would be recorded and participants would be made fully aware of this. Members felt that a list, (a script), should be read out to them prior to starting the interview to ensure that they were fully aware.
- It was confirmed that the departmental lone working policy would be employed if researchers visit patients at home.
- It was confirmed that the answers between patients and their partners would not be correlated; although it may be very interesting it was not the intention to undertake matching at this point in time.

The Committee would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below.

The Committee delegated authority to confirm its final opinion on the application to the Chair.

Further information or clarification required

The Committee gave a provisional opinion and requested the following information before confirming its final opinion:

- 1 The provision of the QoL questionnaire, the body Image questionnaire and the HAD questionnaire. (The Committee is aware that one other questionnaire will be submitted as and when it is formulated).

- 2 The information sheets (patients):
 - 2.1 Provide clarity on the number of questionnaires that will be administered in Phase III and explain how long each will take (approximately).
 - 2.2 Where there is mention of possible future contact, modify to read that they will be explicitly consented for any future contact.
 - 2.3 In the introductory paragraph it should inform that this is partly an educational project.
 - 2.4 Under the appropriate heading it should inform how the tapes will be stored and how long they will be stored.
 - 2.5 Under the appropriate heading it should inform what will happen to their data should they withdraw at some point.
 - 2.6 Any mention of South Sheffield REC should be modified to read 'Sheffield' REC.
 - 2.7 If it is intended to use direct quotes then some mention should be made of this.
 - 2.8 Where there is reference to their partner being contacted to take part in an interview. This should be modified to read that information will be given to them to pass on to their partner.

- 3 The information sheets (Health Care Professionals/Partners):
 - 3.1 (If appropriate). If there is the possibility that they are to be contacted in the future, modify to read that they will be explicitly consented for any future contact.
 - 3.2 In the introductory paragraph it should inform that this is partly an educational project.

- 3.3 Under the appropriate heading it should inform how the tapes will be stored and how long they will be stored.
- 3.4 Under the appropriate heading it should inform what will happen to their data should they withdraw at some point.
- 3.5 Any mention of South Sheffield REC should be modified to read 'Sheffield' REC.
- 3.6 If it is intended to use direct quotes then some mention should be made of this.

4 The consent form(s) (Patients):

Modify the consent form(s), (where appropriate), to add a box and text for them to agree to be contacted at some stage in the future.

- 5 The researchers will be asked to ensure that all modified documents are referenced with an up to date version number and date e.g. version 2 dated 6 October 2009. A request will also be made to state that the committee respectfully requests that only the modifications referenced above should be undertaken, no other changes should be made at this point.

If the investigators have any queries these should, in the first instance, be directed to the Coordinator.

The Committee delegated authority to confirm its final opinion on the application to the Chair or Vice-Chair.

When submitting your response to the Committee, please send revised documentation where appropriate underlining or otherwise highlighting the changes you have made and giving revised version numbers and dates.

If the committee has asked for clarification or changes to any answers given in the application form, please do not submit a revised copy of the application form; these can be addressed in a covering letter to the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 05 February 2010.

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

09/H1308/121

Please quote this number on all correspondence

Yours sincerely

Dr C A Moore

Chair

Email: april.dagnall@sth.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments.

Copy to: STH R & D Department

Sheffield Research Ethics Committee

Attendance at Committee meeting on 05 October 2009

Committee Members:

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>	
Miss Lauren Baxter	Clinical Data Manager	Yes		
Dr J Burr	Lecturer	No		
Ms F Claydon	Stroke Nurse Co-ordinator	Yes		
Dr Mary Cooke	Lecturer	Yes		
Dr Neal Edwards	Consultant in Pain Management	Yes		
Miss Pamela Kingman	Lay Committee Member	Yes		
Mr J Kirkland	Deputy Ward Manager/Charge Nurse	Yes		
Mrs C Leng	Scientist in Histopathology	Yes		
Professor R Loynes	Retired Professor of Statistics	Yes		
Ms Kay Marriott	Solicitor	No		
Dr C A Moore	Consultant Anaesthetist	Yes		
Mr Ian Potter	Senior Operating Department Practitioner	Yes		
Dr Basil Sharrack	Consultant Neurologist	Yes		
Dr Soon Song	Consultant Diabetologist	Yes		
Mr N Sykes	Lay Committee Member	Yes		
Dr S M Thomas	Senior Lecturer/consultant	Yes		

	Vascular Radiologist			
Mr M Wilkinson	Orthopaedic Surgeon	Yes		
Mrs Elaine Woods-Stringer	Nurse Lecturer	Yes		

Also in attendance:

<i>Name</i>	<i>Position (or reason for attending)</i>	
Mrs Sue Rose	Administrator	
Mrs A Dagnall	Admin Assistant	

Written comments received from:

<i>Name</i>	<i>Position</i>	
Dr J Burr	Lecturer	



National Research Ethics Service

NRES Committee Yorkshire & The Humber - Sheffield

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27 September 2011

Ms Lynda Wyld
Senior Lecturer
University of Sheffield
Academic Unit of Surgical Oncology
University of Sheffield
Royal Hallamshire Hospital
Sheffield
S10 2JF

Dear Ms Wyld

Study title: Psychosocial and physical outcomes in women at increased familial breast cancer risk
REC reference: 09/H1308/121
Amendment number: 5.2
Amendment date: 12 September 2011

Thank you for submitting the above amendment, which was received on 13 September 2011. It is noted that this is a modification of an amendment previously rejected by the Committee (our letter of 31 August 2011 refers).

The modified amendment has been considered on behalf of the Committee by the Chair.

Ethical opinion

The Sub Committee had no ethical concerns with items 1-7 at first review but could not give approval as the associated Item 8 was given an unfavourable opinion.

I am pleased to confirm that the Committee has given a favourable ethical opinion of the modified amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved are:

Document	Version	Date
Modified Amendment	5.2	12 September 2011

R&D approval

This Research Ethics Committee is an advisory committee to the Yorkshire and The Humber Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England

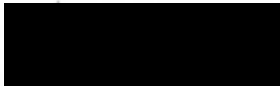
All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

09/H1308/121:	Please quote this number on all correspondence
---------------	------------------------------------------------

Yours sincerely



PP

Basil Sharrack
Chair

E-mail: anne.ward7@nhs.net

Copy to: *Simon Heller, Sheffield Teaching Hospitals NHS Foundation Trust*



National Research Ethics Service

NRES Committee Yorkshire & The Humber - Sheffield

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27 September 2011

Ms Lynda Wyld
Senior Lecturer
University of Sheffield
Academic Unit of Surgical Oncology
University of Sheffield
Royal Hallamshire Hospital
Sheffield
S10 2JF

Dear Ms Wyld

Study title: Psychosocial and physical outcomes in women at increased familial breast cancer risk
REC reference: 09/H1308/121
Amendment number: 5.1
Amendment date: 12 September 2011

Thank you for submitting the above amendment, which was received on 13 September 2011. It is noted that this is a modification of an amendment previously rejected by the Committee (our letter of 31 August 2011 refers).

The modified amendment has been considered on behalf of the Sub Committee by the Chair.

Ethical opinion

This modified amendment clarified that partners will only be approached with their partner's (i.e. the woman at increased risk) consent

I am pleased to confirm that the Committee has given a favourable ethical opinion of the modified amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved are:

Document	Version	Date
List of changes to protocol 5.0	1.0	12 September 2011
Letter of invitation to participant	2.0	12 September 2011
Participant Consent Form	1.0	12 December 2009

This Research Ethics Committee is an advisory committee to the Yorkshire and The Humber Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England

6. CASP study tool

Appraisal Questions

What information did the [researchers](#) seek to obtain? Was there a clear research question, and was this important and sensible? Was a questionnaire the most appropriate research design for this question, what design might have been more appropriate?

What was the sampling frame and was it sufficiently large and [representative](#)? Did all participants in the sample understand what was required of them, and did they attribute the same meaning to the terms in the questionnaire?

Were there any existing measures (questionnaires) that the researchers could have used? If so, why was a new one developed and was this justified?

Were the views of consumers sought about the design, distribution, and [administration](#) of the questionnaire?

What claims for reliability and validity have been made, and are these justified? Did the questions cover all relevant aspects of the problem in a non-threatening and non-directive way? Were open-ended (qualitative) and closed-ended (quantitative) questions used appropriately? Was a pilot version administered to participant's representative of those in the sampling frame, and the instrument modified accordingly?

What claims for validity have been made, and are they justified? (In other words, what evidence is there that the instrument measures what it sets out to measure?)

What claims for reliability have been made, and are they justified? (In other words, what evidence is there that the instrument provides stable responses over time and between researchers?)

Was the title of the questionnaire appropriate and if not, what were its limitations?

What formats did the questionnaire take, and were open and closed questions used appropriately?

Were easy, non-threatening questions placed at the beginning of the measure and sensitive ones near the end?

Was the questionnaire kept as brief as the study allowed? What was the response rate and have non-responders been accounted for?

Did the questions make sense, and could the participants in the sample understand them? Were any questions ambiguous or overly complicated?

Did the questionnaire contain adequate [instructions](#) for completion—e.g. example answers, or an explanation of whether a ticked or written response was required?

Were participants told how to return the questionnaire once completed?

Did the questionnaire contain an explanation of the research, a summary of what would happen to the data, and a thank you message?

Was the questionnaire adequately piloted in terms of the method and means of administration, on people who were representative of the study population?

How was the piloting exercise undertaken? What details are given?

In what ways was the definitive instrument changed as a result of piloting?

What was the sampling frame for the definitive study and was it sufficiently large and representative?

Was the instrument suitable for all participants and potential participants? In particular, did it take account of the likely range of physical/mental/cognitive abilities; language/literacy, understanding of numbers/scaling, and perceived threat of questions or questioner?

How was the questionnaire distributed?

How was the questionnaire administered?

Were the response rates reported fully, including details of participants who were unsuitable for the research or refused to take part?

Have any potential response biases been discussed?

What sort of analysis was carried out and was this appropriate? (e.g. correct statistical tests for quantitative answers, qualitative analysis for open ended questions)

What measures were in place to maintain the accuracy of the data, and were these adequate?

Is there any evidence of data dredging—that is, analyses that were not hypothesis driven?

What were the results and were all relevant data reported?

Are quantitative results definitive (significant), and are relevant non-significant results also reported?

Have qualitative results been adequately interpreted (e.g. using an explicit theoretical framework), and have any quotes been properly justified and contextualized?

Was the analysis appropriate (e.g. statistical analysis for quantitative answers, qualitative analysis for open-ended questions) and were the correct techniques used? Were adequate measures in place to maintain accuracy of data?

What do the results mean and have the researchers drawn an appropriate link between the data and their conclusions?

Have all relevant results ('significant' and 'non-significant') been reported? Is there any evidence of 'data dredging' (i.e., analyses that were not 'hypothesis driven')?

Have the researchers drawn an appropriate link between the data and their conclusions?

Have the findings been placed within the wider body of knowledge in the field (e.g. via a comprehensive literature review), and are any recommendations justified?

Can the results be applied to your organization?

Conflicts of interest are declared.

Rate the overall methodological quality of the study, using the following as a guide:

High quality (++): Majority of criteria met. Little or no risk of bias.

Acceptable (+): Most criteria met. Some flaws in the study with an associated risk of bias.

Low quality (-): Either most criteria not met, or significant flaws relating to key aspects of study design.

Reject (0): Poor quality study with significant flaws. Wrong study type. Not relevant to guideline.

7. Interview prompt sheets

Risk reducing mastectomy interviews

At start

- Introductions
- Brief overview of study
- Explain purpose of interview
- Check had time to read information leaflet
- Any questions
- Check they have signed a consent form
- Confidentiality and anonymity issues
- Check out ok to tape record discussion
- Ensure participants feel free to stop interview at any point or turn off tape

Issues that may be raised during interview:

- Cancer-related anxiety
- Worries about survival/the future
- Life insurance
- Choice of surgery/other management
 - Competing sources of advice
 - indecision
- Input of HCPs/partners/family into this decision
- Expectations of surgery – benefits concerning body image vs cancer-related anxiety
- Satisfaction with surgery/other management
- Complications of surgery
- Psychological and social functioning before and after any surgery/management decisions (including isolation, confidence, quality of life)
- Regret and its variation with time
- Body image
- Close personal and sexual relationships
- Family members who have been affected by breast cancer

At end

- What will happen with the data-timescale
- Ensure participant has contact details of researcher if they wish to contact them or discuss anything relating to the interview
- Ask if wish to receive a summary of the findings of the study and provide timescale
- Check any other questions
- Thank participant for their time and support with the study

Screening women interviews

Beginning

- Introductions
- Brief overview of study
- Explain purpose of interview
- Check had time to read information leaflet
- Any questions
- Check they have signed a consent form
- Confidentiality and anonymity issues
- Check okay to tape record discussion
- Ensure participants feel free to stop interview at any point or turn off tape.

Issues to explore

- Discovery of risk – how, when, who else was involved
- Decisions regarding surgery and screening
- Thoughts regarding surgery
- Thoughts regarding screening
- Risk perception
- Waiting for results/anxiety
- If offered surgery, what puts you off
- Have you thought what you would do regarding surgery if you are diagnosed with cancer.....one or both breasts removed/breast conserving surgery/reconstruction
- Oophorectomy / screening thoughts (and awareness of risk)
- Experience of screening so far
- Timing, anxiety, painful, benign recalls, claustrophobia, flexibility etc
- Longterm plans (e.g. continue screening or surgery)
- Family history – how other women have managed risk, been affected etc.
- Effects of increased risk
- Cancer worry, risk perception, body image, feeling re breasts, general anxiety etc.
- Effects on relationships – partner, children, other family, friends, colleagues etc
- Insurance
- Access to information
- Access to other affected women
- Any comments – e.g. things that could be improved

The end

- What will happen with the data
- Ensure participant has researcher contact details if they wish to contact them
- Ask if they wish to receive a summary of study findings (and timescale)
- Any other questions
- Thanks

Partner interview prompt sheet

Beginning

- Introductions and general chat to break the ice/offer tea/cake/how did they get here and check re travel expenses and if they need them to be reimbursed.
- Brief overview of study and explain purpose of interview
- Check had time to read information leaflet, any questions
- Check they have signed a consent form
- Confidentiality and anonymity issues
- Check okay to tape record discussion
- Ensure participants feel free to stop interview at any point or turn off tape.

Issues to explore

Initial question about the background to your relationship with X....how did you meet, how long together? Do they have kids....how many, how old etc.

- Discovery of partner's risk – how, when, who else was involved
- How did confirmation of risk affect them?
- Were they together at the time? If so, was he involved, attending appointments?
- Did he ever feel he was being ignored/out of the female issues loop
- Awareness of family history
- Did he want her to go for gene test or not
- Did he want her to have surgery/screening
- What was his main concern/worry
- Has he had any first-hand knowledge of her family members who had suffered with cancer and how did this influence his own views
- Fear for children coping with cancer/how would he cope if she had cancer or he lost her
- Risk perception
- Decisions regarding surgery and screening – was he involved? Did they discuss it?
- Thoughts regarding surgery, including reconstruction or not, and options.
- Thoughts regarding screening (and awareness of possible outcomes)
- Oophorectomy / screening thoughts (and awareness of risk)
- Family history – how other women have managed risk, been affected etc.
- Effects of increased risk
- Cancer worry, body image, feeling about breasts, general anxiety etc.
- Effects on relationships – partner, children, other family, friends, colleagues etc
- Insurance
- Cautious exploration of sexuality/physical attractiveness of partner...their view...how they feel their partner thinks it may have affected them and feelings about the scars.....what thoughts do these provoke when you see them. Does your partner let you see her scars/unclothed. Have you touched her breasts and does your partner allow you to do this
- Access to or need for support for him, information, other people in a similar situation
- Any comments – e.g. things that could be improved

The end

- What will happen with the data
- Ensure participant has researcher contact details if they wish to contact them
- Ask if they wish to receive a summary of study findings (and timescale)
- Any other questions
- Thanks

8. An example interview transcript

An example of an interview transcript:

Interview 009 on 2/2/10

Interviewers: Interviewer A and Interviewer B at 009 home

1 – Thanks very much for talking to us today. Could you just tell me a little bit about when you first became aware of your increased risk of getting breast cancer?

P – We did a family history with the genetics people and um they did all the, because my Mum actually died of ovarian cancer

1 – Right

P – and she previously had breast cancer so they started doing a bit of a study on my Mum, and with us, and it sort of put it into that we were in a risk group, that we couldn't they tested for the *BRCA* but it came back negative but also there's breast cancer on my Dad's side of the family. So, we weren't too sure because there was nobody alive to test

1 – Right

P – so they decided that we were at an increased risk and to perhaps have more MMGs

1 – Okay

P – and I had a MMG and it showed up some calcification, so I discussed it with Breast Surgeon and she said I could perhaps be at increased risk and

1 – Mmm Hmm

P – and I've also got MS

1 – Right

P – So my MS consultant wanted this er, sort of, er getting out of the way, because of the treatment he's going to put me on for my MS, which is er, a chemotherapy kind of drug

1 – Okay, okay. So you don't have the gene, or you've not tested positive for the gene so far

P – No.

1 – Okay. and did anyone tell you what your risk would be?

P – Well I had my ovaries removed

1 – Right

P – and they said that my risk would be halved by doing that

1 – Right

P – But then it came back with the calcification, so they said that, there wasn't particularly a percentage of how at risk I was but...

1 – Right, okay.

P – Nobody could really answer the question

1 – Right okay. So when did you decide to have your ovaries removed?

P – Erm, 2008.

1 – Okay and who did you talk to about that?

P – The genetics people, and, (pause) the consultant who'd actually done my Mum's operation

1 – Okay

P – I can't remember his name

1 – Don't worry.

P – small laugh

1 – Right, okay. So how did you make that decision? What sorts of things did you...

P – Well, I'm 53 next so I don't want any more children

1 – Yes,

P – and I thought, well, it's not something you'd particularly see or notice, and if it'll half the risk of ovarian and breast cancer, it was perhaps something that was a good thing to do at the time, which

1 – Right...

P – obviously at 53, you don't want anymore children

1 – Yeah, okay

P – I've got enough, (laughs)

1 – Okay and what about the breast operation, how did you decide about that?

P – Well it was quite a hard decision actually because I wasn't sure what to do, but because of the treatment I'm going to have for my MS and talking to the MS consultant, he thought it was perhaps better to get this out of the way, and not have it to come back to at a later date

1 – Right okay

P – Because apparently, erm, the, drug that he's putting me on, there's a risk of bleeding when you're actually on the drug, if you undergo any operation

1 – Okay

P – So

1 – Okay. So who did you talk to about the breast operation?

P – (Breast consultant), and, obviously family and friends

1 – Mmm hmm

P – And that was it really.

1 – Okay. And how long did you take making that decision?

P – Erm, not an awful long time really, because, between May and , October really, well perhaps 3 months, 4 months, because I wanted to get onto this drug that Mitoxantram they call it.

1 – Right

P – And I want to start the, my MS on that as soon as possible.

1 – Right, so you made your decision quickly

P – Yes

1 – More because of the MS than because you were worried

P – Yes

1 – Right. Okay. So how long had you known about your possible increased risk for, do you think before you made the, before you made your choice?

P – Well when we went through the genetic testing in, er, 2008, I was aware of the risk, but you sort of shove it to the back of your mind,

1 – Mmm

P – You don't think about it, you don't do you?

1 – no

P – It's there, but carry on with your life

1 – Mmm

P – It's not anything that was sort of at the forefront of my mind, it was sort of, just wasn't, don't think about it

1 – Yeah, okay. And did you feel it was your decision when you decided what to do? Or did you feel people were pushing you into

P – No, I don't think anybody, there was any pressure from anybody at all. Erm, I could've done with a little bit of help making the decision

1 – Right

P – A little bit more, but, erm, no, I think it was my decision, and nobody pushed me into it at all

1 – ok

P – I felt rushed a little bit but

1 – Right

P – But that was because of the MS

1 – Right okay. And what things put you off from just having the increased screening

P – I don't really know. It was just sort of a decision at the time

1 – Mmm hmm
P – I didn't want to have to come back to it at a later date
1 – Right
P – I thought cause of my MS is going downhill quite rapidly,
1 – Right, okay
P – and I didn't want to have to come back to this sort of decision if my MS got any
1 – Right
P – any worse
1 – Okay. And what kind of operation did you have
P – For
1 – For the breast
P – For the breast? Not quite sure.
1 – Did you have any kind of reconstruction
P – Yeah, I've had reconstruction
1 – Okay
P – Just an incision from there to there (points) around the sides
1 – Okay
P – both sides
1 – Okay. Did they use muscles from your back at all?
P – No
1 – No. And they didn't use any muscles from your tummy or anything like that?
P – No
1 – Okay. Did it make a difference to you that you could have the reconstruction? Or do you think that you would have had it done anyway?
P – I think that did make a big difference. That made me feel more positive about it
1 – Yeah
P – Rather than just being completely flat chested
1 – Yeah
P – That made it seem that there was, erm, light at the end of the tunnel.
1 – Yeah
P – That I wouldn't look any different really.
1 – Okay. And how much information did you have about the operation before hand? Did you have an idea what it might look like afterwards, and things?
P – Yeah. The BCNs sat down and discussed it with me for some time. Showed me photographs. And discussed what it would actually look like, and
1 – Mmm hmm
P – did like, showed you bad results and good ones
1 – Mmm
P – You was aware of what could go wrong and,
1 – Mmm
P – you know, what if everything goes okay
1 – Yeah
P – How they look.
1 – Mmm. Okay. So when did you actually have the operation?
P – October
1 – Right
P – Last year
1 – so not that long ago
P – No
1 – How did it go?

P – I think the operation went well. It yeah. Erm. I didn't really have any trouble, not with my breasts at all. Erm. It was my legs that were the problem. Because it sent my MS, like spiralling as well.

1 – Did it? Right

P – My legs didn't come back to me for about, 4 weeks afterwards. I was, couldn't really walk very far at all.

1 – Right okay. But you didn't have any complications from the breast surgery itself?

P – No

1 – Did it go, was it what you expected? Did you expect

P – Yeah

1 – Yeah. And what about with the MS? Did you expect that to be upset by it?

P – I did really. Because I know if I get stressed about anything that gets upset

1 – Right

P – So anything, anything that gets, even having a tooth out

1 – Right

P – so, er anything, you get, you tighten up don't you?

1 – Yeah

P – So,

1 – Was it, erm, more painful, less painful than you thought it would be?

P – The operation was exactly as I

1 – Exactly

P – thought it would be, um, afterwards I think i got more pain than I thought, but in areas where I didn't expect to get it

1 – Right okay

P – Sort of thing, really

1 – Where abouts?

P – Right in the middle there (points), there

1 – okay

P – I had a lot of pain there (still pointing) You know not where you'd, where the scars are fine, it's just a feeling there really, really sore. And it's still tender and sore.

1 – Yeah.

P – You can't sort of see anything.

1 – No

P – It's just really sore to touch, but I spoke to (Breast Surgeon) about it, and she said it's actually where they've had to take muscle away from my ribcage

1 – Right

P – Around that area, it's where, you know like, they have to pull it off

1 – Yeah

P – She explained

1 – Right okay, so that's where it's tender.

P – Yeah

1 – Do you have implants?

P – You do.

1 – And have you had any problems with those?

P – No

1 – No. You're happy with how they feel and things?

P – Yeah.

1 – Yeah.

P – they feel harder than I thought they would

1 – Right

P – Um. I thought they'd feel more softer to touch, but they are harder, and

And they're more underneath my arms than I thought they would be

1 – Right

P – There seems to be more there

1 – Okay

P – Than what there was before, because like, you not sort of, when you put your bra on, you move your breasts to erm, the centre

1 – Yeah...

P – Whereas these don't move now

1 – Okay.

P – Laughs

1 – Laughs

P - You know what I mean?

1 – Laughs. How did you feel about your body before you had the operation?

P – Okay. No problems really

1 – Okay. And what about now you've had it done?

P – Erm. It's not upset me or anything. I feel okay about it, erm

1 – Right.

P – Obviously it doesn't look the same and it takes some getting used to.

1 – Mmm

P – But, er, no. Okay with it. I don't, I mean, people who can't really, once I've got my clothes on, they can't tell, they don't think

1 – Mmm

P – I look any different

1 – Yeah. Yeah.

P – So

1 – Okay. And has it stopped what you can do physically at all? I know, surgery, it affected your MS, but has the breast operation had any affect at all?

P – No

1 – It's not affected your arm muscles or anything like that?

P – No

1 – Okay. So. Has it affected you being able to work?

P – No not really

1 – No

P – No, because I'm a secretary, so

1 – Right, okay

P – It's no, I do actually do work from home so

1 – Right okay. Do you have a partner?

P – Yes

1 – And has it altered your relationship with your partner at all?

P – No

1 – do you think?

P – No

1 – Not affected things?

P – No

1 – Has he commented on how it looks, or things like that?

P – He thinks they looks okay. In fact he thinks they look a lot better than he expected

1 – Right

P – He thought they'd look a lot worse than this

1 – Okay

P – Um. And er, I mean it's the really thin line where the actual stitching it

1 – Right

P – I mean, I can hardly imagine in time that that will fade, and not see anything really.
1 – Yeah. Okay. And did, did he, erm, sort of, think you made the right decision about having the operation?
P – I think so, yeah.
1 – Yeah
P – Yeah
1 – He didn't have any objections to it particularly
P – No. He said it was my decision and he'd go along with whatever I decided
1 – Okay. And do you think it's affected your sexual relationship at all?
P – No
1 – Has it made any difference?
P – No, I don't think so
1 – Okay. What about your relationships with the rest of your family?
P – I think they're okay about it, um
1 – Okay
P – I've got two boys, teenaged boys
1 – Right
P – So I mean, they, I think it's really just gone straight over the tops of their heads
1 – Right, okay.
P – Laughs
1 – Did you explain to them, what...
Phone rings – interview interrupted.

Interview recommenced.

1 – Okay, this is just starting again with 009. Okay so we were just talking about erm, your relationship with your family, and you were telling us about your sons. Did they understand what you were having done, and why you were having it done?
P – Yeah
1 – And
P – I explained
1 – so they know about the risk of cancer and so on?
P – Yeah
1 – So, erm, do you think they'll have any kind of testing in the future? Whether they might have the risk, or not, because you didn't?
P – Erm, I'd like to think not, because you don't know do you.
1 – No. Okay. And, you said you went with the rest of your family to have the screening
P – Mmm
1 – Did anybody in your family have the gene?
P – No
1 – No
P – Well there was only me and my sister who had the screening
1 – Right
P – And my aunty lives down south, who was my Mum's sister, and er, she didn't go for any screening at all. But she is, 70.
1 – Right
P – so
1 – and has she had any breast cancer or anything like that?
p – No
1 – Did you sister decide to have the operation?
P – No she's not made any decisions yet
1 – Right

P – she's 10 years younger than me, so
1 – right, okay
P – and at that point they were actually trying for a family, so they were um
1 – okay
P – they were undergoing IVF so
1 – Okay
P – Which has failed, so
1 – Okay, so there are sort of different issues really
P – Yeah
1 – for them. Okay. And are you pleased with the decision that you've made now?
P – Yeah.
1 – Do you think you'd do the same thing again?
P – Yes, I think I would. Erm. There's been ups and downs with it. Erm. You know like your feelings that I went through quite a period of feeling quite weepy. Erm. Cause it's been quite a traumatic year really, because I lost my father as well
1 – Right
P – So, like, I did feel quite emotional about a lot of things.
1 – Mmm
P – But, I think I made the right decision
1 – Was it, was the sort of emotional time while you were making the decision or do you think it's been since you've had the operation
P – Since. It was after. I think, whether its the anaesthetic and things like that, you know,
1 – Mmm
P – The things that you go through all the trauma.
1 – Mmm
P – I think it may be linked to that really.
1 – Mmm hmm. Okay. And, erm, so you've obviously had quite a lot of different things going on in your life, with the MS and with your father.
P – Mmm hmm
1 – Have you had any other problems in the last couple of years?
P – well, my mother died as well
1 – Right
P – so that was the other thing
1 – Okay. Okay. Do you have anything you want to ask? (to interviewer2)
2 – Um, I don't think so no. Is there anything that you think we could have done to have helped with the whole process?
p – No I think everything, you know, I think the hospital really did, you know, they were quite supportive. Erm. Whilst I was in hospital, sort of the nurses and everything, were wonderful, on the ward, they were really kind, considerate. Erm. And I think the aftercare, going, you know, when al went back for the inflating of the
1 – Mmm hmm
P – thought that was okay. And knowing that there was somebody like your BCN that you could talk to, phone up any time of the, you know
1 – Mmm hmm
P – that they were there for you.
1 – yes
P – Thought that was okay, yes.
2 – Did you get much counselling around the time of the gene test, or when you were trying to make the decision about what to do?
P – Erm. Well Breast Surgeon actually explained a lot of it. Mmm. She. Yeah, I think I had two or three meetings with her and discussed it, and, mmm.

1 – And what about with the, with the, gene testing, did you have counselling before you had the gene test itself?

P – Yes. And they were actually in touch with me yesterday.

1 – Oh right

P – And so, they're going to get in touch in the summer, um, for a further discussions

1 – is that, do you know what that's about

P – its about the gene testing, doing the family history

1 – right

P – cause they're building up a family history tree, for like future generations

1 – okay

P – and adding little bits to it, as, erm, obviously you, they've got to start somewhere, and they can't go back can they, to people who are no longer here,

1 – No

P – so I think she's she's building it up from me and my sister.

1 – okay. Okay. Did you find the decision difficult at all because you didn't know that you definitely had the gene?

P – Yeah, that was one of the really

1 – Mmm

P – if you'd have you know, it's er, its like, if you've got the gene you know,

1 – Mmm

P – Don't you, that you've, that it's, that you may have. That there may be something that they're not picking up,

1 – Mmm

P – as part of the gene testing

1 – Mmm

P – Mmm. It was quite difficult

1 – Mmm. What would you advise other women who, perhaps definitely had the gene? What would you advise them to do?

P – I'd advise them to go ahead and have the reconstruction.

1 – right

P – Because, um, my mum had breast cancer, my grandmother had breast cancer

1 – right

P – and I saw my grandmother had quite a bad time with it

1 – Mmm hmm

P – and so living through and seeing her, she, got lymphoedema is it, in her arm

1 – Mmm hmm

P – and her arm swelled up and went purple

1 – right

P – it went horrible. And because she had radio, radition, chemotherapy and radiotherapy, it never healed, you know, the wound?

1 – Mmm

P – And seeing that, it remembering what that was like

1 – Mmm hmm

P – You know, seeing things that don't look very nice in the past

1 – Mmm

P – It always comes to the front of your mind

1 – Yeah. Yeah. Okay. Erm. Have you ever had any problems with insurance? Telling people about your family history?

P – No. Because we've never taken any out since

1 – Right, okay.

P – Yeah

1 – Okay. And do you think you would have made, perhaps, a different decision if you hadn't been thinking about the MS? Do you think?

P – Er, I think I would have delayed the decision

1 – Right

P – And, perhaps had more er, screening.

1 – Right

P – Rather than having the screening, erm. And made perhaps the decision at a later time.

1 – right, okay.

P – Because (Breast Surgeon) put me on, is it arimidex?

1 – Yeah

P – And the mitoxantram, they wasn't quite sure how those two would work together

1 – right

P – the two types of drugs

1 – so you had to stop the arimidex

P – Yeah, with them being both a type of chemotherapy

1 – mmm

P – they weren't sure

1 – okay. And did you seek any advice from anywhere else? Apart from the breast care team?

P – Er. I discussed it with my GP

1 – Right

P – And she was quite helpful. I mean, she's been my GP for like the last 23 years, so she does know

1 – yeah

P – the family, and erm

1 – Okay, okay. And did you get information, booklets and things from the hospital?

P – Yes

1 – were they helpful? Do you think?

P – Yes

1 – Yes

P – I mean, obviously, you look on the internet don't you,

1 – yes

P – but quite a lot of the information on there, erm,

1 – did you find that helpful, the internet? That information

P – yes, I think so, cause I look upon the internet, as somethings give you negative vibes, and I mean if you look at where people aren't happy with things, I sort of read over that and erm,

1 – yeah

P – read the positive

1 – yeah

P – results, I don't read everybody's negative answers

1 – did you talk to anybody who'd had the operation, or not had the operation

P – no

1 – or anything like that? Did you not want to, or, was it not sort of offered to you?

P – I don't think it was offered

1 – Right

P – I don't remember. No. I don't think anybody said there was someone that you could speak to

1 – do you think it would have helped?

P – I think so yes

1 – Yes. Yeah. So, do people know why you've had the operation?

p – Yes

1 – They do. And how do they react to that, have they been?

P – Erm, Everybody, I mean all the women who I've spoke to about it, they're all positive, and say you've done the right thing

1 – Mmm
P – I mean, I work in an office at work, full of men, and
1 – okay
P – and they find it amusing,
1 – right
P – whereas you can imagine they all think I'm going to look like Jordan
1 – Laughs
P – Laughs
1 – Okay
P – that's, I mean, but I have told them all, and been quite open with them. I'm not, I don't feel ashamed, or that I shouldn't discuss it, and I think it's better if you're open and you tell people.
1 – Yeah.
P – Well, they've all spoke to me about it, in the office, all the men, and they've been quite, you know. They might as well know
1 – Yeah
P – I'd rather they talk to my face than behind my back sniggering, so
1 – Yeah.
P – Laughs.
1 – Laughs
P - I also work in a big factory with about 200 people, so it'll be around that
1 – Right, yeah. Has anyone else that you know had this kind of operation
P – No
1 – Or had an increased risk of breast cancer?
P – No. Er, yes, actually. My cousins on my Dad's side,
1 – Right
P – 2 of them, cause they're Mum had breast cancer, and they, actually, do have er, regular MMGs which I think because they were under 50 at the time they went private.
1 – Okay. Okay. So do they have the gene, or are they just
P – No, I don't think they've tested them for the gene
1 – Right okay
P – I'm not sure
1 – But they were concerned because their mother had had the breast cancer?
p- mmm
1 -Okay. Is there anything else at all that has been important to you whilst you've been making these kinds of decisions?
P – I mean one of the, the things that I've found most important is you wonder what you're going to look like.
1 – Mmm
P – Erm. One thing I would say is that I was quite and I know that this is like, sounds really strange, but. I feel really uncomfortable wearing underwired bras, so you've got to wear non-wired bras. And there's just no choice! There really plain and boring
1 – Okay
P – Laughs. And that, because I like nice underwear, and, no, you can't get any nice matching sets.
1 – Yeah.
P – Laughs.
1 – And I suppose that's something you might not have thought about before hand
P – No, not at all
1 – No. No-one would have mentioned it probably
P – No never
1 – No
P – All the non-wired bras are all plain white or black

1 – yeah
P – that’s the choice which you’ve got
2 – that’s annoying isn’t it!
P – it is yeah, Because there’s some absolutely beautiful underwear. And the other thing, I’ve had to throw all my other underwear away, and you know, you’ve got nice sets, and you don’t know what to do with it all, so it all went in the jumble bag all the bras
1 – Mmm
P – Wondered if anybody might get any use out of them.
1 – Yeah
P – You know, the one’s that were quite new.
1 – Yeah. Were you offered any other kinds of operations, so were you offered reconstructions with muscles from other parts of the body?
P – No because Breast Surgeon didn’t think I’d got enough muscle on my back, because I’m quite bony
1 – Okay
P – Breast Surgeon, she also thought that because with my MS I use my arms to pull myself upstairs quite a lot,
1 – Right
P – And my arms to balance, that she didn’t want me having any more
1 – Right okay
P – anything to make it any worse, so um
1 – Yeah. So, sort of it was the implants or not having the implants was the choice that you made.
P – Yeah.
1 – Okay. Erm. Anything else at all that you’d like to talk about, either to do with your decision or things that could’ve been done better?
P – No I don’t think so
1 – No
P - think everything was okay.
1 – any other questions (to 2)
2 – No, it’s been really helpful, thanks
1 – Yeah, thanks very much. Okay I’ll stop recording.

Footnote

As soon as microphone was stopped pt discussed the bra issue again, would have made her feel much better to get some new underwear, she had planned to go on a big shopping spree for it. She said she knew she didn’t have to wear a bra anymore but she didn’t feel comfortable with out especially in the winter and this was a really important issue for her. The underwiring was uncomfortable because the breasts were more lateral than previously.

She re-iterated that it hadn’t really affected her as she was off work for the MS that was the main problem but that she can work from home.

Pt also discussed fact that she was about to pick her children up from school to attend their friends funeral who had died from pneumonia which was a shock.

9. Samples of framework analysis

FILE	HOME	CREATE	DATA	ANALYZE	QUERY	EXPLORE	LAYOUT	VIEW	FRAMEWORK MATRIX
<p> <input type="checkbox"/> Highlight <input type="checkbox"/> Coding Context <input type="checkbox"/> Layout <input type="checkbox"/> Coding Information <input checked="" type="checkbox"/> Rich Text <input type="checkbox"/> Coding Excerpt Associated View </p> <p> <input type="checkbox"/> Delete Summary Link <input type="checkbox"/> Auto Summarize <input checked="" type="checkbox"/> Highlight Summary Links Summary </p>									
AD : significant	AE : still worry after surgery	AF : worry reduced by screening	AG : benefits of knowing risk	AH : detrimental effects	AI : difficult interfamily relationships caused	AJ : improved relationships	AK : no change	AL : worry about kids	AM : worry about my sc or sz affecting them
10 : 015	<p>s always in the ground</p>	<p>I don't think so because I had the. What's the tests you have? The</p> <p>S: mammograms?</p> <p>015: Yes sorry, I had a mammogram and I also had a, is it a CT scan?</p> <p>S: It could have been or a MRI?</p> <p>015: A MRI scan yeah and they were both negative</p>	<p>feel in a way I feel lucky that we are able to have these tests, find out because we could do something about it you know</p> <p>Yeah I think its important. I do think that the rest of our family are now aware that the gene is in the family and then they have got the options themselves whether they choose to have the test or not.</p>	<p>It was all my own decision anyway and he supported, he fully supported me and if he felt it was the right thing to do but it was my decision you know and he fully support whatever decision I would have taken, he was just scared I think</p>	<p>Breast cancer I think from what breast surgeon has told me is its more likely to be on the surface obviously it could go</p>	<p>it was quite lucky that we had got my mums blood</p> <p>I think once my sister got the cancer it was</p>	<p>I thought it had brought me and my sister a little bit closer together</p>	<p>my husband, we had a bed and breakfast at the time, so my husband kind of ran that and looked after me so I could literally</p>	
Summary Links: Cell 0									

FILE	HOME	CREATE	DATA	ANALYZE	QUERY	EXPLORE	LAYOUT	VIEW	FRAMEWORK MATRIX
<p> <input type="checkbox"/> Highlight <input type="checkbox"/> Coding Context <input type="checkbox"/> Layout <input type="checkbox"/> Coding Information <input checked="" type="checkbox"/> Rich Text <input type="checkbox"/> Coding Excerpt Associated View </p> <p> <input type="checkbox"/> Delete Summary Link <input type="checkbox"/> Auto Summarize <input checked="" type="checkbox"/> Highlight Summary Links Summary </p>									
AS : effect on getting a new partner	AT : effect on partner	AU : opinion on surgery	AV : partner role in decision	AW : sex	AX : Shock	AY : Not a shock	AZ : Time bomb	BA : Upset	BB : cancer is a death sentence
9 : 014	<p>my mum, because obviously she was upset it had passed on to me was quite upsetting erm and when I went for my results my husband obviously got upset because he had to deal with the aftermath of sort of me.</p> <p>don't forget you can remember I used to have to help you get out of the bath</p>	<p>know I didn't want to put you off or anything but when I said to you on holiday I noticed...</p> <p>014: Yeah its all lumpy</p> <p>H: like obviously my back is more smoother but with your back because theres nothing, because the muscle has been took away you obviously got a little bit of a void haven't you?</p> <p>I can remember her saying to me you know "im not going</p>	<p>I said to you I want you here its as simple as that and to me, don't get me wrong, you have a fantastic pair of boobs however (laugh) but</p> <p>014: The thing is you can still....</p> <p>H: That's just looking at something to me you know you're here and you know. You still went topless didn't you and you couldn't tell that much different, yeah ones more out of shape that the other but you look from a distance you couldn't tell I don't</p>	<p>it don't really effect you until you are either in swim wear or here at home.</p> <p>I can remember her saying to me you know "im not going to look the same and you'll go off me" and I haven't and she knows that I haven't.</p>	<p>Was it a shock or?</p> <p>014: No</p>	<p>a lady came out to my home to discuss it obviously it came out of the blue I was upset but just didn't twig what sort, what the outcome of it could be</p> <p>my mum, because obviously she was upset it had passed on to me was quite upsetting erm and when I went for my results my husband obviously got upset because he had to deal with the aftermath of sort of me.</p> <p>its bad news you have got the gene it stated they had this defective BRCA2</p>	<p>When I first found out about it, I think</p>	<p>It was all my own decision anyway and</p>	<p>The family is quite a big family or we had</p>
Summary Links: Cell 0									

FRAMEWORK MATRIX										
	Layout	BO : uncertainty	BP : reconstruction avail ability	BQ : supportive family et c	BR : would reduce risk of cancer	BS : Timing	BT : get on with it	BU : when I was younger maybe	BV : Your own decision	BW : fe
9 : 014	<p>es but if - if like, if I somebody going to me I would nk I were ut people</p>	<p>ould have been helpful to talk to them, to anybody about it or was it something sort of what you wanted to.....</p> <p>014: Er I don't know because I think you can scare yourself too much and then you probably think do I really want to have this done and then your living with the risk aren't you?</p>	<p>told me how much of a high risk because of my age and the risk was getting higher and the percentage was getting higher towards me getting it. So I had the option of sort of living with it or having treatment er having surgery. So erm I made the decision there and then to have erm full mastectomy and full reconstruction at the same time</p> <p>I said to you I want you here its as simple as that and to me, don't get me wrong , you have a fantastic</p>		<p>told me how much of a high risk because of my age and the risk was getting higher and the percentage was getting higher towards me getting it. So I had the option of sort of living with it or having treatment er having surgery. So erm I made the decision there and then to have erm full mastectomy and full reconstruction at the same time</p> <p>now I know that obviously my risks are only same as every normal woman rather than sort of the</p>				<p>at my age I wanted to get it all over and done with because I was young enough to sort of not just have one done at a time. So that's when I knew that I would have to have it done.</p>	
			<p>If I was not offered any reconstruction at</p>		<p>I needed to do something about it</p>		<p>I just wanted really to get on with it.</p>		<p>would have had that surgery if the other</p>	

Summary Links: Cell 0

FRAMEWORK MATRIX										
	CG : re service	CH : other women at h igh risk	CI : didnt want support	CJ : needs that were met	CK : re support group	CL : role of family and fri ends	CM : unmet needs	CN : Body image	CO : negatives post op	CP : pleased post
9 : 014	<p>rather than sort of just cope with it after. I think speaking to people who has had it done after would be more beneficial.</p> <p>Only like I say if you could speak to somebody when you have had it done for some sort of group for you to be put in contact with to see if what you are experiencing is normal. That's the big thing. Its sort of like an after, post- surgery?</p>				<p>would have been helpful to talk to them, to anybody about it or was it something sort of what you wanted to.....</p> <p>014: Er I don't know because I think you can scare yourself too much and then you probably think do I really want to have this done and then your living with the risk aren't you?</p> <p>rather than sort of just cope with it after. I think speaking to people who has had it done</p>		<p>think it is the after care that needs to be improved and I think that's more or less, even if its only a group sort of contacts that you can sort of e-mail or sort of telephone erm because sometimes some of the questions that you are asking they just don't know because they have not come across it before.</p>		<p>like capsulating yeah and it does feel strange and they are sometimes strange shaped which don't make you feel quite normal</p> <p>you are conscious of but only when you are undressed</p>	<p>The won't be do to my knees whe I'm 70, that's a l bonus</p>
		<p>could be of help to anybody that is</p>	<p>do you think it would have been helpful for</p>		<p>she just got chatting to me and asking me</p>	<p>My friends have been brilliant, they</p>		<p>don't feel I can wear a bikini anymore on a</p>	<p>just like having n down breasts.</p>	

Summary Links: Cell 0

10. Focus group transcript

Representative section of focus group transcript

E – so what I want to start off with really, if we look at the couple of questionnaires to being with, this is a questionnaire that's going to be sent to women who are at increased risk and having screening, so women who haven't had any surgery. Just really to get your thoughts when you looked at this, whether there's anything that jumps out at you immediately or if there's anything that, you know, we can focus in on when we get further into it.

1 – on a minor point, section 9

E – mmm hmmm

1 – if there's any had screening they shouldn't be asked about surgery

E - okay, the reason we have included that is because most people who are having screening may have either been offered or considered this and ruled it out

1 – right

E – so it's to try and get people's thoughts even if they haven't had surgery to kind of look at that

1 – right

E – does that seem reasonable?

1 – it does, I'm not entirely sure that it gets across

E – the phrasing?

1 – yeah,

E – okay

1 – erm,

E – that's on page 15

1 – when I first looked at it I thought you were asking how, how surgery had affected your relationship so maybe you need to rephrase it in terms of, even if you haven't had surgery, considering the surgery

E – that's an excellent point, it does read very much like you've had surgery doesn't it

1 – yeah! So to avoid it looking like a mistake in the questionnaire

E – okay, we'll have a look at that. Any suggestions for how we could rephrase? Just to think about rephrasing it so that it's more obvious

1 – acknowledging that people thinking about

3 – you could put how could

E – how surgery...

3 – how surgery could affect your relationship

E – or perhaps we could sort of get rid of the surgery bit altogether and say we want to know how your increased risk has affected your relationship and keep it a bit more general

2 – or perhaps having to think about surgery has affected your relationship

General mmm

2 – because having to think about and discuss it and worry about it

General mmm

E – so it's kind of two questions really isn't it, we could have one part about how thinking about surgery is kind of impacted and one part about how the increased risk itself

3 – or you could put, if you're thinking about having surgery could this affect your relationship

E – mmm, mmm hmm, that's quite a nice way of doing it, okay. Fine, thank you, that's a good point to start with. Anything generally that you just sort of look at the questionnaire that you think ooh, or that seems quite nice

2 – I like the photographs, that's quite nice

1 – yeah, I do, especially this one as it's multigeneration

E – uh huh

1 – but that one

E – uh huh, the final one (flowers) that's on page 18

1 – yeah, I know it's like flowers to say thank you, but really, it also means like somebody died

General agreement

E – okay, it's got a slightly funereal

1 – yeah, it has! That's only personal

E – does everyone agree with that, the flowers maybe aren't the best

2 – well if you've been in hospital having surgery you get a hell of a lot of flowers and they can make you think twice about, maybe, I guess it's symbolic of quite a few things like that really

3 – maybe you don't need to put a picture

E – just thank you might be better

General mmm

E – okay, fine that's a good point. Um. Anything else sort of jumping out? There are a few specific things I sort of wanted to ask really, the first thing is whether the presentation and format seem okay. So at the moment it's lots of grey boxes where you can tick in one of the boxes, does that seem a reasonable way of doing it? Is it fairly obvious how to fill it in?

1 – I think so

E – yeah, okay. Erm. The amount of space in between the questions... is that all kind of acceptable do you think? Does it need more space and fewer questions on the page, or vice versa?

4 – I think the first couple of sections it's good, I think possibly here when you get to percentages

E – that's page 6

General agreement

4 – section 3...

3 – it looks a bit daunting

E – yeah

4 – knowing that people sometimes freeze when they see numbers in boxes and percentages and tables and things like that maybe a bit more spread out or something

E – okay, yeah. Do you think the questions are reasonable, those questions, sort of asking what people think about risk? And they are very numeric at the moment.

2 – what about one of those symbolic things where you can have the thermometer or they do it pictorially don't they because sometimes that's easier to look at and understand it with a visual...

1 – that's a good idea

2 – like a thermometer that goes across the page or something

E – would that be a more attractive question do you think?

1 – that page 6 does look very dry

2 – cause if you had a couple of visuals you could put that, I've seen that thermometer where you put a cross where you think and I think it might be an easier way for people to visualise it

E – okay, erm. Further down there are quite a lot of questions on single pages, maybe page 8, erm, page 9 and 10, there's all quite big charts, is that a reasonable way of doing it? And the reason we've done it that way is that you can ask one question on one page instead of having lots and lots of individual ones

4 – yeah, that's nice

3 – going back to your front page, you need to offer it in foreign languages as well and maybe in big print

E – that's an excellent point, I've not thought about large print. Erm, in terms of length of the questionnaires, are there any thought initially, if you received this in the post what would you think of it, or...

4 – I'd probably think when I first saw it, that's a lot to get through

E – yeah

1 – it is longer than any I've seen

4 – yeah

2 – so maybe if it was a bit more visual it would help

3 – if you did it back to back, it wouldn't seem as big

E – that's true, it would be a thinner wedge wouldn't it

3 – and you wouldn't think, you'd fill it in quicker

E – okay, we can certainly do that

3 – or you're more likely to fill it in that to leave it on the side

E – yeah, there's ways of getting around the length aren't there... If we're thinking it's perhaps a bit long, is there anything perhaps when you're reading through it, erm, I'm not sure that that really added very much, or

4 – I don't think that these, you know the percentage ones, I don't think that they may be that necessary, erm, if you, I mean, how likely do you think, and then how likely do you think you are and then it goes one and this one, for women who develop it how likely do you think they are, and I think that personally, I think it's a case of I'd sit here and percentage wise, I don't know what I'd put down, erm, it's a bit too much I think, that one.

2 – are you asking that because you want to find out if women understand it

3 – how much women actually know

2 – is that quite important for the research you know whether people

E – I suppose it's potentially interesting, erm, if people are, er, think that they're at very high risk, whether that sort of correlates with their view towards

2 – yeah

3 – why don't you just leave it blank?

E – just not have the numbers at all?

3 – yeah, and just put what you think

E – free text box?

3 – instead of putting

2 – if you had that range with a thermometer people would put a cross you'd probably have 0 to 100 and then they'd mark it anywhere and that'd be a quick way, but you haven't given

3 – but it's like this one, what, 3.1, er how likely do you think an average british woman is to develop breast cancer, well we know it's one in five

4 – well you see I thought it was one in nince

2 – but it's not though, it's about one in nine

1 – it's one in ten now isn't it

4 – one in five

E – mmm. Do you think it would be better to give a box and see what people think

3 – yeah

1 – but you might get multiple ways of people expressing that answer

3 – well, why don't you put what is the average age?

E – mmm, there's different ways

3 – do you know the average age that a british could develop breast cancer

E – mmm, okay. We'll have a look at that page because I think it's

3 – and then you could put do you think

4 – it's not an easy page

3 – and then you could put next one, you could either answer it if you have family history and then continue on, and which age are you more likely to get it

E – mmm hmm, and just keep it a bit simpler than perhaps

3 – cause like,

4 – cause, sorry, sorry, go on

3 – what average age, the average risk is it? And you could have that and then you could have like, what average age do you think you're going to get it?

E – mmm, it's a different way of asking the same question really isn't it

3 – and then if it's family history then you can, or you can put if they know or if they don't know if, so you don't have to put all these percentages in

E – mmm

4 – if it's women like us, I've got the gene, we're going to know whereas before I had my ovaries and breasts done, it was 80% and 20% for my ovaries, ovarian cancer

General mmm

4 – so we are going to know

3 – yeah, but I didn't know, how er, I'd seen other breast surgeon and they'd said I hadn't got a family history or anything

4 – but once you've found out that you have, that's what they talk about, now that you've got *BRCA2*, you know, you're increased risks

E – some of the people getting the questionnaire won't have a genetic abnormality that was diagnosed, some of them will have an increased family history risk

4 – okay

E – erm, and it can be a lot more of a sort of grey area then

Mmm

2 – so that might be important for you to know, because you might be thinking you know, like you've said, most women immediately think they're going to be 80-90% whereas they're not actually

E – mmm

2 – only some women are, so it might be that you need to know that

1 – yeah it is, isn't it

4 – I think the cured one, I wouldn't know what to say to that one

E – mmm okay

4 – how likely they are to be cured with modern treatments

2 – the reason that's a bit odd is that I would immediately say it depends on what stage, what grade, what age,

3 – absolutely

2 – well, if you're age 40, it would be this, but I know that

3 – so I think that's a question that I wouldn't be able to answer

2 – so do you think that's needs a bit more rephrasing then?

E – I think we'll have a look at this page generally, because it's raising a few issues isn't it, the, erm, the way we're asking the questions and what we're trying to get from them, I think we need to be quite clear about that, but at the moment would I be right in thinking it's off putting as it is?

4 – as it is, it is off putting

General mmm

4 – yeah

1 – I think risk probably is important and what people understand by risk and the fact that risk can change, erm, and certainly I guess risk in your er decisions to have surgery is presumably one of the contributing factors as well as your view of your own image and so on

E – yeah

1 – so it sure is important but asking people to answer that question....

E – perhaps forcing people to answer a question in a way they wouldn't necessarily feel they knew how, okay... we'll certainly look at that, that's helpful. Erm, are there any other questions that have sort of popped up as being not quite right, when you're reading through?

Pause.

3 – say on this next one on page 7 it says for women who develop breast cancer are likely to have the following treatments, well

E – that's sort of part of that last question

3 – yeah, well, why then just scrap that and say what surgery do you think, have you thought about having? If you needed it...

E – mmm

3 – because, like, if you're going to have it as prophylactic, you're not going to want chemo or radio probably

E – mmm well it's possible it's just the question doesn't quite work very well, but I think

3 – do you have tamoxifen for *BRCA2*

E – it depends upon the cancer, sometimes it would be helpful and sometimes it wouldn't be helpful so it depends

4 – my sister did and my cousin didn't because even though they've both got *BRCA2*, one's hormone receptive and the other wasn't, so

3 – yeah

E – that's right

4 – so cousin doesn't have to take it but she had the chemo, sister's got it for 5 years but didn't have the chemo

E – yeah, it's all very individualised isn't it

2 – so this question, is it because you want to know what people understand before, is that why you're asking it

E – well perhaps expectations, it might be that

2 – so it would reveal your expectations of what your understanding is, you know

E – but it might be that the question doesn't add an awful lot and it's kind of a difficult question

4 – it is, that's another difficult one for me

3 – you could just put have you thought about having this surgery and what surgery have you thought about

E – mmm, yeah, because this is for women who haven't had surgery

Several people talk at once....

3 – you could put mastectomy, lumpectomy, if you're going to have, just brief as a tick box thing

4 – but not knowing

3 – not all these percentage things

4 – not knowing how many percentage would, I wouldn't be able to answer that again

E – it's quite off putting, the number perhaps?

4 – yeah,

E - well we'll have a rejig of that

General mmm

E – this is really helpful to hear back, because it's quite easy for us to write things and not not be able to remain objective, that's that's kind of the purpose of tonight really, to pick up on these things

General yeah.

11. Questionnaires

The questionnaires are very similar with a number of identical sections: 1, 2, 5, 6, section 10 in screening which is the same as section 11 in the surgical questionnaire, and section 11 in screening which is the same as section 12 in the surgical questionnaire.

The screening questionnaire is included below from start to finish.

The surgical questionnaire pages that differ (sections 3, 4 and 7-10) follow.



The
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Sheffield Teaching Hospitals **NHS**
NHS Foundation Trust
Excellence as standard

Study of women at increased breast cancer risk because of their family history



Screening Questionnaire Version 2.0 05.07.11

1

Study of women at increased breast cancer risk because of their family history

Thank you for agreeing to take part in a research study.

We want to find out what women at increased risk of breast cancer think about the different ways of managing this problem. Your views are very important to us. It will help us to better understand what women in your situation want as part of their care. Hopefully this will allow us to provide more personalised treatment and advice to women in the future. This study is specifically looking at women who have had surgery to their breasts to help to reduce their cancer risk.

Taking part in this part of the study is entirely voluntary. If you do not wish to take part, simply dispose of the questionnaire. You need take no further action and no-one will question this and it will not affect your future care in any way. If you do take part, you will not benefit directly but will be increasing our knowledge and understanding so that future women's care may be improved.



If you are happy to take part in the study, we would like you to complete the attached questionnaire. It will take about 30 minutes and the questions are very straight forward. Once you have completed the questionnaire, please post it back to us in the FREEPOST envelope provided. You do not need to use a stamp.

The questions have no right or wrong answers, but are a reflection of your opinion.

Most of the questions are in the form of a statement and we would like you to say whether you agree or disagree with the statement, (or have no opinion about the statement: neutral).

We would like you to take your time and think carefully about what you really think. Please do not try and answer in response to what you think we would want you to say.



If you need any help in answering the questions, please feel free to ask the Study Team by ringing 0114 2261426 and a member of the team will call you back as soon as possible.

Some of the questions ask for details about items of a sensitive nature. All information provided in this questionnaire will be dealt

with in the strictest confidence and will be kept in an anonymised fashion so you could never be identified from it. However, if you do not wish to answer certain sections, please move on to the next part of the questionnaire and leave the section blank.

Some of the questions are designed to assess how anxious or depressed this issue makes you feel. If this is a problem with which you would like help and support, you can either contact the study team who will confidentially arrange for you to be put in touch with someone who can help, or contact your GP or breast surgeon who will arrange this for you.

Thank you for giving us your time and help with this study.

Section 1: Some background information about you

Please fill in the shaded boxes and either tick or circle the Yes or No boxes clearly.

1.1 How old are you? years

1.2 If you are or have been in employment, what did you / do you do?

1.3 Please tick the box that best describes you:

Single	Single but in a relationship with a partner	Married	Divorced	Separated	Widowed
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

1.4 Do you have children? Yes No

If yes, how many and how old are they?

1.5 Have you ever had breast cancer?..... Yes No

If no, please go to question 1.7

1.6 If yes, how old were you when you were diagnosed? years

1.7 What operation(s) did you need to treat your cancer?

Lumpectomy (Wide local excision)	Further breast surgery to remove cancer	Mastectomy	I didn't have an operation
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

1.8 Have you ever had any other cancers? Yes No

1.9 If yes, please specify what type:

Section 2: About your family members with cancer

2.1 In the table below please give details of any family members who have been affected by cancer. An example is shown in the first line.

Relationship (e.g. mother)	Type of cancer (e.g. breast)	Age at diagnosis	Is this relative still living?
mother	breast cancer	48	yes

2.2 Have any member(s) of your family or you had gene testing Yes No
to look for genes linked to breast cancer?

2.3 If yes, what was the result? Positive Negative

2.4 If positive, what is the name of the abnormal gene identified?

BRCA1	BRCA2	P53 / Li Fraumeni	Ataxia telangectasia	Not known	Other (please specify)

2.5 Have you had a gene test? Yes No

2.6 If yes, have you inherited the abnormal gene? Yes No

2.7 How old were you when you became aware that you might be at an increased risk of developing breast cancer? years

Section 3: We want to know what level of breast cancer risk you feel you have.

Please tick the box that most accurately reflects your thoughts on the following questions.

3.1 How likely do you think you are to develop breast cancer during your life?

Very unlikely <1% risk	Unlikely 10% risk	Low risk 20% risk	Moderate risk 50% risk	High risk 80-90% risk

3.2 For women who do develop breast cancer, how likely do you think they are to be cured with modern treatments?

Very likely to be cured, (90% cure rate)	Likely to be cured, (70-80% cure rate)	Moderate chance of cure, (50-70% cure rate)	Low chance of cure, (30-50% cure rate)	Unlikely to be cured, (<30% cure rate)

3.3 Please tick the boxes that reflect how you have felt over the last week

	Not at all	A little	Somewhat	A lot
How often have you thought about the possibility of getting cancer?				
Have these thoughts affected your mood?				
Have these thoughts interfered with your ability to do daily activities?				
How concerned are you about the possibility of getting cancer one day?				
How often do you worry about developing cancer?				
How much of a problem is this worry?				

Section 4: We want to know how you felt when you first became aware that you were at increased breast cancer risk.

4.1 How did you feel when you found out that you were at an increased risk of breast cancer? This may have been when you had a gene test result or when you had a consultation with a doctor about your risk.

	I felt strongly...	I felt a little bit...	I didn't feel this at all
Isolated			
Panic stricken			
Traumatised			
Surprised			
I felt it confirmed what I already knew			
Relieved			
Shocked			
I felt I needed emotional support			
I felt I needed lots of information			
I felt positive about the news			
Upset			
Numb			
Angry			
Resentful that this had happened to me			
Frightened of developing cancer			
Frightened of dying			
Confused			
I didn't want to know, I wanted it to go away			
Guilty that I might pass this onto my children			
Why me!			
I didn't feel in control of the situation			
Other (please detail)			

7

4.2 What sources of support / information were available and were they helpful?

	Very helpful	Moderately helpful	Not at all helpful	Not available	Not applicable
Partner					
Family member e.g. mother / sister / cousin					
Friends					
Nurses in the clinic e.g. (breast care nurses)					
Genetic nurses					
GP practice nurses					
General practitioner (GP)					
Doctor in clinic					
Support group					
Books					
Leaflets					
Websites / the internet					
Other (please specify)					

4.3 Do you, or have you had any contact with any support groups for women with an increased risk of breast cancer? Yes No

4.4 If yes, which of the following have you had contact with?

Internet support group	Telephone support group	Face to face support group	Other

4.5 If no, would you like to have had this option? Yes No

4.6 If yes, please indicate when you would have wanted it: Tick as many as apply

Before finding out about my risk	After finding out about my risk	When I go to screening tests	Long-term

4.7 Please tick the boxes below about the support you received:

Poor support / info	Not quite enough	Just enough	Good level of support / info

4.8 How open are you about your increased risk with people?

	Very open, I'm happy to talk about it	I prefer not to, but when asked I will talk about it	I don't talk about it at all	Not applicable
Family				
Friends				
Children				
Work colleagues				

Section 5: We would like to know whether your experiences have resulted in other people turning to you for advice.

5.1 Have other people turned to you for advice about increased familial breast cancer risk? (Please tick any relevant boxes)

Family have asked me for advice	
Friends have asked me for advice	
Work colleagues have asked me for advice	
People I don't know directly have asked me for advice	

5.2 Have other people turned to you for advice about breast problems in general? (Please tick any relevant boxes)

Family have asked me for advice	
Friends have asked me for advice	
Work colleagues have asked me for advice	
People I don't know directly have asked me for advice	

5.3 Are you comfortable being a source of advice for others?

Yes	No
-----	----

Section 6: We would now like to know about what options you were given to deal with your increased risk of developing breast cancer.

6.1 When you attended the clinics, what options were discussed with you by the doctors you saw? (Please tick all that were mentioned to you)

That I could take no action / do nothing	
That I should check / examine my breast regularly	
That I should be examined regularly by a Doctor	
That I could start mammographic breast screening from an earlier age	
That I could start MRI breast screening	
That I could enter a study to evaluate a drug to reduce breast cancer risk (this option is not suitable for everyone and so may not have been mentioned)	
That I could have surgery to remove my breasts (this option may not be appropriate for all women)	
That I could have surgery to remove my ovaries (this option may not be appropriate for all women)	
Lifestyle advice – Keep weight in a healthy range	
Lifestyle advice – Take regular exercise	
Lifestyle advice – Avoid HRT when you become post-menopausal/go through 'the change'	
Lifestyle advice – Avoid heavy alcohol consumption	

Section 7: We would now like to know about your feelings about breast screening

7.1 Do you or did you have breast screening with mammograms?

Yes	No
-----	----

7.2 Do you or did you have breast screening with MRI scans?

Yes	No
-----	----

If no, please move to Section 8 on page 12

7.3 Please tick the boxes reflecting your feelings about screening below

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I feel confident that screening will identify any problems in my breast at an early stage					
I worry that cancer might develop in the time between screening tests					
I worry that screening might miss something					
I feel anxious when attending for screening tests					
I feel anxious when waiting for screening results					
I find the wait for results acceptable					
I find the screening tests acceptable					
I find the screening tests painful					
I find the screening tests inconvenient					
I find the time required for screening tests to be problematic					
I find getting time off work to go for screening difficult					
Other (please specify)					

7.4 Have you ever been recalled after a screening test? Yes No

7.5 If yes, how anxious did you feel when you were contacted to go for further tests?

Extremely anxious	Somewhat anxious	Slightly anxious	Not at all anxious

7.6 Did you lose sleep whilst waiting for the results of these Yes No
further tests?

7.7 Do you think you have made the right decision to have Yes No
screening?

7.8 Do you regularly self-examine your breasts? Yes No

7.9 Please tick the boxes below regarding how you feel about examining your own breasts

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I am confident examining my breasts					
I don't feel as if I know how to examine my breasts properly					
Examining my breasts makes me very uncomfortable					
I don't examine my breasts as I am frightened I might find something					
I always feel lumps and this worries me					
I forget to do it regularly					
It is uncomfortable					
I think it is a waste of time					
I regularly examine my breasts as it will help me to find problems earlier					

Section 8: We would like to know your views about surgery to remove the breasts as a possible method of reducing the risk of cancer.

This option is offered to some women at a very high breast cancer risk but is not appropriate for everyone and may not have been discussed with you for this reason.

8.1 Were you ever offered the option of surgery to remove your Yes No
breasts?

If no, please move on to section 9 on page 15. If yes, please answer the following questions.

8.2 What are your views about surgery of this type?

	Agree	Neutral	Disagree
It is too drastic			
My husband/partner does not want me to have this surgery			
I might never get cancer, so it may be unnecessary			
I wouldn't want to have no breasts			
I do not want surgery as it would be painful			
I wouldn't want to/be able to take the time off work to have surgery			
I would not be able to look after my children for several months after surgery			
I wouldn't feel like a woman if I have this type of surgery			
I have seen bad results from surgery and never want to go through anything similar			
If I get cancer I will have surgery but not otherwise			
I am too old to have surgery			
I don't see any need for surgery when screening is available			
I would be afraid to have surgery			
It is too expensive for the NHS – the money would be better spent on other people			
I feel I ought to have surgery but I cannot bring myself to do so			
Other (please specify)			

8.3 Might you consider having breast surgery in the future?

If no, please go to question 8.5

8.4 If yes, we would like to know why you want to wait. Please tick all that apply

I want to develop my career/job before considering surgery	
I want to be able to care for my children	
I want to be able to breast feed any future children	
I want to have children before considering surgery	
I want the surgery near the age at which my relatives developed cancer	
I want it when I am older so that I won't mind losing my breasts as much	
I want to be in a stable relationship before considering surgery	

8.5 If you were to consider surgery, would you want reconstruction?

Yes, definitely	Yes, maybe	I don't know	No, probably not	No, definitely not

8.6 If there is anything you would like to add that we have not asked about relating to preventative breast surgery, please do so in the box below:

Section 9: We want to know how you feel about your appearance

9.1 How do you feel about your appearance?

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I feel good					
I don't feel comfortable using public changing rooms					
I am satisfied with my appearance					
I feel self-conscious about my appearance					
I feel attractive					
I feel confident					
I feel feminine					
I prefer to keep covered up					
Other (please specify)					

9.2 Do you avoid looking at your breasts?

Yes No

9.3 Do you avoid touching your breasts?

Yes No

Section 10: We want to know about your risk of ovarian cancer.

10.1 Have you been told that you are at increased risk of

Yes	No
-----	----

ovarian cancer?

Not all women are at increased ovarian risk. If no, please move on to section 11 on page 17. If yes, please answer the following questions.

10.2 When you attended the clinics, what options were discussed with you by the doctors you saw? (Please tick all that were mentioned to you)

That I could take no action / do nothing	
That I could have regular blood tests	
That I could have regular ultrasound scans of my ovaries	
That I could take part in a trial of ovarian screening	
That I could have surgery to remove my ovaries	
That I needed to wait until I was older before considering any of the above options	

10.3 Are you having or have you ever had ovarian screening?

Yes	No
-----	----

10.4 Have you had an operation to remove your ovaries?

Yes	No
-----	----

If no, please move on to section 11 on page 17. If yes, please answer the following questions.

10.5 Have you experienced any menopausal symptoms?

Yes	No
-----	----

10.6 Were you expecting menopausal symptoms?

Yes	No
-----	----

10.7 To what extent have these symptoms bothered you?

Greatly	Moderately	A little	Not at all	I don't have symptoms

10.8 Have you been able to get help with these symptoms easily?

Yes	No
-----	----

Section 11: We want to know about how your increased risk has affected your relationships. Please skip this section if you aren't presently in a relationship, or if you feel this is too intrusive or private.

11.1 If you are in a relationship or were at the time you found out about your increased risk, do you think it has changed?

Yes	No	N/A
-----	----	-----

11.2 If yes, in what way? Please tick as many as apply

We are closer now, than ever	
We are more distant with each other	
Physically, our relationship has changed in a good way	
Physically, our relationship has changed in a bad way	
Emotionally our relationship has got worse	
Emotionally our relationship is better	
We are no longer together	

11.3 If you are sexually active, has this changed since you found out about your increased risk?

Yes	No	N/A
-----	----	-----

11.4 If yes, in what way has it changed?

I have less interest in sex now	I have more interest in sex now

11.5 Do you feel your partner's attitude to sex has changed?

My partner has less interest in sex now	My partner has more interest in sex now	Unchanged

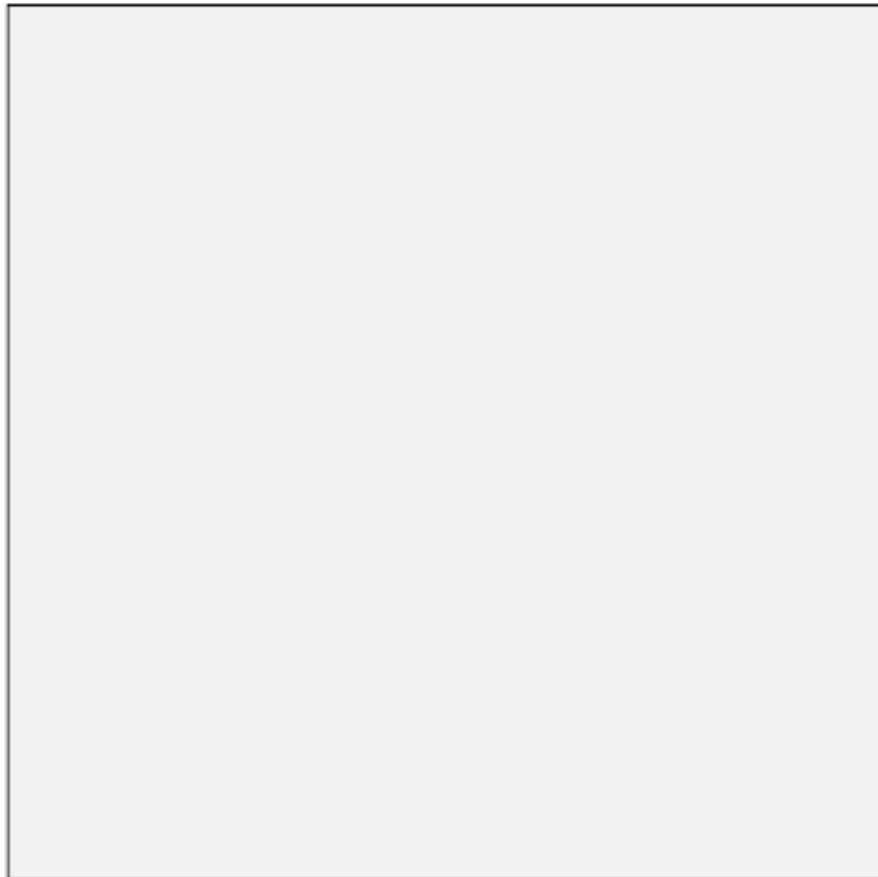
Thank you

We appreciate your taking the time to complete this questionnaire.

Please return it to us in the freepost, stamped addressed envelope.

If you have any comments, we would like to hear them. For example there may be other issues that you feel need to be covered which we have missed, expand on a particular area or give us feedback on the questionnaire itself.

Please write these comments below.



Section 3: We want to know what level of breast cancer risk you thought you had before you had surgery.

Please tick the box that most accurately reflects your thoughts on the following questions.

3.1 How likely did you think you were to develop breast cancer during your life, before you had surgery?

Very unlikely <1% risk	Unlikely 10% risk	Low risk 20% risk	Moderate risk 50% risk	High risk 80-90% risk

3.2 Now that you have had preventative surgery, how likely do you think you are to develop breast cancer in your lifetime?

Very unlikely <1% risk	Unlikely 10% risk	Low risk 20% risk	Moderate risk 50% risk	High risk 80-90% risk

3.3 For women who do develop breast cancer, how likely do you think they are to be cured with modern treatments?

Very likely to be cured, (90% cure rate)	Likely to be cured, (70-80% cure rate)	Moderate chance of cure, (50-70% cure rate)	Low chance of cure, (30-50% cure rate)	Unlikely to be cured, (<30% cure rate)

3.4 Please tick the boxes that reflect how you have felt over the last week.

	Not at all	A little	Somewhat	A lot
How often have you thought about the possibility of getting cancer?				
Have these thoughts affected your mood?				
Have these thoughts interfered with your ability to do daily activities?				
How concerned are you about the possibility of getting cancer one day?				
How often do you worry about developing cancer?				
How much of a problem is this worry?				

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Section 4: We want to know how you felt when you first became aware that you were at increased breast cancer risk.

4.1 How did you feel when you found out that you were at an increased risk of breast cancer? This may have been when you had a gene test result or when you had a consultation with a doctor about your risk.

	I felt strongly...	I felt a little bit...	I didn't feel this at all
Isolated			
Panic stricken			
Traumatised			
Surprised			
I felt it confirmed what I already knew			
Relieved			
Shocked			
I felt I needed emotional support			
I felt I needed lots of information			
I felt positive about the news			
Upset			
Numb			
Angry			
Resentful that this had happened to me			
Frightened of developing cancer			
Frightened of dying			
Confused			
I didn't want to know, I wanted it to go away			
Guilty that I might pass this onto my children			
Why me!			
I didn't feel in control of the situation			
Other (please detail)			

4.2 What sources of support / information were available and were they helpful?

	Very helpful	Moderately helpful	Not at all helpful	Not available	Not applicable
Partner					
Family member e.g. mother / sister / cousin					
Friends					
Nurses in the clinic e.g. (breast care nurses)					
Genetic nurses					
GP practice nurses					
General practitioner (GP)					
Doctor in clinic					
Support group					
Books					
Leaflets					
Websites / the internet					
Other (please specify)					

4.3 Do you, or have you had any contact with any support groups for women with an increased risk of breast cancer?..... Yes No

4.4 If yes, which of the following have you had contact with?

Internet support group	Telephone support group	Face to face support group	Other

4.5 If no, would you like to have had this option? Yes No

4.6 If yes, please indicate when you would have wanted it: Tick as many as apply

After finding out about my risk	Before my operation	After my operation	Long-term

4.7 Please tick the boxes below about the support you received:

	Poor support / info	Not quite enough	Just enough	Good level of support / info
Before surgery				
After surgery				

4.8 How open are you about your increased risk with people?

	Very open, I'm happy to talk about it	I prefer not to, but when asked I will talk about it	I don't talk about it at all	Not applicable
Family				
Friends				
Children				
Work colleagues				

Section 5: We would like to know whether your experiences have resulted in other people turning to you for advice.

5.1 Have other people turned to you for advice about increased familial breast cancer risk? (Please tick any relevant boxes)

Family have asked me for advice	
Friends have asked me for advice	
Work colleagues have asked me for advice	
People I don't know directly have asked me for advice	

5.2 Have other people turned to you for advice about breast problems in general? (Please tick any relevant boxes)

Family have asked me for advice	
Friends have asked me for advice	
Work colleagues have asked me for advice	
People I don't know directly have asked me for advice	

5.3 Are you comfortable being a source of advice for others?

Yes	No
-----	----

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Section 6: We would now like to know about what options you were given to deal with your increased risk of developing breast cancer.

6.1 When you attended the clinics, what options were discussed with you by the doctors you saw?(Please tick all that were mentioned to you)

That I could take no action / do nothing	
That I should check / examine my breast regularly	
That I should be examined regularly by a Doctor	
That I could start mammographic breast screening from an earlier age	
That I could start MRI breast screening	
That I could enter a study to evaluate a drug to reduce breast cancer risk (this option is not suitable for everyone and so may not have been mentioned)	
That I could have surgery to remove my breasts (this option may not be appropriate for all women)	
That I could have surgery to remove my ovaries (this option may not be appropriate for all women)	
Lifestyle advice – Keep weight in a healthy range	
Lifestyle advice – Take regular exercise	
Lifestyle advice – Avoid HRT when you become post-menopausal/go through 'the change'	
Lifestyle advice – Avoid heavy alcohol consumption	

Section 7: We would now like to know about whether you have ever had breast screening and what you thought about it

7.1 Were you ever offered breast screening? Yes No

If no, please move to Section 8 on page 12

7.2 Have you previously had breast screening with mammograms? Yes No

7.3 Have you previously had breast screening with MRI? Yes No

7.4 Please tick the boxes reflecting your feelings about screening below

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I felt confident that screening would identify any problems in my breast at an early stage					
I worried that cancer might develop in the time between screening tests					
I worried that screening might miss something					
I felt anxious when attending for screening tests					
I felt anxious when waiting for screening results					
I found the wait for results acceptable					
I found the screening test acceptable					
I found the screening tests painful					
I found the screening tests inconvenient					
I found the time required for screening tests to be problematic					
I found getting time off work to go for screening difficult					
Other (please specify)					

7.5 Were you ever recalled after a screening test? Yes No

7.6 If yes, how anxious did you feel when you were contacted to go for further tests?

Extremely anxious	Somewhat anxious	Slightly anxious	Not at all anxious

7.7 Did you lose sleep whilst waiting for the results of these Yes No
further tests?

Section 8: We now want to find out about your surgery

8.1 Why did you choose to have surgery to remove your breasts?

	Agree	Neutral	Disagree
I couldn't live with the risk of getting cancer			
I didn't want my breasts any more – they were a threat to me			
I didn't feel confident that screening would protect me			
I didn't like the screening tests			
I wanted to ensure I would be there for my children in the future			
I wanted to avoid needing chemotherapy or radiotherapy if I got cancer			
I thought I was sure to die of cancer if I didn't have the operation			
I didn't want the operation but felt I had to do it for my family's sake			
I saw what happened to my relatives with cancer and couldn't face going through the same thing			
It meant I felt in control			
I had a cancer diagnosed through screening and had surgery to treat the cancer			
I felt pressured to have the surgery by my doctor/surgeon			
I felt pressured to have the surgery by my family/partner			
Other (please specify)			

8.2 What factors were important in deciding the timing of your surgery?

	Not important	Slightly important	Moderately important	Very important
I wanted to develop my career/job before having the surgery.				
I wanted to be able to care for my children				
I wanted to be able to breast feed any future children				
I wanted to have children before having the surgery				
I wanted the surgery before the age at which my relatives developed cancer				
I wanted the operation as soon as possible				
I wanted to get it over with so I could get on with my life				
I wanted it when I was older so that I wouldn't mind losing my breasts as much				
I wanted to be in a stable relationship before having surgery				
Other (please specify)				

8.3 Please indicate how the following factors affected your choice of operation:

	Not important	Slightly important	moderately important	Very important
I wanted a normal appearance when fully dressed				
I wanted my breasts to be identical before and after the operation				
I wanted my reconstructed breasts to be different (bigger/smaller/less droopy than they were before)				
I wanted a normal appearance when undressed				
I wanted a short recovery period				
I wanted the risk of cancer reduced as much as possible				
I wanted the potential reduction in worry and anxiety				
I would not have had the surgery if I was unable to have reconstruction				
I was prepared to have more major surgery to get a good cosmetic result				
I did not mind what my breasts looked like as long as I got rid of the cancer risk				

8.4 If you were offered screening but chose to have an operation to remove your breasts instead, we would like to understand why. If there is anything you would like to add that we have not asked about, please do so in the box below:

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Section 9: What type of surgery did you have?

9.1 In what year did you have your (first or only) breast operation?

9.2 How old were you when you had your operation? years

9.3 Regarding your first operation, please tick the appropriate box below

I had a mastectomy with no reconstruction	I had a mastectomy with reconstruction at a second operation	I had a mastectomy with reconstruction at the same time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

if you never had any reconstruction please go to question 9.9

9.4 If you have had reconstruction, what type did you have?

I had an implant put under the muscle under my breast	<input type="checkbox"/>
I had an implant and they used a muscle from my back (Latissimus Dorsi or LD) to cover the implant	<input type="checkbox"/>
I had the muscle (LD) from my back used to make a new breast with no implant	<input type="checkbox"/>
I had my tummy muscle and fat used to make new breasts (TRAM flap / DIEP)	<input type="checkbox"/>
Other (please specify)	

9.5 Were your nipples taken away when you had your surgery?..... Yes No

9.6 If yes, have you had new nipples created? Yes No

9.7 Have you needed further surgery since your reconstruction..... Yes No
to correct or improve the appearance?

9.8 If reconstruction hadn't been available, would you still have Yes No
chosen to have your breasts removed?

9.9 Did you have any complications when you had your surgery? ... Yes No

9.10 If yes, please tick the appropriate boxes below

	Yes	No
I had fluid collect under my wound (seroma)		
I had a blood clot in the wound (haematoma)		
I had an infection that required antibiotics		
I had an infection that required further surgery to drain the infection		
I had loss of the skin over my breast		
I had loss of the skin flap moved from another part of my body		
I had long term pain (which lasted more than 2 months) after surgery		
I had an implant rupture		
I had implant hardening (capsule formation)		
Other (please specify)		

Section 10: We want to know how you feel generally and about your appearance after your surgery

10.1 Please tick the box to indicate your feelings regarding how you feel now about the outcomes of your surgery.

	Very poor	Poor	Okay	Good	Excellent
Appearance of breasts					
Size of breasts					
Shape of breasts					
Feel of breasts (when you touch them)					
Sensation in breasts (what you can feel)					
Appearance of scars					
Movement (e.g. of your arms)					
Comfort					
Other (please specify)					

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10.2 Do you feel that your breasts are 'your own'?

Yes	No
-----	----

10.3 How did you feel in the first few days after your operation?

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I was in severe pain					
I was in pain but it was bearable					
I was comfortable with the pain killers					
The level of pain was as less than expected					
Upset					
I was afraid that something might still go wrong					
I felt sure I'd made the right decision to have surgery					
I felt relieved that the surgery was over					
I felt the appearance was awful					
I felt relieved that I didn't have to worry so much about breast cancer any more					
I felt vulnerable					
I felt concerned about my appearance after surgery					
I felt pleased with the initial results of the surgery					
I felt euphoric					
Other (please specify)					

10.4 How do you feel about your operation now?

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I feel I made the right decision to have my breasts removed					
I still worry about getting cancer					
I get pain where I had my surgery					
I feel embarrassed when people see me without my clothes because of the surgery					
I feel relieved my breasts are gone					
I wish I had chosen a different type of operation					
I am content that I had my breasts removed but wish I had not had reconstruction					
I am pleased that I had reconstruction					
Other (please specify)					

10.5 In terms of your recovery, was it?

Quicker than I had expected	About what I had expected	Longer than I had expected

10.6 Did you feel any sense of guilt about having your operation?

Yes	No
-----	----

If no, please move on to question 10.8

10.7 If you did feel a sense of guilt about having your operation, why?

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
It meant I wasn't able to do as much for my family					
I felt like a burden to people					
I didn't feel as deserving as other patients who had cancer					
Other – please specify					

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10.8 How do you feel about your body since your operation? Tick as many as apply

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I look better than before my operation					
I don't feel comfortable using public changing rooms					
I am satisfied with my appearance					
I feel self-conscious about the scars					
I feel upset when I think about how I look after the surgery					
I look worse than before my operation					
I feel attractive					
I feel confident					
I feel happy					
I feel unattractive					
I prefer to keep covered up					
I don't think I am as feminine since my operation					
Other (please specify)					

10.9 Do you avoid looking at your chest now? Yes No

10.10 Do you avoid touching your chest now? Yes No

10.11 How do you feel about the result of your operation now?

It is awful	It is poor	It is what I expected	It is good	It is excellent

10.12 Have either of the following changed because of your operation?

	Yes	No
I have changed my job because of my operation		
I have changed my lifestyle because of my operation		