**Bridging the Age Gap in Breast Cancer:**

**Improving outcomes for older women**



**Bone Health in Older Women with Breast Cancer**

**A study nested within the Age Gap Cohort study.**

**Version 1.1**

**22nd February 2022**

**Evaluation of Bone Health in Older Women with Early Breast Cancer. A study nested within the Age Gap Cohort study.**

**Lay Summary**

This observational study is aiming to improve the management of bone health in older patients with breast cancer. Data will be collected from the participants of the Age Gap study which closed to recruitment in 2018. The Age Gap study recruited over 3400 older patients with early breast cancer from the UK with a plan to optimise the care of these older women so treatment can be better tailored to their health and fitness levels and also to help to reduce some of the wide practice variation that exists across the UK. During the original study, no data was collected on bone health.

The majority of breast cancer patients have a type of breast cancer that is sensitive to the female hormone oestrogen. Oestrogen makes these cancers grow and oestrogen blocking drugs kill these cancers. These women are given oestrogen blocking drugs called Aromatase Inhibitors (AIs). Based on patients’ fitness status, aromatase inhibitors might be either the main breast cancer treatment that patients receive or given alongside chemotherapy following their cancer surgery.

Aromatase Inhibitors are known to cause thinning of the bones with studies to show that they speed up bone loss that naturally happens with menopause. Bone thinning dramatically increases the risk of bone fractures which affect mobility, independence and increase the risk of dying. National and international guidelines recommend that older patients receiving aromatase inhibitors, who already have evidence of weakened bones or who are at increased risk of bone fractures should be advised to exercise more, take calcium and vitamin D supplements and also to be commenced on special drugs to help strengthen bones (for example denosumab or bisphosphonates).

This study is part of a higher degree and it will be run by a full time Clinical Research Fellow under the close supervision of Professor Lynda Wyld and Professor Janet Brown. It aims to increase our understanding of how bone health is monitored, preserved and treated in older women with early breast cancer and to identify areas of improvement with the ultimate aim to optimise bone health in this group of patients.

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# **Background**

## Breast Cancer and Bone Health

Breast cancer is the most common cancer in women with around 55,000 cases annually in the UK, with one quarter in women over the age of 75 (1). Despite the recent improvements in the diagnosis and treatment of breast cancer, management of early disease in the older population (women ≥70 years old) has lagged behind, with women in this group more likely to receive non-standard care.

According to the current guidelines, management of early breast cancer includes surgery for all patients plus varying combinations of chemotherapy, radiotherapy, endocrine therapy, anti-HER2 therapies and bisphosphonates depending on disease stage, biology and patient tolerance (2). About 75% of newly diagnosed early breast cancers are oestrogen receptor positive (ER+ve) and these patients should receive endocrine therapy either as primary or adjuvant treatment. Primary endocrine treatment is offered as a therapeutic alternative to patients who are not fit for breast cancer surgery and undoubtedly the majority of them are significantly older, with a poor performance status, and multiple comorbidities. In contrast, adjuvant (post breast cancer surgery) endocrine treatment is offered to the majority of ER+ve patients with the aim to improve survival and reduce the risk of disease recurrence. There are two available hormone treatment options which are offered based on the menopausal status of the patient. Premenopausal women with ER+ve disease receive Tamoxifen, a selective oestrogen receptor modulator (SERM) and postmenopausal women are offered Aromatase Inhibitors (AIs) (2). There are 2 types of Aromatase Inhibitors: steroidal (exemestane) and nonsteroidal (letrozole, anastrozole). Both act by blocking the peripheral synthesis of oestrogen.

Women achieve 90% of their adult bone mass by the age of 20 and their maximum bone mass in their late 20’s. Bone mass is affected by controlled (nutrition, lifestyle, daily exercise) and non-controlled (sex, race, hormone status) factors. In the female population, bone loss is an unavoidable process which starts with menopause as the low oestrogen environment has a negative impact on bones strength. This process is accelerated in women with hormone receptor positive breast cancer who receive endocrine treatment. Unlike Tamoxifen, AIs are known to reduce bone mineral density and studies have shown that in postmenopausal patients AI treatment increases the rate of bone loss by 2-4 times (3-12). As a consequence, patients are at risk of bone fractures which is 18-20% in the first 5 years of AI therapy and for those receive extended endocrine treatment (10 years), fracture risk increases by 2-3% every year (13-20).

Dual-energy X-ray absorptiometry (DXA) is typically used to diagnose and monitor osteoporosis. European Society of Medical Oncology (ESMO) guidelines suggests that patients who are due to be commenced on AIs should first undergo a DXA scan to assess their bone mineral density (BMD) and are advised to exercise moderately and take calcium and Vitamin D supplements (21). Treatment with bone targeting agents (BTAs) should be started if the T score is <-2 on DXA scan. For older women (≥75 years old), a UK expert group recommended treatment if they receive AIs and have at least 1 risk factor for bone fracture (22). Advice has recently been updated by ESMO suggesting that women older than 65 with more than 1 risk factor for bone fracture and who are due to start AI treatment should be offered BTAs (21).

The bone targeting therapies of choice for treatment or prevention of cancer treatment induced bone loss (CTIBL) are denosumab or bisphosphonates (21,22). Since the ABCSG-18 randomised trial (comparing denosumab or placebo in early breast cancer patients) showed that denosumab is significantly reducing the risk of fractures in postmenopausal women with EBC who receive AI, ESMO is recommending it as first line treatment for this indication (21,23). In contrast, National Institute for Health and Care Excellence (NICE) is still suggesting bisphosphonates as the treatment of choice for CTIBL in view of their additional oncological benefit (22,24). Denosumab is a RANK inhibitor which prevents bone resorption by blocking osteoclast activity. It is given subcutaneously every 6 months. Bisphosphonates are pyrophosphate analogues and act against osteoclast-mediated bone loss with multiple studies demonstrating that they can prevent bone loss in AI treated early breast cancer (20,25-34). They can be given either orally (weekly alendronate or risedronate or monthly ibandronate) or intravenously (6 monthly zoledronate) depending on patients’ and physicians’ choice. In terms of monitoring of BMD, it is recommended that at DXA scan is performed every 2 years for those on BTAs and every 1-2 years based on individuals’ risk if not on BTAs (21).

Additionally, bisphosphonates have been found to prevent disease recurrence and bone metastases but only in postmenopausal patients (natural or induced) with early breast cancer (25,26,35-39). Their adjuvant use has been gradually increasing since national bodies adopted them into their recommendations (UK Breast Cancer Group, 2015). Since 2018, they are also part of the NICE recommendation for the management of early breast cancer (24). Therefore, their use in this setting was not assessed in the original Age Gap study as this closed to recruitment in 2018. Denosumab has been assessed in the adjuvant setting but found to have no oncological benefit despite its ability to reduce bone fractures and hence is not the preferred BTA in the adjuvant setting at present (40).

## Bone Health in Older Women with Early Breast Cancer

The Age Gap Study, was a multicentre cohort study, which has now completed recruitment. Between 2013 and 2018, 3456 patients over the age of 70 were recruited to the study from 56 UK centres. Its aim was to improve breast cancer outcomes in this age group by establishing age and health stratified guidelines for treatment and to help both patients and clinicians to make better treatment choices.

This amended protocol is introducing new data items relevant to bone health, to update the Age Gap dataset in a limited number of Age Gap recruiting centres. The findings of this project will add value to the original study by giving us a better understanding of bone health management in this age group so we can optimise bone health and management of cancer treatment induced bone loss in older women in future.

# **Aims and Objectives**

## Research questions

* What is the clinical management of bone health in older women with early breast cancer?
* What is the impact of age and frailty on bone health in this group of patients?

## Aims

* To understand how bone health is monitored and managed in older women with early breast cancer
* To map bone health screening and use of DXA scans in this population
* To map use of BTAs in this population
* To determine how age, health status, fitness and frailty affect bone health in older women with breast cancer

## Study Objectives

**Bone Health Screening**

* To describe how bone screening is performed in older women with early breast cancer and to assess the use of bone density scans
* To determine bone mineral density loss in older women with breast cancer
* To describe the patient and cancer characteristics which predict bone mineral density loss in older patients with breast cancer. Bone mineral density loss will be correlated with patients’ age, frailty scores and comorbidities.

**Bone Targeted Agents (BTAs)**

* To assess the use of BTAs in older women with early breast cancer and to describe the patient and cancer characteristics that predict treatment with these agents. Use of BTAs will be correlated with patients’ age, frailty scores and comorbidities.

**Bone Fractures**

* To describe bone fractures in older women with breast cancer
* To determine patient and cancer characteristic which predict bone fractures in older women with breast cancer. Bone fracture incidence will be correlated with patients’ age, frailty scores and comorbidities.

For the purpose of this study cancer characteristics are the following:

* Tumour Grade
* Tumour Size
* ER and PR Hormone status
* HER2 status
* Positive lymph nodes
* Oncotype DX score if available

# **Study Design and Methods**

## Study Design

Non-randomised, observational cohort study nested within the Age Gap Cohort study. No new patients will be recruited. This study simply involves collecting additional data about bone health from the existing cohort using electronic patient records held by Trusts.

Study will remain open between April 2022 until April 2024.

## Study Setting

Data will be collected from participants of the Age Gap study from the following participating sites:

|  |  |
| --- | --- |
| Site | Number recruited |
| Sheffield Teaching Hospitals NHS Foundation Trust | 153 |
| Leeds Teaching Hospitals NHS Trust | 213 |
| Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust | 73 |
| Rotherham NHS Foundation Trust | 72 |
| Chesterfield Royal Hospital NHS Foundation Trust | 67 |
| Barnsley Hospital NHS Foundation Trust | 47 |
| Liverpool University Hospitals NHS Foundation Trust | 196 |
| Manchester University NHS Foundation Trust | 50 |
| Total | 871 |

This should provide an adequate number of cases to determine variation in practice and test for correlation between use of bone protection measures and adverse BMD impacts.

## Eligibility

All the Age Gap study participants from the above-mentioned centres who meet all the inclusion and none of the exclusion criteria will be included in this study.

### **Inclusion Criteria**

* Female patients recruited to the Age Gap cohort with ER+ve early breast cancer who have been offered endocrine therapy with an AI (aromatase inhibitor) or tamoxifen, either as primary or adjuvant treatment, with or without subsequent chemotherapy.

### **Exclusion Criteria**

Patients who have requested withdrawal from the study since initial recruitment.

### **Defining ER+ve participants**

From the existing database of the Age Gap study we will identify patients with hormone positive (ER+ve) early breast cancer. Hormone positive (ER+ve) cancers are those with immunohistochemistry ER Allred score of ≥ 3 (positive when 3-8), an H score of >50/300 or a notation that their disease is categorised by the host breast unit as ER+ve.

# **Recruitment and Identification of Patients**

Patients already recruited to the Age Gap study from Sheffield, Leeds, Rotherham, Doncaster, Chesterfield, Barnsley, Liverpool and Manchester will be identified from the Age Gap database and screened. If patients meet the inclusion criteria they will be included in the study. Eligible patients will not be contacted. Upon recruitment to the study, we will proceed with additional data collection from existing hospital electronic records. It should not be necessary to request case notes for the majority of patients.

# **Informed Consent**

Patients who took part in the Age Gap study have already signed a consent form which permits the study team to collect data about their cancer diagnosis, treatment and follow up, including an amendment to permit us to collect longer term survival and recurrence data beyond the original 2 years of follow up which was included in the original protocol. Use of bisphosphonates is a routine part of care for breast cancer or is added in to minimize adverse events related to bone health. This study simply wishes to collect this data which was not part of the original data set when the study was designed. We also wish to collect information about adverse events related to bone health and once again the original study protocol allowed us to collect data on adverse events, this study would simply extend the time envelope for this beyond the original two years. We therefore feel that no new consent is indicated for this study.

# **Data collection and Management**

## Data Source

Data used in this study will come from data entered into the following sources:

* Data which has already been collected by the Age Gap study on skeletal related adverse events, drug history (baseline bisphosphonate use, steroid use etc), use of endocrine therapy for their breast cancer and type of endocrine therapy
* Medical notes held by the host trust (we expect most of the data we require will be found in hospital electronic records but may request case notes for some patients)
* Hospital online systems such as electronic results system (ICE)

## Data Management

Study data will be recorded in the electronic or paper-based CRFs. Data from completed CRFs will be transferred to the study database, hosted on secure servers at the University of Sheffield. Data will be verified and checked.

## Data items for collection

The existing Age Gap dataset already holds much of the data we need for our analyses including age, frailty, comorbidities, breast cancer stage and grade and type, treatment types and follow up for 2 years including whether any skeletal adverse events such as fractures occurred.

To this we plan to add the following:

* Duration of antioestrogen therapy
* Was a DXA scan performed at baseline (within 6 months of starting antioestrogen therapy)?
* The result of the DXA scan if performed in terms of T scores at the hip and spine and whether a diagnosis of osteopenia or osteoporosis was made
* Were any future follow up scans performed and if so what were the results?
* Were patients prescribed bisphosphonates, calcium of vitamin D at the start of their antioestrogen therapy and if so, which type?
* Were they subsequently prescribed these medications?
* Did they suffer any fractures between the time of diagnosis of cancer and the date of data collection?
* Site and type of fracture and any treatment needed
* Death (plus date of death and cause of death)
* Cancer recurrence or progression (plus date of recurrence and site of recurrence)

# **Outcome Measures**

**Bone Screening**

* To determine the pattern of bone screening in older women with early breast cancer
* To observe and describe bone mineral density loss in this group of patients and also to relate bone mineral density loss to age, frailty scores and cancer characteristics

**Bone Targeted Agents (BTAs)**

* To determine the pattern of BTAs use in older women with early breast cancer
* To relate the use of these agents to age, frailty scores and cancer characteristics

**Bone Fractures**

* To observe and describe bone fractures in this group of patients and also to include, when available, hospital admissions, need for surgical interventions and death due to bone fractures
* To relate age, frailty scores and cancer characteristics to bone fractures in this group of patients

For the purpose of this study cancer characteristics are the following:

* Tumour Grade
* Tumour Size
* ER and PR Hormone status
* HER2 status
* Positive lymph nodes
* Oncotype DX score if available

# **Statistical considerations**

## Sample Size

Data will be collected from patients who were recruited to the original Age Gap study from 8 NHS Trusts. The 8 NHS Trusts are Sheffield, Leeds, Doncaster, Rotherham, Chesterfield, Barnsley, Liverpool and Manchester.

Patients per centre who recruited to the original Age Gap study are as follow:

|  |  |  |
| --- | --- | --- |
| **Centres** | **Number of Recruited Patients** | **Local PI** |
| Sheffield | 153 | Janet Brown |
| Leeds | 213 | Raj Achuthan |
| Doncaster | 73 | Lynda Wyld |
| Rotherham | 72 | Tahir Masudi |
| Chesterfield | 67 | Iman Azmy |
| Barnsley | 47 | Julia Dicks |
| Liverpool | 196 | Julia Henderson |
| Manchester | 50 | Cliona Kirwan |

The total number of participants from the above centres is 871. About 75% of the early breast cancers are oestrogen receptor positive (ER+ve) and therefore we anticipate that over 600 patients from this pool of patients will be eligible for this study which will give us a powerful insight into the management of bone health in older women and their bone health outcomes.

## Statistical Analysis

Descriptive statistics will be used to describe findings including reporting means and standard errors for parametric data, medians and ranges for non-parametric data. Also, correlation analysis will be performed in order to describe the correlation between age, frailty and bone health in this group of patients. The risk of fractures and risk of osteoporosis in the study group according to age strata, antioestrogen type, use of chemotherapy or not will be described using hazard ratios and 95% confidence intervals. Statistical analysis will be performed using SPSS or R.

# **Ethical considerations**

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 World Medical Association General Assembly, Seoul, Korea, October 2008. The study will be submitted to and approved by an NHS REC prior to collecting any data. Data will be collected only from participants who have given a written consent to main Age Gap study and who have not requested withdrawal.

## Data collection from deceased participants of the Age Gap study

For the purposes of this study, data will be collected from all the eligible participants of the Age Gap study including participants who might be deceased. Cause of death will be recorded. Next of kin, families, friends or carers of deceased participants will not be contacted.

## Good Medical Practice

This study will be conducted in accordance with the principles of GCP in clinical trials, as applicable under UK regulations, and the NHS Research Governance Framework (and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 for studies conducted in Scotland).

## Protocol Amendments

The protocol will be adhered to and any amendments will be made by a formal procedure to receive approval from the Ethics Committee that approved the original protocol for this current study prior to implementation.

## Informed Consent

Full details on the process of obtaining informed consent are described in section 6. Participants of the original Age Gap study, their next of kin, family members or friends will not be contacted. Participant will remain free to withdraw consent at any time from the original Age Gap study without giving reasons. In this case, they will not be included in this current study.

## Confidentiality and Storage Methods

Confidentiality and security will be managed in accordance with Caldicott principles and the 1998 Data Protection Act. Clinical Research Fellow who will do data collection and access patients' records is on University of Sheffield contracts of employment and will have research passports for all the NHS Trust involved in this study.

Patient data will be anonymised using unique study numbers from the original Age Gap study. Some patients’ identifiers will be used in order to identify patients from the original Age Gap study and collect data for the purpose of this project. Any information that would allow patients and clinicians to be identified will not be released into the public domain. Patients who request removal of their data from the original Age Gap study will have this performed, leaving just an anonymised tracking marker for the study consort diagram.

Trial data will be recorded in the study specific CRFs and then transferred to a study database. All data will be handled, computerised and stored in accordance with the Data Protection Act 1998. Quality control will be maintained through adherence to departmental standard operating procedures (SOPs), and by following the principles of GCP according to the EU Directive 2005/28/EC (GCP Directive), which was implemented in The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.

It is the responsibility of the study team to maintain the Trial Master File in which all the study documents will be stored. Trial Mater File will be kept at the Academic Unit of Surgical Oncology.

## Archiving

At the end of the study, data and the Trial Master File will be securely archived at the Department of Oncology and Metabolism 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.

## Dissemination of Results

This current study is part of a higher degree. The Clinical Research Fellow is working full time towards the completion of the higher degree at the University of Sheffield.

The results from this study will add value to the current data from the original Age Gap study. It is expected that the results will be presented at national and international bone and cancer conferences. A manuscript detailing the results of the study will be prepared for submission to high impact peer review journals.

# **Strategy for the Future**

The results of this study will be used to inform current and future clinical practice in the care of older breast cancer patients. Data will contribute to the improvement of the care of older patients with breast cancer and also to improve clinical outcomes for this group of patients.

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