BONE HEALTH AND OSTEOPOROSIS

IN WOMEN DIAGNOSED WITH BREAST CANCER

IN BRITISH COLUMBIA

by

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Abstract

Background: Women diagnosed with breast cancer are at higher risk of osteoporosis and osteoporotic fractures. Information is lacking on utilization of bone mineral density testing in British Columbia, and fracture risks associated with tamoxifen and aromatase inhibitors to plan care.

Methods: Three studies were conducted on women diagnosed with breast cancer. Study 1, a retrospective cross-sectional study evaluated the utilization of bone mineral density testing in 1995-2008 and identified factors associated with different testing rates using secondary data-linkage in older women aged ≥65 and diagnosed with breast cancer for ≥3 years in British Columbia, Canada. Study 2, a pilot randomized controlled trial, assessed the feasibility of a protocol designed to improve bone health management, especially bone mineral density testing rates, with educational material in older women aged ≥65 and diagnosed with breast cancer for ≥3 years. And study 3, a systematic review with meta-analysis, estimated fracture risks associated with tamoxifen and aromatase inhibitors in younger women aged ≤65.

Results: In older women aged ≥65, proportions of women with ≥1 bone mineral density test per calendar year increased from 1.0% in 1995 to 10.1% in 2008. Women with lower socio-economic status or rural residence were significantly less likely to have a bone mineral density test. The study protocol is feasible with a promising effect of educational material on bone mineral density testing rates (17%, 95% CI=6 to 33) in the 54 participants during the pilot study six-month follow-up period. In younger women aged ≤65, fracture risk did not differ between the

tamoxifen and no-tamoxifen groups. Aromatase inhibitor-associated fracture risk was 17% and 35% higher than the risks in the no-aromatase inhibitor group and tamoxifen group respectively. The higher aromatase inhibitor-associated fracture risk compared with tamoxifen descreased slowly over time. The risk was significantly higher during the treatment period, but not the post-treatment period.

Conclusions: Increased risk of fractures is reported in women diagnosed with breast cancer and treated with aromatase inhibitors, while screening for osteoporosis with bone mineral density testing is sub-optimal. There is a need to improve bone health management programs which should include educational materials.

Lay Summary

Women diagnosed with breast cancer are at higher risk of developing osteoporosis and breaking bones. Bone health management including bone scans, plays a key role in preventing fractures for this group of women. My studies show low rates of bone scans for women aged 65 years and over, especially women with lower income or living in rural areas. Nine of the 54 women had bone scans within six months after being provided with our educational material. An additional 35 broken bones happen to every 100 women, aged 65 years and under, taking aromatase inhibitor treatment compared with women taking tamoxifen treatment. Broken bones are more likely to happen during the treatment period. Women diagnosed with breast cancer should be encouraged to have bone scans. Bone health management programs including physical activity and calcium/vitamin D intake are important for women diagnosed with breast cancer, especially those taking aromatase inhibitors.

Preface

This dissertation is original and independent work completed by Ling-I Olivia Tseng (me). This thesis is manuscript-based. I am the lead author of all three manuscripts included in this thesis.

A version of ***Chapter Two (study 1)*** of this thesis has been submitted to Osteoporosis International. The co-authors include Martin Dawes, John Spinelli, Carolyn Gotay, and Mary McBride. The title is "Utilization of bone mineral density testing among breast cancer survivors in British Columbia, Canada". This study provides a better understanding of the utilization of bone mineral density (BMD) testing using secondary administrative healthcare data linkage. I developed this project using data acquired under Mary McBride's research project "Late morbidity and health care utilization among three-year survivors of breast cancer in BC, Canada". Ethics approval H09-01957 was obtained from the University of British Columbia (UBC) / British Columbia (BC) Cancer Agency Ethics Board. Financial support for this project was provided through Mary McBride's Canadian Breast Cancer Foundation research grant. I designed the study, prepared the study protocol, analyzed and interpreted the data, and prepared the manuscript. The co-authors contributed to the study design and data interpretation. Mary McBride also provided administrative support for the data-linkage and John Spinelli aided in the statistical analysis. All co-authors reviewed and involved in revising the manuscript. All inferences, opinions, and conclusions drawn in this chapter are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

A version of ***Chapter Three (study 2)*** from this thesis will be submitted for journal publication. The co-authors include Martin Dawes, John Spinelli, Carolyn Gotay, Mary McBride, and Wan

Yu (Julia) Ho. The title is “Promoting bone health management in women diagnosed with breast Cancer: a pilot randomized controlled trial”. This project evaluated the feasibility of a randomized controlled trial protocol designed to evaluate the effect of educational material on bone health management. I developed and designed this project with guidance from Martin Dawes. I prepared the ethics application and obtained ethics approval H15-00849, from the UBC / BC Cancer Agency Ethics Board. I obtained a Janus research grant provided by the College of Family Physicians Canada to support this study. I wrote the study protocol and educational material, and selected validated questionnaires based on literature review. The first four co-authors contributed to the study design, data interpretation, educational material review, and questionnaire preparation. John Spinelli also contributed to the statistical analysis. All co-authors reviewed and were involved in revising the manuscript.

A version of ***Chapter Four (study 3)*** will be submitted for journal publication. The co-authors include Martin Dawes, John Spinelli, Carolyn Gotay, Mary McBride and W.Y. (Julia) Ho. The title is “Aromatase inhibitors are associated with a higher fracture risk than tamoxifen: a systematic review and meta-analysis. This study evaluated fracture risks associated with breast cancer treatments, tamoxifen and aromatase inhibitors, using a systematic review format with meta-analysis. No ethics approval was required and no research grant was obtained for this study. I developed this project, wrote the study protocol and selected tools to assess methodology quality with guidance from Martin Dawes. I conducted article searches with the guidance of a UBC biomedical librarian. I recruited and supervised a first-year family practice resident Nicole Redding, who screened the selected articles by title and abstract. I also recruited and supervised W.Y. (Julia) Ho, who reviewed the selected full-text articles and extracted data from the

included articles. I screened the selected articles by title and abstract, reviewed the selected full-text articles, prepared Excel worksheets for data extraction, conducted methodology quality assessment, and extracted data from the included studies. I conducted all data analyses. The first four co-authors contributed to the study design, data interpretation and manuscript preparation. Martin Dawes and John Spinelli also contributed to the statistical analysis. All co-authors reviewed and were involved in revising the manuscript.

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List of Symbols

%	percent
±	plus or minus
≥	greater than or equal to
≤	less than or equal to
>	greater than
<	less than
=	equal

List of Abbreviations

AAPCs	Average annual percentage changes
ABCSG	Austrian Breast and Colorectal Cancer Study
aHR	Adjusted hazard ratio
AIs	Aromatase inhibitors
APCs	Average percent changes
ARNO	Arimidex-Nolvadex
ATAC	Arimidex, Tamoxifen, Alone or in Combination
BC	British Columbia
BCOU	Breast Cancer Outcome Unit
BIG	Breast International Group
BMD	Bone mineral density
CAT	Calcium Assessment Tool
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trails
DBCG	Danish Breast Cancer Cooperative Group
DXA	Dual-energy X-ray absorptiometry
FRAX	Fracture risk assessment
GLTEQ	Godin Leisure-Time Exercise Questionnaire
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
IES	Intergroup Exemestane Study

IRR	Incidence rate ratio
IU	International unit
MSP	Medical Service Plan
OR	Odds ratio
aPR	Adjusted prevalence ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
RCT	Randomized controlled trial
RR	Risk ratio
SAS	Statistical Analysis System
SD	Standard deviation
SERM	Selective estrogen receptor modulator
SES	Socio-economic status
SOFT	Suppression of Ovarian Function Trial
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TEAM	Tamoxifen, Exemestane Adjuvant Multinational
TEXT	Tamoxifen and Exemestane Trial
TNM	Tumor node metastasis
UBC	University of British Columbia
VIDSUN	Vitamin D & Sun

Acknowledgements

I would like to express my deepest appreciation to my two co-supervisors Mary L. McBride, the clinical professor at the School of Population and Public Health at the University of British Columbia (UBC), and Martin G. Dawes, a professor and the head of the UBC Department of Family Practice. They both provided me with incredible support for my thesis work by guiding me to explore my own research journey. My PhD study has been a unique experience allowing me to conduct research projects from concepts right through to the completion of studies.

My sincere thanks goes to my two other committee members John J. Spinelli, a professor at the UBC School of Population and Public Health and head of the Cancer Control Research of the British Columbia Cancer Agency, and Carolyn G. Gotay, a professor at the UBC School of Population and Public Health and the Canadian Cancer Society Chair in Cancer Primary Prevention. They both shared their years of research experience with me whenever I was in need.

I would like to express my sincere gratitude to all funding agencies supporting my PhD study – the UBC Clinician Scholar Program, the Canadian Breast Cancer Foundation (Telus-Canadian Breast Cancer Foundation Fellowship), the Faculty of Medicine (Graduate Award), the Interdisciplinary Oncology Program (Travel Award), Mr. Roman M. Babicki (Roman M. Babicki Fellowship in Medical Research), and the College of Family Physicians Canada (Janus Research Grant).

I would like to express my personal appreciation to volunteer student W.Y. Julia Ho, volunteer family practice resident Nicole Redding, the educational director of the Centre of Excellence in

Cancer Prevention Melissa Ashman, pharmacist Jun Qing Pan, all study participants, and team members consisting of my co-supervisors and committee members. This thesis wouldn’t have been completed without their support.

And special thanks goes to my husband Richard, my sisters Sophia and Suzen, and my parents. Without their love, continued encouragement, and nonstop support, this thesis wouldn’t exist.

Chapter 1: Introduction

This thesis provides a better understanding of osteoporosis and bone health management in women diagnosed with breast cancer. Osteoporosis is a major public health issue while breast cancer is the most common female cancer worldwide. Both osteoporosis and breast cancer are strongly associated with advancing age. This thesis was developed upon two main concepts. First, women diagnosed with breast cancer are at higher risk of osteoporotic fractures compared with women without breast cancer. Second, BMD testing is recommended to high risk populations – by age (old women aged ≥65) or risk factors (younger women aged <65 with risk factors while breast cancer treatment is not consistently considered a risk factor for BMD testing eligibility). Study 1 and study 2 focus on the utilization of BMD testing in old women, a high-risk population by age. Study 3 focuses on fracture risk estimates associated with hormonal treatments in younger women, a high-risk population by risk factors. A better understanding on the effects of hormonal treatments on fracture risk in younger women may alter their eligibility for BMD testing. Older women are eligible for BMD testing regardless of breast cancer diagnosis and treatment.

Sections 1.1 and 1.2 fundamentally review both breast cancer and osteoporosis in the general population. Section 1.3 specifically reviews osteoporosis in women diagnosed with breast cancer. ***Study 1*** evaluated the utilization of bone mineral density (BMD) testing in older women based on section 1.3.3, “Guidelines for BMD measurement with dual-energy X-ray absorptiometry (DXA) in women diagnosed with breast cancer in Canada”. ***Study 2*** determined the feasibility of a study protocol designed to improve bone health management including BMD testing rates and lifestyle modifications in older women. This study was developed based on the

results from study 1, section 1.2.5.4 “Potential barriers to access BMD testing”, and section 1.2.5.5 “Potential interventions to improve utilization of DXA”. ***Study 3*** systematically reviewed the effects of tamoxifen and aromatase inhibitors (AIs) on fracture risk in younger women based on section 1.3.2 “Effects of breast cancer treatments on bones and fractures”.

1.1 Breast Cancer

1.1.1 Introduction

Breast cancer is defined by the National Cancer Institute as “cancer that forms in tissues of the breast”. Common breast cancers include ductal carcinoma starting in the lining of the mammary ducts (80-90%) and lobular carcinoma starting in the lobules of the milk-producing glands (10%) (*www.cancer.gov/publications/dictionaries/cancer-terms*). Nearly 99% of all breast cancers occur in women [1].

1.1.2 Epidemiology

Breast cancer is the most common female cancer worldwide. There were approximately 1.7 million new female breast cancer cases globally in 2012. The highest incidence rates were reported in North America, Australia, New Zealand, and in western and northern Europe. The lowest incidence rates were noted in Asia and Sub-Saharan Africa [2].

Breast cancer accounts for 26% of all female cancers in Canada. One in every nine Canadian women is expected to develop breast cancer in their lifetime. The majority of female breast cancer cases are diagnosed at the age range of 50-69 years. There were an estimated 25,000 new breast cancer cases and 5,000 deaths in 2015 in Canada alone [1].

The historical age-standardized incidence rates in Canada increased by 15% during the period 1986-1992 (Figure 1-1). This rate increase was associated with the implementation of organized provincial screening mammogram programs in 1988. Age-standardized incidence rates had been stable over the period 1988-2015. The highest historical age-standardized mortality rate was reported in 1986. Age-standardized mortality rates had been trending down and dropped by 44% during the period 1987-2015 [1]. This was likely due to early cancer identification through screening mammogram programs and the use of more effective cancer treatment.

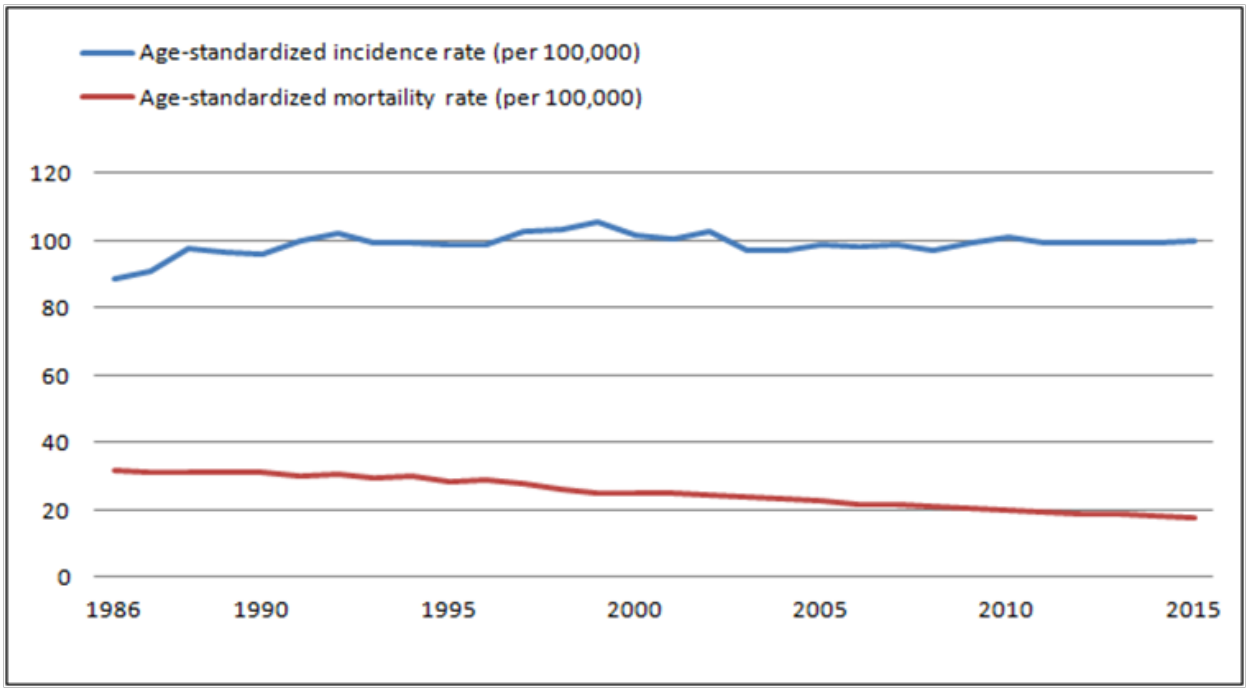


Figure 1-1 Age-standardized incidence rates and age-standardized mortality rates for breast cancer, females, Canada 1986-2015

Rates are age-standardized to the 1991 Canadian population. This figure was created based on data from reference article [1].

1.1.3 Risk factors

Many risk factors have been established for female breast cancer. The most important risk factor is “advancing age”. The probabilities of a Canadian woman developing breast cancer over her next 10-year period of life per her current age are as follows [1]:

- Age 30 – 0.4% (1 in 250 women or one in every 250 women who are currently aged 30 years, will develop breast cancer over their next 10 years.)
- Age 40 – 1.4% (1 in 71 women)
- Age 50 – 2.2% (1 in 45 women)
- Age 60 – 3.2% (1 in 31 women)
- Age 70 – 3.3% (1 in 30 women)
- Age 80 – 2.6% (1 in 38 women)

The risk factors associated with breast cancer are categorized into three groups as follows [3]:

High risk (relative risk (RR) > 4.0)

- Old age [3]
- White race [4, 5]
- BRCA 1 / 2 gene positive [3]
- Two first-degree relatives with breast cancer diagnosed at an early age [3]
- Previous breast cancer [6]
- Dense breast tissue [7]

Moderate risk (2 > RR ≥ 4.0)

- One first-degree relative with breast cancer [3]
- Benign breast disease [8, 9]
- Therapeutic ionizing radiation exposure [10-13]

- No oophorectomy at younger age [3]

Weak risk (2 ≥ RR)

- Reproductive factors, including early menarche or late menopause [9, 14-17], nulliparity [17, 18], and older age at first pregnancy [9, 17, 18]
- Short or no breast feeding [19]
- Hormonal factors, including hormonal replacement therapy [20] and oral contraceptive use [21]
- High socio-economic status (SES)
- Obesity [22]
- Tall stature [23-25]
- Life style factors, including smoking [26, 27], alcohol [28-31], and night shift work [32]

1.1.4 Clinical manifestations

A breast mass or lump is the most common breast cancer presentation, accounting for 55-92% of new cases. A cancerous breast mass commonly presents as a single, hard, immovable subcutaneous lesion with an irregular border. Other common manifestations of breast cancer include breast pain, nipple discharge, skin changes, and nipple changes [33-36].

Manifestations of breast cancer can change when cancer progresses. When breast cancer spreads beyond the breast(s) at the locally advanced stage, a lump or multiple lumps may develop in the armpits (axilla). These lumps are lymph nodes infiltrated by cancer cells, which could be painless, hard, and immovable. When breast cancer spreads to other organs at the metastatic stage, the manifestations that develop mainly depend on the organs involved. The common

organs (related symptoms) involved are bones (bone pain and pathological fracture), liver (abdominal pain, nausea, and jaundice), lungs (cough and shortness of breath), and brain (headache, nausea, vomiting, weakness, and confusion) [37].

1.1.5 Screening and early detection

Screening plays a key role in the early detection of breast cancer. It can be used to identify individuals with breast cancers before symptoms occur. Mammogram, a breast imaging test using low-dose X-ray, remains the primary screening test for early detection of breast cancer. Screening mammogram has been recommended by major health authorities in North America with variations in screening intervals, and ages to initiate and discontinue screening [38, 39]. In Canada, a screening mammogram at a two- to three-year interval is recommended for women aged 50-74 years with average breast cancer risk [38].

Screening mammogram has been shown to be associated with an approximate 20% reduction in breast cancer mortality based on three meta-analyses conducted by the UK Independent Panel (relative risk (RR)=0.80, 95% confidence intervals (CI)=0.73 to 0.89; using a random-effects model) [40], the Canadian Task Force (RR=0.83, 95% CI=0.76 to 0.92; using a random-effects model) [38], and Cochrane (RR=0.81, 95% CI=0.74 to 0.87; using a fixed-effect model) [41]. However, a more recent study reported no impact of screening mammogram on breast cancer mortality after a 25-year follow-up in Canadian women aged 40-59 years [42].

1.1.6 Diagnosis

1.1.6.1 Diagnostic evaluation

A diagnostic evaluation is conducted to identify the causes of mammogram-detected abnormalities or presented symptoms commonly associated with breast cancer. The diagnostic evaluation may include a full personal and family health history, a physical examination, diagnostic imaging tests, and a breast biopsy.

The individual's personal and family health history information is used to determine the risk of breast cancer development. The physical examination by a health care provider looks for signs of breast cancer, such as a breast lump. The two most common initial diagnostic imaging tests are diagnostic mammogram (more views than a screening mammogram) and ultrasound to locate possible cancer lesions [43]. A breast biopsy is used to confirm the presence of cancer cells in the suspected lesion by primarily using needles to obtain a small sample of the lesion. The sample is then examined by a pathologist.

1.1.6.2 Diagnostic criteria

A breast cancer diagnosis is confirmed by the presence of breast cancer cells with a pathological examination.

1.1.6.3 Staging, grading, and receptor status

The extent and features of the cancer should be evaluated and classified by stage, receptor status, and cancer relapse risk right after a breast cancer diagnosis is made. This information is used to determine prognosis and guide treatment.

Stage

The Tumor, Node, and Metastasis (TNM) staging of breast cancer is summarized in Table 1-1. The T category describes the size of the primary breast cancer. The N category describes the number and location of any regional lymph node(s) containing cancer cells. And the M category describes whether the cancer has spread beyond the breast(s). The TNM staging information is grouped into prognostic stage ranging from 0 (zero) to IV (four) with increasing severity of the cancer [44]. Stages I-II, III, and IV are also commonly referred to as early, locally advanced, and advanced/metastatic stages respectively. .

Table 1-1 TNM staging of breast cancer

Overall stage		**Tumor (T)**	**Nodes (N)**	**Metastasis (M)**
	Stage 0	Non-invasive, cancer cells are contained in the milk duct	0	No
Early breast cancer	Stage I / II	Size ≤ 5cm	≤ 3 involved nodes	No
Locally advanced breast cancer	Stage III	Any size	≥ 4 involved nodes	No
		Any size	Nodes other than in axilla	No
		Size > 5cm or tumor fixed to skin or chest wall	Any nodes	No
Metastatic breast cancer	Stage IV	Any size	Any nodes	Metastasis

Receptor status

The status of three receptors, either positive or negative, is evaluated using immunohistochemistry staining. The three receptors evaluated are the estrogen receptor, the progesterone receptor, and the human epidermal growth factor receptor 2 (HER2). These receptors may receive signals from corresponding hormones, estrogen, progesterone, and human epidermal growth factor, to promote the growth of breast cancer cells. Women with estrogen

and/or progesterone receptor-positive breast cancers are likely to benefit from hormonal treatment, which are associated with better outcomes [45-47]. Women with HER2-positive breast cancers are likely to benefit from biological treatment [48].

Cancer relapse risk

Categories of cancer relapse risk are determined in women with non-metastatic stage 0-3 breast cancer based on age, tumor size, and histological features (Table 1-2) [49]. Three different histological features of tubule formation, nuclear pleomorphism, and mitotic count, are evaluated in breast cancer cells under a microscopic exam. Each feature is scored from one to three. The total score of the three features is classified into three grades: grade 1 or low grade (total score 3-5), grade 2 or intermediate grade (total score 6-7), and grade 3 or high grade (total score 8-9). Higher grade cancer cells tend to grow faster and are more likely to spread [50].

Table 1-2 Definition of categories of cancer relapse risk for patients with operated breast cancer. Reprinted with permission [49]

Risk category	
Low risk [a]	Node negative and all of following features
	pT ≤ 2cm, AND
	Grade 1 [b], AND
	Absence of peritumoral vascular invasion [c], AND
	HER2/neu gene neither overexpressed nor amplified [d], AND
	Age ≥ 35 years
Intermediate risk [e]	Node negative AND at least one of the following features:
	pT > 2cm, OR
	Grade 2-3 [b], OR
	Presence of peritumoral vascular invasion [c], OR
	HER2/neu gene overexpressed or amplified [d], OR
	Age < 35 years
	Node positive (1-3 involved nodes) AND
	HER2 / neu gene neither overexpressed nor amplified [d]
High risk	Node positive (1-3 involved nodes) AND
	HER/neu gene overexpressed or amplified [d]
	Node positive (4 or more involved nodes).

pT pathological tumor size (i.e. size of the invasive component), *HER* human epidermal growth factor receptor

[a] Some Panel members view pT1a and pT1b (i.e. pT <1 cm) tumors with node-negative disease as representing low risk even if higher grade and/or younger age

[b] Histologic and/or nuclear grade

[c] Peritumoral vascular invasion was considered controversial as a discriminatory feature of increased risk; its presence defined intermediate risk for node-negative disease, but did not influence risk category for node-positive disease

[d] HER2/*neu* gene overexpression or amplification must be determined by quality-controlled assays using immunohistochemistry or fluorescence *in situ* hybridization analysis

[e] Note that the intermediate-risk category includes both node-negative and node-positive 1–3 disease

1.1.7 Treatment

Breast cancer treatments are primarily determined by menopausal status, receptor status, and cancer relapse risk. Breast cancer treatments are categorized into two major groups – loco-regional treatments and adjuvant systemic treatments. The loco-regional treatments include surgery and radiation therapy. The adjuvant systematic treatments include chemotherapy, hormonal treatment, and biological therapy.

1.1.7.1 Surgery

Surgery involves the removal of the cancer tissues. Lumpectomy is primarily performed as a definite treatment in women with early breast cancer. This is a surgical removal of the cancerous tissues and some surrounding normal breast tissues [51]. Mastectomy and lymph node dissection in the ipsilateral axilla are primarily performed in women with locally advanced breast cancer. This is a surgical removal of the entire breast with cancer and the axillary lymph nodes [52]. Surgery may also be an option for women with metastatic breast cancer.

1.1.7.2 Radiation therapy

Radiation therapy shrinks or kills cancer cells using high-energy radiation. Radiation therapy is primarily provided after breast surgery to reduce the local recurrence of the breast cancer in women with early or locally advanced breast cancer [53, 54]. Radiation therapy may also be offered to women with metastatic cancer to relieve symptoms, such as pain associated with bone metastasis and neurological symptoms associated with brain metastasis.

1.1.7.3 Chemotherapy

Chemotherapy uses both oral and injectable drugs to kill cancer cells. It is primarily provided after surgery, but before radiation therapy, to reduce the recurrence of the breast cancer. Common chemotherapy drugs are cyclophosphamide, methotrexate, 5-fluorouracil, adriamycin, doxorubicin, and epirubicin [55, 56]. Chemotherapy is indicated in women at intermediate or high cancer relapse risk, regardless of menopausal status.

1.1.7.4 Hormonal treatment

Hormonal treatment is primarily given to women with hormone receptor-positive (estrogen and/or progesterone receptor-positive) breast cancer, and determined based on menopausal status and cancer relapse risk [49]. Hormonal treatment stops or slows cancer growth by reducing the available estrogen to cancer cells. Hormonal treatments are selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), and ovarian suppression treatment. SERMs, such as tamoxifen, block estrogen from binding to breast tissues. AIs, such as letrozole, reduce the production of estrogen. Ovarian suppression by radiation, surgery, or gonadotropin-releasing hormone agonists, are commonly provided after surgery [55-57]. Ovarian suppression is primarily used to treat pre-menopausal women, especially those at intermediate or high cancer relapse risk. Tamoxifen is primarily used to treat pre-menopausal women, and post-menopausal women at lower cancer relapse risk. AIs are primarily used to treat post-menopausal women at higher cancer relapse risk.

1.1.7.5 Biological treatment

Biological treatment stops or slows cancer cell growth by blocking the growth signals with antibodies, such as trastuzumab. Biological treatment is an option for women with HER2-positive breast cancer [58].

1.1.8 Follow-up care after completing breast cancer treatment

The impact of the care needs in women with breast cancer is escalating due to (1) an increasing population of women diagnosed with breast cancer; (2) the increasing complexity of care needs in this population; and (3) new recognition of the long-term and late effects associated with breast cancer and cancer treatment.

1.1.8.1 Increasing population of women diagnosed with breast cancer

The projected Canadian population will increase by 19% from 32 million residents in 2000 to 38 million residents over the period from 2000 to 2028 [59]. Over the same time period, the estimated new cases of female breast cancer will increase by 63% (19,200 cases in 2000 to 31,255 cases in 2028) in Canada [60, 61] and by 80% (2,600 cases in 2000 to 4,675 cases in 2028) in BC [62]. At least 87% of these women diagnosed with breast cancer will survive five years or more [60].

1.1.8.2 Follow-up care in women completing initial breast cancer treatments

The care needs differ in women at different phases of their breast cancer such as at the phases of cancer diagnosis, cancer treatment, and post-cancer treatment [63, 64]. Caring for women after completing their initial breast cancer treatments is challenging due to a lack of standardized

guidelines. A recognized care gap in women completing their cancer treatments has been emphasized by the Institute of Medicine and the American Society of Clinical Oncology [65]. Women completing their initial cancer treatments require care for cancer recurrence surveillance, primary or secondary cancer prevention, and monitoring and management of common long-term and late effects such as treatment related osteoporosis, heart failure, coronary artery disease, diabetes, and premature menopause [66-71].

1.2 Osteoporosis and Osteoporotic Fractures

1.2.1 Introduction

Osteoporosis was first defined as "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a subsequent increase in fragility and susceptibility of fracture" at the 1993 consensus development conference [72]. This definition has recently been modified to be "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture" by the National Institutes of Health in 2001 [73]. The term "osteopenia" describes a lower loss of bone mass than osteoporosis. Osteoporotic fractures or fragility fractures are fractures associated with low bone mass or osteoporosis, which commonly occur on the spine, wrist, or hip [74].

1.2.2 Epidemiology

Osteoporosis is a major public health issue strongly associated with advancing age. The prevalence and incidence of osteoporosis are continuing to increase due to progressively aging populations [75]. Osteoporosis affects an estimated 200 million women worldwide. When stratified by age, osteoporosis affects approximately one-tenth, one-fifth, two-fifths, and two-

thirds of women aged 60, 70, 80, and 90 respectively [76]. Approximately one in four Canadian women have osteoporosis [77]. An estimated 15.8% and 45.9% of Canadian women aged over 50 suffer from osteoporosis and osteopenia respectively, per the osteoporosis diagnostic criteria defined by the World Health Organization [78].

There were an estimated nine million osteoporotic fractures in 2000 worldwide. One in every three women over age 50 years will develop osteoporotic fractures [79, 80]. Projected new hip fracture cases in women will increase by 240% from 1990 to 2050 [81]. Osteoporotic fractures account for 80% of all fractures in post-menopausal Canadian women over age 50 [82]. Projected annual new hip fracture cases among women aged 65 and over, will increase by threefold over the period from 1993 to 2041 [83].

1.2.3 Risk factors for osteoporosis and osteoporotic fractures

Many risk factors for osteoporosis and osteoporotic fractures have been identified. The major risk factors for osteoporosis listed in the 2002 Canadian Osteoporosis guideline are summarized in Table 1-3. The four major risk factors for osteoporotic fractures are advanced age, osteoporotic fracture, family history of osteoporotic fracture, and low bone mineral density (BMD) [84]. The first three risk factors for osteoporotic fracture are also risk factors for osteoporosis.

Table 1-3 Risk factors for osteoporosis in general female population based on the 2002 Canadian osteoporosis guideline

Major risk factors of osteoporosis	**Minor risk factors of osteoporotic**
Age >65	Rheumatoid arthritis
Vertebral compression fracture	Past history of clinical hyperthyroidism
Osteoporotic fractures over age 40	Chronic anticonvulsant therapy
Family history of osteoporotic fracture	Low dietary calcium intake
Systemic glucocorticoid therapy >3 month duration	Smoker
Malabsorption syndrome	Excessive alcohol intake
Primary hyperparathyroidism	Excessive caffeine intake
Propensity to fall	Weight <57 kg
Osteopenia apparent on x-ray film	Weight loss of >10% of weight at age 25
Hypogonadism	Chronic heparin therapy
Early menopause (before age 45)	

1.2.4 Osteoporosis fulfills the Wilson-Jungner criteria for a screening program

The Wilson-Jungner criteria guide the selection of diseases that would benefit from and are suitable for screening. These criteria were defined for the World Health Organisation in 1968 [85]. Osteoporosis was first considered for screening programs by the World Health Organization in 1994. Osteoporosis meets the criteria for a screening program except the criterion “there should be a recognizable latent or early symptomatic stage”. While osteoporosis remains silent without symptoms before fractures occur, the target population for osteoporosis screening can be identified using validated risk factors, such as age and gender instead. The criteria and rationales supporting osteoporosis screening with BMD testing are summarized in **Error! Reference source not found.**

The target population for osteoporosis screening with BMD testing are the high-risk individuals (high-risk screening), but not everyone in the population (population screening). The efficacy of

population screening has been lacking whereas benefits of high-risk screening from cost-effective fracture prevention strategy of treating high-risk individuals with screen-detected osteoporosis, have been demonstrated [86, 87]. However, the effect of high-risk screening on mortality remains unclear.

The goal of osteoporosis screening has been shifting from identifying “individuals at high risk of osteoporosis” to “individuals at high risk of osteoporotic fractures” [88]. This is because (1) osteoporotic fractures have a higher impact than osteoporosis diagnosis on the individual’s life quality and healthcare systems; (2) not every individual diagnosed with osteoporosis will develop osteoporotic fractures in their lifetime [89]; and (3) individuals without osteoporosis diagnosis could develop osteoporotic fractures [90, 91].

Table 1-4 Summary of the Wilson-Jungner Criteria and corresponding evidence to support osteoporosis for screening programs

Criteria	**Evidence supporting osteoporosis screening**
The condition sought should be an important health problem	- A globally significant health issue - An estimated 200 million women with osteoporosis worldwide [75] - Increasing prevalence and incidence of osteoporosis due to aging populations [75] - One fracture in every three women over age 50 years [79, 80]
The natural history of the condition, including development from latent to declared disease, should be adequately understood	- Well-understood pathophysiology of osteoporosis [92]
There should be a recognizable latent or early symptomatic stage *	- Osteoporosis develops slowly over years [93] - Lacking symptoms till fractures occur [93] - Target populations could be identified using the validated risk factors (Table 1-3)
There should be a suitable test or examination	- BMD testing is a suitable test - BMD testing could be done using different technologies. Of them, DXA scan is the most effective and widely used test for osteoporosis screening [94-96]
The test should be acceptable to the population	- BMD testing is widely accepted
Case finding should be a continuing process and not a “once and for all” project	- A BMD test at a one- to three-year interval is recommended by major guidelines [97]
Facilities for diagnosis and treatment should be available	- BMD testing with DXA is readily available in hospitals and imaging clinics in Canada - Osteoporosis could be treated by family doctors or specialists in the community
There should be an accepted treatment for patients with recognized disease	- Osteoporosis treatment is associated with a 11% reduction in mortality (pooled risk ratio (RR)=0.89, 95% CI=0.80 to 0.99, p=0.036) in post-menopausal women [98] - The number needed to treat for over two year treatment in post-menopausal women at higher osteoporosis risk is 24 (95% CI=19 to 37) for alendronate and 43 (95% CI=30 to 89) for residronate [99] - The number needed to treat would be lower over longer time periods and in individuals at higher osteoporosis risk [99]

Continued

Criteria	Evidence supporting osteoporosis screening
There should be an agreed policy on whom to treat as patients	- Diagnostic criteria of osteoporosis were initially defined by the World Health Organization in 1994 [95]. - Osteoporosis treatment has been recommended for anyone with osteoporosis, high risk of osteoporotic fracture or history of osteoporotic fracture [88, 97]
The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole	- Treating women with screening-detected osteoporosis is cost-effective for fracture prevention in older women - The cost per quality-adjusted life year is US$43,000 for women aged 65 and US$5,600 for women aged 75 [86, 87]

DXA dual-energy X-ray absorptiometry, *RR* risk ratio, *CI* confidence interval

*Did not match criteria

1.2.5 Screening for osteoporosis

Osteoporosis screening primarily involves the two stages of identifying high-risk individuals for BMD testing, and diagnosing osteoporosis and determining fracture risk based on BMD measurements. The goal of osteoporosis screening is to identify individuals at high risk who would benefit from treatment before fractures occur [97].

1.2.5.1 Risk assessment to identify high risk individuals for bone mineral density testing

Any individuals aged 50 years and over should be assessed for risk. Risk assessment involves either (1) identifying specific risk factors [97], or (2) determining fracture risk using risk assessment instruments (*www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines*).

Risk factor identification

Identifying risk factors involves appropriate history taking, physical examinations, biochemical testing, and possibly radiographic examinations. Important risk factors that can be identified during this process are summarized in Table 1-5 [97].

Table 1-5 Identification of risk factors during osteoporosis screening

Risk assessment	Risk factors
History taking	Family history of osteoporotic fractures
	Personal history of osteoporotic fractures
	High-risk medications (e.g. aromatase inhibitors, glucocorticoids)
	Smoking
	Excessive drinking
	Diseases (e.g. rheumatoid arthritis)
	Post-menopausal status
Physical examination	Low body mass index
Biochemical tests	25-hydrocyvitamin D (detecting vitamin D deficiency)
	Thyroid-stimulating hormone (detecting thyroid disease)
Radiological examination	Vertebral compression fractures

Risk assessment instruments

Multiple risk assessment instruments have been developed using different combinations of risk factors. In British Columbia (BC), the FRAX tool without BMD is suggested. FRAX is an international tool developed by the World Health Organization and calibrated for each country [100]. The Canadian version of FRAX was released in 2008. Any individuals with moderate fracture risk (10-20%) should have BMD testing for further fracture risk stratification (*www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines*).

1.2.5.2 Bone mineral density testing to diagnose osteoporosis or determine fracture risk

BMD is used to quantify bone mass as the bone mineral content per unit in g/cm^2 [101]. BMD can be measured using a variety of imaging technologies, such as dual-energy X-ray absorptiometry (DXA), calcaneal quantitative ultrasound, and quantitative computer tomography. The DXA scan is favored over the other technologies due to lower radiation exposure, reasonable cost, greater precision, and better sensitivity to detect osteoporosis [84, 102]. A DXA scan of the spine and hip (total hip, femoral neck or trochanter) is the gold

standard test and widely accepted for BMD measurements in Canada. BMD testing with DXA remains a better single quantifiable risk predictor while its sensitivity increases when combined with FRAX [103].

Indications of BMD testing vary significantly among international and local guidelines. In Canada, one BMD test is recommended for individuals aged 65 and over, or individuals aged under 65 with pre-selected risk factors at one- to five-year intervals based on each individual's risk level [97].

Dual-energy X-ray absorptiometry

A DXA scan involves an individual lying on a flat surface table. Two distinct X-ray energy beams, one high and one low, pass through the bones being examined. High- and low-energy X-rays are absorbed by both soft tissues and bone tissues at different ratios. BMD is then calculated using a mathematical formula based on absorption ratios. A DXA scan of the spine or hip is the only diagnostic tool for osteoporosis before fractures occur [94-96]. DXA can detect osteoporosis with 88.2% sensitivity and 62.5% specificity [104].

DXA is non-invasive with low radiation exposure equivalent to one-tenth the amount of a chest X-ray. A DXA scan only takes 10-15 minutes to complete. Having a DXA scan increases an individual's willingness to promote lifestyle modifications and initiate osteoporosis treatment [105-109]. A major disadvantage of DXA is that DXA machines are not easily portable, which may lead to poor access to DXA machines in remote areas. DXA reading can be influenced by factors, such as inappropriate patient positioning, osteoarthritis, and vertebral compression

fracture [110]. Another limitation of DXA is that DXA only estimates relative fracture risk. DXA is unable to identify every individual who will develop fractures in the future [89-91, 111]. False-negative results from DXA tests may lead to future missed treatment opportunities [91, 111]. False-positive results from DXA tests may also lead to unnecessary treatment and potential adverse events associated with treatment.

1.2.5.3 Benefits and harms of osteoporosis screening

The benefits of high-risk screening come from cost-effective fracture prevention when treating high-risk individuals with screen-detected osteoporosis [86, 87]. Several potential harmful effects associated with osteoporosis screening have been reported. Osteoporosis diagnosis may cause anxiety perceived from vulnerability to fracture [112].

1.2.5.4 Potential barriers to access bone mineral density testing

Potential barriers to access osteoporosis screening can be categorized into three groups – patient, physician, and healthcare system.

Many patient factors associated with lower utilization of BMD testing have been reported. These reported factors include advancing age [113], lower socio-economic status (SES) [114], comorbidities [113], cognitive impairment [115], nursing home residency [116], recent osteoporotic fracture [117], underestimated perceived fracture risk [118-120], and poor access to DXA machines due to limited mobility [121] or long travel distance [122]. Personal perceived fracture risk is underestimated among 52% of women with moderate fracture risk and 70-80% of women with high fracture risk, when compared with calculated fracture risk based on each

individual's risk factors [118, 119]. This is consistent with the findings that osteoporosis is of less concern to women, compared with cancers, cardiovascular diseases, and neurological diseases [119]. Underestimated personal perceived fracture risk can reduce the personal willingness to have BMD testing.

The potential physician barriers for patients accessing BMD testing include patients' frailty [123], time restraint for preventive care [124], and inconsistent guideline recommendations for BMD testing [125, 126]. The potential barriers associated with healthcare system include a lack of consistent guidelines for BMD testing, standardized reporting, and incentive for preventive care, and limited availability of BMD testing machines [127].

1.2.5.5 Potential interventions to improve utilization of dual-energy X-ray absorptiometry

Patient intervention combined with or without physician intervention has shown positive effects on BMD testing rates in different populations. Interventions improve BMD testing rates by 22-51% in high-risk populations with recent fractures [128], and by 18% in patients aged 65 and over in primary care settings [129]. The most common patient intervention is educational material, followed by notification and counseling. The most common physician intervention is reminders [128, 129]. Two interventions are directed at family doctors through patient education; five questions to take to their family doctors regarding investigation, diagnosis, and management of osteoporosis [130], and advice to visit their family doctors for further investigation [131].

1.2.6 Clinical manifestation – osteoporotic fractures

Osteoporosis presents with no clinical manifestation until fractures occur. The most common manifestations of osteoporosis are associated with osteoporotic vertebral fractures, such as kyphosis, height loss, back pain, and reduced rib-pelvis distance.

1.2.6.1 The impact of osteoporotic fractures – morbidity, mortality and economic burdens

Excess mortality during the first year after hip fractures ranges from 8.4 to 36% [132]. Worldwide, osteoporotic fractures caused a loss of 5.8 million disability-adjusted life-years in the year 2002. Of the total, more than 50% of the loss was associated with fracture events in America and Europe [133]. Physical disability and nursing home admissions are reported in 10% and 19% of patients with hip fractures respectively [134]. The estimated annual cost of hip fracture care in Canada will increase from CA$650 million in 1997 to CA$2.4 billion in 2041 [135].

1.2.7 Diagnosis

Osteoporosis is diagnosed by T and Z scores which are calculated based on BMD measurements with DXA. A T score compares a woman's BMD to an average BMD of a reference young female adult group. A Z score compares a woman's BMD to an average BMD of a healthy female population at the same age. Both T and Z scores are measurement units expressed in standard deviations (SD). Formulas for calculating T and Z scores are as follows [136]:

$$\text{T score} = \frac{\text{invididual's BMD} - \text{population peak BMD}}{\text{standard deviation of population peak BMD}}$$

$$\text{Z score} = \frac{\text{invididual's BMD} - \text{population age related BMD}}{\text{standard deviation of population age} - \text{related BMD}}$$

1.2.7.1 Post-menopausal women

A post-menopausal woman's T score is categorized into four groups which were established by the World Health Organization in 1994. Osteoporosis diagnosis is made when a woman's T score is -2.5 or below. The four categories include:

- *Normal:* a woman's T score ≥ -1
- *Low bone mass (osteopenia):* a woman's T score between -1 and -2.49
- *Osteoporosis:* a woman's T score ≤ -2.5
- *Severe osteoporosis:* osteoporosis with the presence of one or more osteoporotic fractures

1.2.7.2 Pre-menopausal women

Two diagnostic categories in pre-menopausal women were suggested by the International Society for Clinical Densitometry in 2003 [137] and adopted in Canada in 2005 [110]. The Z score is preferred over the T score. The two categories include:

- *Normal:* a woman's Z score > -2.5
- *Reduced bone density:* a women's Z score ≤ - 2.5

1.2.8 Treatment

The goal of treatment is to prevent future fractures. Treatments could be categorized into two groups – non-pharmacological and pharmacological treatments.

1.2.8.1 Non-pharmacological treatment – lifestyle advice

Non-pharmacological treatment is recommended for individuals with osteoporosis and is used to promote bone health in any individuals over age 50. The most current Canadian osteoporosis guidelines recommend adequate vitamin D and calcium intake, exercise, fall prevention, smoking cessation, and avoiding excessive alcohol consumption [97].

Calcium and vitamin D intake

The recommended daily intake of elemental calcium through diet and supplements is 1,200 mg. The recommended daily intake of vitamin D3 in individuals is based on their risk of vitamin D deficiency: 400-800 international units (IU) for low risk; 800-1,000 IU for moderate risk; and 1000 IU for high risk. Calcium, combined with vitamin D or not, may reduce fracture risk by 3% to 23% [138].

Exercise and fall prevention

Resistance, balance, and core strengthening exercises are suggested to strengthen muscles, compensate for posture abnormalities, and improve balance [139]. This could reduce risk of falls, improve physical functions, and reduce pain in individuals with osteoporotic fractures. There seems to be a potentially small effect of exercise on reducing fracture risk in elders [140]. Fall prevention, including improved home safety such as better lighting and walking aids, might reduce the risk of fall-induced osteoporotic fractures.

1.2.8.2 Pharmacological treatment - medications

Medications are indicated in any individuals with high fracture risk (> 20% of 10-year fracture risk), osteoporotic hip fracture, or more than one osteoporotic fracture [97]. An individual's 10-year fracture risk is determined using the Canadian Association of Radiologists and Osteoporosis Canada tool [110]. Available medications in Canada include bisphosphonates, receptor activator for nuclear factor kappa-B ligand inhibitor, selective estrogen receptor modulators (SERMs), hormone replacement therapy, calcitonin, and teriparatide. Most medications have shown to reduce fracture risk at varied degrees, especially in post-menopausal women [99, 141]. Raloxifene, but not tamoxifen, is the only SERM approved for prevention and treatment of osteoporosis.

1.2.8.3 Monitoring

Repeated BMD testing with DXA could be a useful clinical tool to monitor BMD changes and identify individuals with poor compliance to treatment or lacking response to treatment. However, recommendations for testing intervals between successive DXA tests have not gained consensus. A short testing interval may lead to mistaking random fluctuation or artifact as true BMD changes [142]. Testing intervals increased from a one- to two-year interval in the 2002 Canadian osteoporosis guideline to one- to three-year interval in the 2010 guideline. The testing interval may be prolonged beyond a three-year interval once treatment effectiveness is shown.

1.3 Osteoporosis in Women Diagnosed with Breast Cancer

1.3.1 Epidemiology

Breast cancer diagnosis is associated with a 32% higher prevalence of osteoporosis diagnosis, compared with women without breast cancer in the US [143]. The prevalence of osteoporosis diagnosis in women with breast cancer is 33.4% in the US [143] and remains unclear in Canada. The majority (77%) of post-menopausal women with osteoporosis remain undiagnosed in the US [144]. Higher fracture risk in women diagnosed with breast cancer was reported in the Tsa *et. al.* and Chen *et.al.* studies with more than 80,000 participants [145, 146]. The estimated fracture rate in post-menopausal women diagnosed with breast cancer is 20 per 1,000 women-years [147].

1.3.2 Effects of breast cancer treatments on bones and fractures

1.3.2.1 Overall review

Estrogen, a type of hormone, plays a key role in both breast cancer treatment and bone health. Estrogen preserves bone mass by reducing bone reabsorption [148]. Estrogen deficiency, which could be caused by most adjuvant systemic breast cancer treatments, increases the risk of osteoporosis and osteoporotic fractures. Adjuvant systemic treatments have been widely used to reduce the risk of cancer recurrence and improve survival. The adjuvant systemic treatments can be categorized into hormonal treatment, chemotherapy, and ovarian suppression. Hormonal treatment is primarily provided to women with hormone receptor-positive breast cancer, which accounts for two-third of all breast cancers [149, 150]. Chemotherapy is offered to any women at higher cancer relapse risk, which is especially true for women with hormone receptor-negative breast cancer [151]. Ovarian suppression by radiation, surgery, or gonadotropin-releasing hormone agonists is only offered to a small percentage of pre-menopausal women with breast

cancer and at higher cancer relapse risk [55, 57]. A comparison between tamoxifen and AIs for treating hormone receptor positive breast cancer is summarized in Table 1-6.

1.3.2.2 Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM). A SERM acts as either an estrogen agonist (stimulation) or antagonist (inhibition) depending on the target tissues that tamoxifen binds to. Tamoxifen acts as an antagonist in breast tissues that competitively inhibits the binding of estrogen to estrogen receptors which will reduce available estrogen to breast cancer cells.

The indications for which tamoxifen is used for treating breast cancer have been extending over time. Tamoxifen was only initially approved to treat advanced breast cancer in the late 1970s and then added to treat early stage breast cancer in the early 1990s by the US Food & Drug Administration (*www.fda.gov).* The use of tamoxifen was extended again to women with stage 0 / ductal carcinoma in situ in 2003 [152]. Tamoxifen is currently recommended for pre-menopausal women, and post-menopausal women with lower cancer relapse risk. Tamoxifen is also an optional treatment in women with stage 0 / ductal carcinoma in situ breast cancer with higher cancer relapse risk [151]. Tamoxifen is primarily given for two to five years, alone or as part of sequential treatments with AIs. Tamoxifen should be avoided in women with personal or family history of deep vein thrombosis, pulmonary embolism, severe depression, or newly diagnosed endometrial cancer *(www.bccancer.bc.ca*).

The common side effects of tamoxifen are associated with its estrogenic activity on the tissues that tamoxifen binds to. The common important side effects include hot flashes, amenorrhea, and mood changes [153]. The effect of tamoxifen on bone tissue is inconsistent across studies. In animal models, estrogen stimulates bone formation as an agonist, which leads to higher bone mass [154]. In clinical studies, tamoxifen cause a BMD decrease in healthy pre-menopausal women but a BMD increase in healthy post-menopausal women [155]. Tamoxifen may slightly increase or decrease BMD by up to 2% in both pre- and post-menopausal women diagnosed with breast cancer [156-161]. Tamoxifen is associated with a 9% lower fracture risk in post-menopausal women diagnosed with breast cancer when compared with healthy post-menopausal women [147]. Tamoxifen, compared with no hormonal treatment, is not associated with an increased fracture risk in post-menopausal women with breast cancer [162, 163]. The effect of tamoxifen on prevention of osteoporotic fractures is neutral in the general population [164]. There might be a positive effect of tamoxifen on fracture risk. However, tamoxifen has not been approved for the prevention or the treatment of osteoporosis by the US Food & Drug Administration.

1.3.2.3 Aromatase inhibitors

Aromatase is an enzyme responsible for the synthesis of estrogen in the ovaries, normal breast tissues, breast-cancer tissues, etc. Aromatase inhibitors (AIs) reduce circulating estrogen levels in post-menopausal women by inhibiting or inactivating the aromatase enzymes in non-ovary tissues [165]. AIs act as an estrogen antagonist (inhibitors) in all tissues including bone tissues while tamoxifen act as either an estrogen antagonist or agonist depending on the target tissues that tamoxifen binds to.

Aminoglutethimide was the first AI used to treat post-menopausal advanced breast cancer in the 1980s, but was withdrawn from the market due to severe adverse events associated with its non-selective binding properties later [166]. Second and third generation AIs with more selective inhibition properties and fewer adverse events were then developed (*www.fda.gov)*. Third generation AIs include non-steroidal AIs (letrozole and anastrozole) with reversible binding properties and steroidal AI (exemestane) with irreversible binding properties. AIs were approved for treating post-menopausal advanced breast cancer in the 1990s and for treating post-menopausal early breast cancer in the early 2000s. AIs were recommended for post-menopausal early breast cancer in 2005 guidelines [167]. AIs are primarily given for two to five years alone or as part of sequential treatments with tamoxifen. AIs have recently been suggested to be combined with ovarian suppression in pre-menopausal women at higher cancer relapse risk [151]. AIs should be avoided in women with severe osteopenia or osteoporosis, moderate to severe joint pain, or moderate to severe dyslipidemia (*www.bccancer.bc.ca*).

The common and important side effects of AIs include hot flushes, vaginal dryness, bone toxicity (osteoporosis, bone fracture, and arthralgia), and high cholesterol [168]. AI treatment reduces BMD significantly [158, 159, 169] by reducing circulating estrogen levels. AI treatment has shown to be associated with higher fracture rates in clinical trials while its degree of effect on that remains unclear [170-172].

1.3.2.4 Sequential treatments with tamoxifen and aromatase inhibitors

Tamoxifen and AIs can be given alone or in sequence. A sequential tamoxifen-AI treatment has tamoxifen treatment given first for two to three years and then switched to AIs for a total treatment duration of five years. A sequential AI-tamoxifen treatment has AIs given first, followed by tamoxifen [151, 152, 167]. In some special circumstances, prolonged hormonal treatment of up to 10 years would be considered. For example, AIs might be given for another five years after an initial five years of tamoxifen in women at high cancer relapse risk [151]. Sequential treatments, compared with either tamoxifen or AIs alone treatment, reduce the exposure time to both tamoxifen and AIs, which may theoretically reduce the long-term side effects associated with either tamoxifen or AIs alone, such as fracture risk.

1.3.3 Guidelines for bone mineral density measurements with dual-energy X-ray absorptiometry in women diagnosed with breast cancer in Canada

Guidelines for BMD measurements with DXA vary significantly in intervals and indications among countries and women diagnosed with breast cancer (Table 1-7). Non-Canadian guidelines recommend a BMD test with DXA at one- to two-year intervals for women 65 and over, women initiating AIs, pre-menopausal women with ovarian suppression treatment, or women aged 60-64 at high osteoporosis risk [173, 174]. In Canada, the indications and intervals of BMD testing with DXA for women diagnosed with breast cancer have been changing over time, and vary among national and provincial guidelines. The most current national guideline, the 2010 Canadian osteoporosis guidelines, recommend a BMD test with DXA at a one- to three-year interval for women 65 and over, and women under 65 with listed risk factors, such as AI treatment and premature menopause.

Table 1-6 A comparison between tamoxifen and aromatase inhibitors for treating hormone receptor positive breast cancer without metastasis

	Tamoxifen	**Exemestane, anastrozole and letrozole**
Class	- Selective estrogen receptor modulator (SERM)	- Aromatase inhibitors (AIs) - Non-steroidal AIs (letrozole and anastrozole); reversible binding - Steroidal AI (exemestane); irreversible binding
Effect on breast cancer tissues	- Inhibition - Prevent estrogen from binding to breast tissues	- Inhibition - Reduce production of estrogen
Treatment indication by menopausal status [151, 152, 167]	- Pre-menopausal women - Post-menopausal women at lower cancer relapse risk	- Pre-menopausal women at higher recurrent risk when AIs are combined with ovarian suppression treatment - Post-menopausal women at higher cancer relapse risk
Treatment indication by stages [151]	- Ductal carcinoma in situ (stage 0, optional) - Early breast cancer - Advanced breast cancer	- Early breast cancer - Advanced breast cancer
Treatment duration [151]	- Tamoxifen alone for 5 years - Sequential tamoxifen (2-3 years) – AI (2-3 years) - Sequential tamoxifen (5 years) – AI (2-3 years)	- AI alone for 5 years - Sequential tamoxifen (2-3 years) – AI (2-3 years) - Sequential tamoxifen (2-3 years) – AI (5 years)
Contraindications	- Newly diagnosed endometrial cancer - Personal or family history of deep vein thrombosis / pulmonary embolism - Severe depression	- Pre-menopausal - Severe osteopenia or osteoporosis - Moderate to severe joint pain - Moderate to severe dyslipidemia
Effect on bone mineral density (BMD)	- Stable with a small increase or decrease in BMD [156-161]	- Significant loss [158, 159, 169]
Effect on fracture risk	- Limited information - No additional fracture risk when compared with women without hormonal treatments [162, 163]	- Increase when compared with tamoxifen in major randomized controlled trials [170-172]. - Uncertain degree of additional fracture risk

Table 1-7 Summary of guideline recommendations on bone mineral density measurement with dual-energy X-ray absorptiometry in women with breast cancer in Canada

Year	Organization	Target population	Indication of BMD measurement with DXA	Interval
National level				
2002	Osteoporosis Society of Canada [84]	General population	- Women ≥65 - Post-menopausal women aged <65 with one major or two minor risk factors (Table 1-3)	- Every 2-3 years in women with normal BMD - Every 1-2 years in women with osteopenia or osteoporosis
2004	Canadian Task Force on Preventive Health Care [175]	General Population	- Women ≥ 65 - Post-menopausal women with osteoporotic fracture(s) - Post-menopausal women with weight < 60kg - Post-menopausal women at high osteoporosis risk	- Every 2 years in women with normal BMD - Every 1-2 years in women with osteopenia or osteoporosis
2005	Health Canada [176]	Breast cancer	- Post-menopausal women - Pre-menopausal women at high risk of osteoporosis - Any women taking aromatase inhibitors	- Not specified
2010	Osteoporosis Canada [97]	General population	- Women ≥ 65 - Women aged 50-64 with listed risk factors - Women aged <50 with listed risk factors	- Every 5 years in women at low (<10%) 10-year fracture risk - Every 1-3 years in women at moderate (10-20%) or high (>20%) 10-year fracture risk
Provincial level – British Columbia (BC)				
2005	Medical Services Commission of British Columbia [177]	General population	- Women≥65 - Women aged ≥50 with one major or two minor risk factors (Table 1-3)	- Every 2 years
2011	Medical Services Commission of British Columbia [178]	General population	- Women aged ≥65 at moderate (10-20%) or high (>20%) 10-year fracture risk using FRAX without BMD - Women aged <65 with significant clinical risk factors	- Every 3-10 years based on a women's risk profile

DXA dual-energy X-ray absorptiometry, *BC* British Columbia, *BMD* bone mineral density, *FRAX* fracture risk assessment

1.4 Rationale, Objectives, and Hypotheses

1.4.1 Utilization of bone mineral density testing in women diagnosed with breast cancer in British Columbia, Canada (Chapter Two, study 1)

Rationale

Women diagnosed with breast cancer are at higher risk of osteoporosis [143] and osteoporotic fractures [179]. Bone Mineral Testing (BMD) testing with dual-energy X-ray absorptiometry (DXA) is the primary tool used for osteoporosis screening and treatment monitoring in Canada. BMD testing at one- to three-year intervals is recommended for women aged 65 years and over, regardless of breast cancer diagnosis. Utilization of BMD testing is unknown in women aged 65 and over, and diagnosed with breast cancer for three or more years in British Columbia (BC), Canada. Only women diagnosed with breast cancer for three or more years were included for this study as the focus of care after three years is likely to have shifted from acute active cancer treatment, to screening and management of long-term and late effects, such as osteoporosis.

Objectives

1. To evaluate trends in proportion of women, aged ≥65 and diagnosed with breast cancer for three or more years, with at least one BMD test per calendar year from 1995 to 2008 in BC, Canada.
2. To identify clinical and socio-demographic factors associated with different BMD testing rates in the three-year period 2006-2008.

Hypotheses

H_{A-1}: Trends in proportion of women with at least one BMD test per calendar year from 1995 to 2008 will be positive as the population has become aware of osteoporosis.

H_{0-1}: Trends will be stable.

H_{A-2}: Factors, such as socio-economic status, remote residency, history of osteoporosis diagnosis, history of previous BMD testing, will be associated with different BMD testing rates.

H_{0-2}: No factors associated with different utilization of BMD testing will be identified.

1.4.2 Promoting bone health management in women diagnosed with breast cancer: A pilot randomized controlled trial (Chapter Three, study 2)

Rationale

Results from study 1 (Chapter Two) showed that less than 15% of women, aged ≥65 and diagnosed with breast cancer for three or more years, had at least one BMD test in any calendar year from 1995 to 2008. BMD testing plays a key role to identify women at higher risk of osteoporosis and osteoporotic fractures. It is important to identify an intervention to improve BMD testing rates. One way of promoting BMD is with educational material in the high-risk populations such as patients with recent fractures, and women 65 and over. However, it remains unclear whether educational material could improve BMD testing rates in another high-risk population – women diagnosed with breast cancer. In BC, prevention information sent to patients is primarily delivered by postal mail in primary care settings. With advances in communication technologies, there is an increasing interest in conveying information by email or text messaging.

A pilot randomized controlled trail (RCT) was designed to answer the questions - ”Does educational material improve BMD testing rates in older female breast cancer survivors” and “Do the different delivery methods of postal mail vs. patient choice of mail, email or smartphone text messaging for educational material, affect BMD testing rate differently?

Objective

To determine the feasibility of the RCT protocol by evaluating the response rate, recruitment rate and participation rate, and collecting information about effectiveness of the intervention and loss to follow-up, to inform design of a future large scale study.

Hypothesis

H_A: This study protocol is feasible for a future large-scale study.

H_0: This study protocol is not feasible for a future large-scale study.

1.4.3 Aromatase inhibitors are associated with a higher fracture risk than tamoxifen: a systematic review and, meta-analysis (Chapter Four, study 3)

Rationale

Women diagnosed with breast cancer are at higher risk of osteoporosis and osteoporotic fractures, primarily due to adjuvant systemic breast cancer treatments, such as hormonal treatment. Aromatase inhibitors (AIs) and tamoxifen are the most common hormonal treatments in women diagnosed with breast cancer. Tamoxifen may slightly increase or decrease BMD by up to 2% in both pre- and post-menopausal women diagnosed with breast cancer. AIs significantly decrease BMD and have been associated with increased fracture risk in clinical

trials. The extents of effect of AIs and tamoxifen on fracture risk remain unclear. This study focuses on younger women aged 65 and under, and diagnosed with non-metastatic breast cancer. A better understanding on the effects of hormonal treatment on fracture risk may alter the future eligibility for BMD testing in younger women. Older women aged 65 and above are already eligible for BMD testing regardless of their breast cancer diagnosis and treatment. Women diagnosed with metastatic-breast cancer were excluded due to a high likelihood of pathological fractures associated with breast cancer.

Objective

To estimate fracture risk (risk ratios) in younger women aged 65 years and under, diagnosed with breast cancer, and treated with tamoxifen or AIs.

Hypotheses

$H_{A\text{-}1}$: Tamoxifen increases fracture risk in younger women diagnosed with non-metastatic breast cancer.

$H_{0\text{-}1}$: Tamoxifen does not increase fracture risk.

$H_{A\text{-}2}$: AIs increases fracture risk in younger women diagnosed with non-metastatic breast cancer.

$H_{0\text{-}2}$: AIs do not increase fracture risk.

$H_{A\text{-}3}$: AIs increase fracture risk more than tamoxifen in younger women diagnosed with non-metastatic breast cancer.

$H_{0\text{-}3}$: AIs do not increase fracture risk more than tamoxifen.

Chapter 2: Utilization of Bone Mineral Density Testing in Women Diagnosed with Breast Cancer in British Columbia, Canada (study 1)

2.1 Introduction:

One in nine Canadian women will develop breast cancer in her lifetimes [180]. Almost 90% of these women will complete their initial cancer treatments. Most adjuvant systemic breast cancer treatments, including aromatase inhibitors (AIs), promote bone loss [66, 174]. Women with a history of breast cancer have a 32% higher prevalence of osteoporosis diagnosis than women without breast cancer history [143]. This leads to higher fracture rates compared with the general population [179].

Osteoporosis is a global medical issue with a high economic burden regardless of cancer history [181]. Osteoporotic fractures are associated with excessive mortality, physical function impairment, and more long-term care facility admissions [181]. Bone mineral density (BMD) testing using the dual-energy X-ray absorptiometry (DXA) technique plays a key role in osteoporosis screening and management. BMD testing can be used to screen individuals for osteoporosis before fractures occur. It is cost-effective to treat screen-detected osteoporosis in post-menopausal women to prevent fractures [87]. This strategy is associated with an 11% reduction in mortality associated with osteoporotic fractures [98]. For individuals with osteoporosis diagnosis, repeated BMD testing can be used to monitor treatment effectiveness by identifying individuals with persistent bone loss despite treatment.

Utilization of BMD testing remains unclear in women diagnosed with breast cancer in British Columbia (BC), Canada. This study was to provide an overall utilization picture of BMD testing

during the period from 1995 to 2008 in older female breast cancer survivors women aged 65 years and over, and diagnosed with breast cancer for three or more years.

2.2 Method

We conducted an observational study with two independent analyses using a provincial cancer registry and secondary administrative healthcare data linkage: (1) *trend analysis* to evaluate trends in the proportion of survivors with ≥1 BMD test by calendar year and osteoporosis diagnosis from 1995 to 2008 using a descriptive, serial cross-sectional study design, and (2) *association analysis* to evaluate associations between factors and BMD testing rates during the three-year period 2006-2008 using a cross-sectional study design. We reported study results using criteria from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [182].

2.2.1 Study groups

Women who had completed their initial breast cancer treatments with the exception of hormonal treatment were considered for this study. The care focus for this group has already shifted from active cancer treatment to surveillance and management of common long-term and late effects associated with the cancer or cancer treatment. The required duration of initial breast cancer treatment was analyzed in approximately 37,000 women diagnosed with breast cancer in BC using secondary data-linkage. The durations for different breast cancer treatments were as follows:

- Surgery alone, radiation alone or a combination of both surgery and radiation: 0.3±0.25 (mean ± standard deviation (SD)) year

- Chemotherapy: 0.25-0.5 year
- Biological therapy: 1 year

Nearly 99% of the women diagnosed with breast cancer completed their initial cancer treatments with the exception of hormonal treatment by the end of the third year after their initial breast cancer diagnosis. Hence, a three year survival time was chosen for this study.

For each observation period, we identified BC female residents from the provincial BC Cancer Agency (BCCA) registry, who were aged 65 and over; were diagnosed with breast cancer from 1989 (start of available data) to 2005; were diagnosed with breast cancer at least three years prior to the observation start date and were not in the last year of their lives based on data from the provincial BC Cancer registry [183]. The BC Cancer Registry records virtually all new breast cancer cases among BC residents, includes treatment information, and is routinely linked with death registrations.

2.2.2 Data sources

We linked the BC Cancer Registry and BC Cancer Agency Breast Cancer Outcome Unit (BCOU) databases to the provincial healthcare administrative datasets using person-specific lifetime Personal Health Numbers. Personal Health Numbers are assigned to over 90% of BC residents who are eligible and covered under provincial health insurance plan for all “medically necessary” health services. All datasets used are summarized in Appendix A.

2.2.3 Outcome variable, bone mineral density test

BMD tests were identified from the Medical Service Plan (*MSP) Payment Information File* [184] by fee codes 08688/08681/09810 (DXA, whole body), 08689/08682/09811 (DXA, single area) and 08696/08683/09812 (DXA, second area). For the *trend analysis*, BMD tests were identified for each survivor for each calendar year. Proportions of survivors with ≥1 BMD test were calculated for each calendar year as "number of survivors with ≥1BMD test" divided by "number of total survivors" for that year. The proportions were then stratified by survivors' osteoporosis diagnosis which was made prior to 1st January of each calendar year and identified using diagnostic codes of International Classification of Diseases, Ninth Revision (ICD-9, *www.cdc.gov/nchs/icd/icd9.htm*) and Tenth Revision (ICD-10, *www.cdc.gov/nchs/icd/icd10.htm*) from the *MSP Payment Information File* [184] and *Discharge Abstracts Database [185]* (Appendix B). For the *association analysis*, BMD tests were identified for each survivor for the three-year period 2006-2008. BMD testing rate during the period 2006-2008 was calculated as proportion of survivors with at ≥1 BMD test. A three-year period was selected to maximize capture of survivors who had BMD testing as recommended (one BMD test every 1-3 years) by the 2002 Canadian Osteoporosis guideline in effect during the study period in BC [84].

2.2.4 Potential modifying factors for association analysis

We selected *socio-demographic* and *clinical factors* that could potentially influence utilization of BMD testing based on literature review and discussions with clinicians. Attained age was determined using birth date and observation period start date. Socio-economic status (SES) quintile, based on the average income per person in the survivor's 2006 census enumeration dissemination area (identified using postal codes from the *Consolidation File [186]),* was created

using the Statistics Canada Postal Code Conversion File, Version 5J [187]. Categorization of urban/rural residential status in year 2006 was based on population size and socio-economic homogeneity using census data and a methodology developed by Statistic Canada [188]. The health service regions were categorized by the five regional health administrative areas in BC as of January 1st, 2006. Survivors (1.2%) with unknown urban/rural residential status, SES status or health service regions in 2006, were assigned with their latest available information prior to 2006. The five major non-cancer chronic diseases (coronary heart disease, cerebrovascular disease, chronic pulmonary disease, diabetes mellitus, and dementia) [189], as well as osteoporosis diagnosis and recent osteoporotic fractures, were identified separately using corresponding diagnostic ICD-9 and ICD-10 codes from the *MSP Payment Information File* [184] and *Discharge Abstracts Database [185]* (Appendix B). These five major chronic diseases account for 35% of mortality among Canadians (*www.statcan.gc.ca*) [190]. Each survivor's chronic disease count was based on the number of chronic disease(s) identified prior to January 1st, 2006. Survivors with three or more chronic disease counts were grouped together due to their small sample sizes. Osteoporosis diagnosis was classified as "yes" for survivors with any osteoporosis diagnosis prior to January 1st, 2006. Osteoporotic fractures were defined as spine, hip or wrist fracture(s). Recent osteoporotic fracture was classified as "yes" for survivors who had at least one fracture within the six months prior to their BMD test, or survivors who had fractures but no BMD test, and "no" for remaining survivors. Previous BMD tests were identified with the same fee codes for the outcome variable - BMD test. Nursing home residence status on January 1st, 2006 was determined using nursing home services associated fee codes from the *MSP Payment Information File* (Appendix B) *[184]*. Age at initial cancer diagnosis was calculated using birth date and date of initial cancer diagnosis. Time since initial breast cancer

diagnosis was calculated by the interval between date of initial cancer diagnosis and January 1st, 2006. Stage of initial breast cancer diagnosis was obtained from the *BCOU dataset*. Detailed initial breast cancer treatment information was retrieved from the *BCOU dataset* and categorized either by type of treatments (surgery, radiation, systematic treatment, and combinations of two or three treatments) and type of initial hormonal treatment (none, tamoxifen only, and aromatase inhibitors (AIs)/ovary suppression) respectively.

2.2.5 Statistical analysis

We assessed characteristics of the study group by examining the distribution of frequency counts and percentages of key variables. *Trends* in proportion of survivors with ≥1 BMD per calendar year by survivors' osteoporosis diagnosis from 1995 to 2008 were evaluated using log-linear models. Up to two join points per model were fit using the Joinpoint Trend Program, Version 4.3.1.0 [191]. The statistical significance of each join point was tested using a Monte Carlo permutation procedure. Trend segments were created between join points. Average percent changes (APCs) were estimated for each trend segment. Average annual percentage changes (AAPCs) were estimated for the entire observation period from 1995 to 2008. Each AAPC was calculated as a weighted average of APCs with weights equal to the length of each corresponding trend segment. *Associations* between factors and BMD testing rates during the three-year period 2006-2008 were evaluated using log-binomial models. We did not use a traditional logistic model approach to avoid overestimated associations in a common outcome situation [192]. All prevalence ratios and 95% confidence intervals (CIs) were adjusted for socio-demographic factors, including attained age, SES, health service region, and urban/rural status using log-

binomial models. Log-binomial models were fit using Statistical Analysis System version 9.3 (SAS Institute Inc., Cary, NC).

2.3 Results

2.3.1 Trend analysis

The eligible survivor group nearly doubled from 4,974 in 1995 to 9,662 in 2008 period (Table 2-1, Figure 2-1). The prevalence of osteoporosis diagnosis increased from 295 (6% of all survivors) to 2,475 (25.6%) over the same period.

The proportions of survivors with ≥1 BMD were under 20% for any calendar year from 1995 to 2008. For survivors with osteoporosis diagnosis, the proportions with ≥1 BMD test during a calendar year increased from 4.4 % in 1995 to 16.8 in 2006 and then decreased slightly to 15.5% in 2008. On average, the proportions increased by 19.4% annually (95% CI=11.5 to 28.0) from 1995 to 2002 and remained relatively stable around 16% from 2002 to 2008. For the survivors without osteoporosis diagnosis, the proportions with ≥1BMD test during a calendar year increased from 0.8% in 1995 to 9.3% in 2005 and then decreased slightly to 8.2% in 2008. On average, the proportions with ≥1 BMD test during a calendar year increased annually by 33.4% (95% CI=24.6 to 42.9) from 1995 to 2001 and by 12.4% (95% CI=0.9 to 25.2) from 2001 to 2005. The proportions remained relatively stable around 8.5% in 2005-2008.

Table 2-1 Trends in proportion of survivors with at least one bone mineral density test, overall and stratified by osteoporosis diagnosis from 1995 to 2008

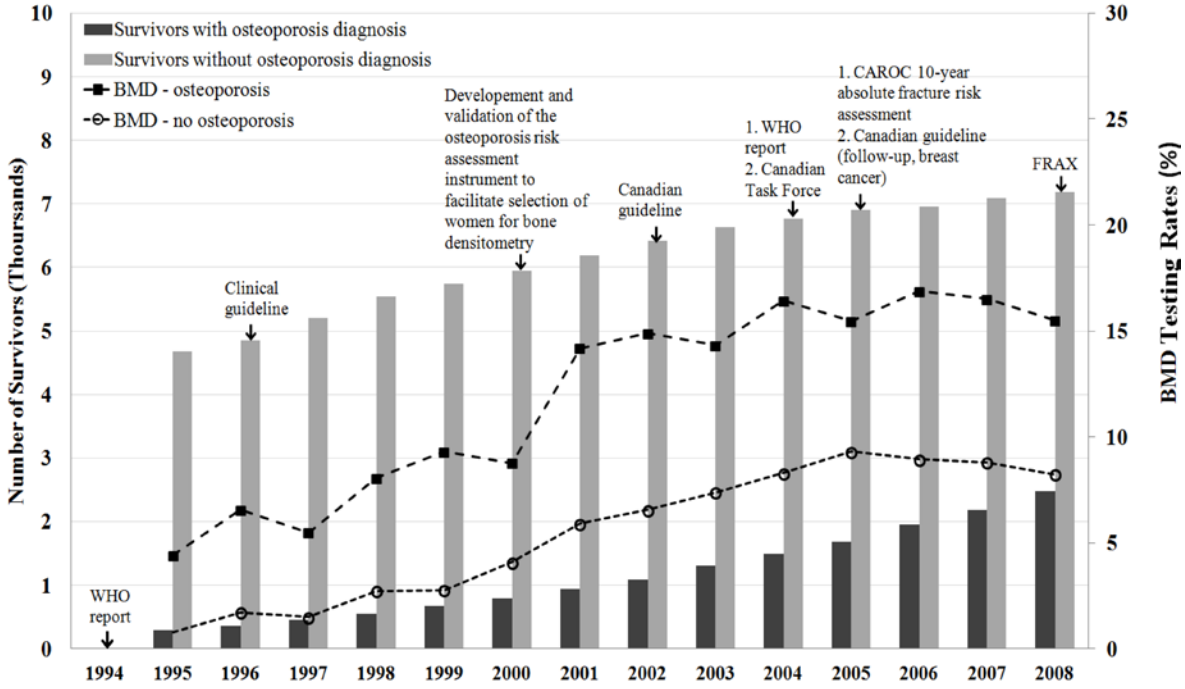
	Overall		**Osteoporosis**		**No osteoporosis**	
Year	Total	BMD [a] (%)	Total	BMD [a] (%)	Total	BMD [a] (%)
1995	4974	1.0	295	4.4	4679	0.8
1996	5217	2.1	365	6.6	4852	1.7
1997	5657	1.8	455	5.5	5202	1.5
1998	6086	3.2	546	8.1	5540	2.7
1999	6413	3.5	676	9.3	5737	2.8
2000	6747	4.6	799	8.8	5948	4.1
2001	7119	7.0	937	14.2	6182	5.9
2002	7510	7.8	1087	14.9	6423	6.6
2003	7931	8.5	1299	14.3	6632	7.4
2004	8266	9.8	1498	16.4	6768	8.3
2005	8590	10.5	1683	15.5	6907	9.3
2006	8909	10.7	1956	16.8	6953	8.9
2007	9278	10.6	2187	16.5	7091	8.8
2008	9662	10.1	2475	15.5	7187	8.2
***Trend 1*- Period**		1995-2001		1995-2002		1995-2001
APC [b]		32.6		19.4		33.4
95% CI		25.7, 39.9		11.5, 28.0		24.6, 42.9
***Trend 2*- Period**		2001-2005		2002-2008		2001-2005
APC [b]		10.9		1.2		12.4
95% CI		4.6, 17.7		-1.7, 4.1		0.9, 25.2
***Trend 3* -Period**		2005-2008				2005-2008
APC [b]		-2.8				-4.0
95% CI		-10.2, 5.3				-13.3, 6.4
AAPC [c]		17.7		10.4		17.6
95% CI		14.2, 21.3		6.7, 14.2		12.7, 22.8

BMD bone mineral density, *APC* annual percent change, *AAPC* average annual percent *change, CI* confidence interval

[a] Proportions of survivors who had at least one BMD test(s)

[b] Calculated as $(e^{beta}-1)*100$ using log-linear models. The beta equals to the coefficient of the regression model.

[c] Calculated as weighted average of APCs



Numver of survivors														
Osteoporosis	295	365	455	546	676	799	937	1087	1299	1498	1683	1956	2187	2475
Non-osteoporosis	4679	4852	5202	5540	5737	5948	6182	6423	6632	6768	6907	6953	7091	7187
APC (95% CI) for utilization														
Osteoporosis	19.4 (11.5 - 28.0)							1.2 (-1.7 - 4.1)						
No osteoporosis	33.4 (24.6 - 42.9)							12.4 (0.9 - 25.2)			-4.0 (-13.3 - 6.4)			

Figure 2-1 Numbers of female breast cancer survivors and proportions of women with at least one BMD test by osteoprososis diagnosis and calendar year from 1995 to 2008

WHO World Health Organization, *ATAC* Arimidex, Tamoxifen, Alone or in Combination, *CAROC* Canadian Association of Radiologists and Osteoporosis Canada, *APC* average percent change, *FRAX* fracture risk assessment tool, *CI* confidence interval

References included from left to right: 1994 WHO Report [95]; 1996 Canadian Guidelines [193]; development and validation of the osteoporosis risk assessment instrument to facilitate selection of women for bone densitometry [194]; 2002 Canadian guideline [84]; 2004 WHO report [88]; 2004 Canadian Task Force [175]; CAROC 10-year absolute fracture risk assessment [110]; 2005 Canadian guidelines – follow-up after treatment for breast cancer [176]; 2008 FRAX [195]

2.3.2 Association analysis

From the initial survivor groups, we identified 7,632 eligible survivors with complete data during the period 2006-2008, to assess for the analysis of associations between potential clinical and socio-demographic factors, and BMD testing rates. Slightly more than half of the survivors were aged 75 years and over at the start of the observation period, and 13% of the group were living in rural areas (Table 2-2). More than 80% of survivors had at least one of five selected chronic diseases. The prevalence of osteoporosis diagnosis at the end of 2005 was 21.6%. Recent osteoporotic fracture history was found among 5% of survivors. Slightly less than 40% of survivors received initial hormonal treatments. The BMD testing rate within the three-year period 2006-2008 was 26.5%.

Table 2-2 Characteristics of female breast cancer survivors for associations between factors and bone mineral density testing rates during the period 2006-2008

	N = 7632	%
Attained age		
65-74	3535	46.3
75+	4097	53.7
Health Authority region		
Vancouver Coastal	1791	23.5
Interior	1509	19.8
Fraser	2305	30.2
Vancouver Island	1711	22.4
Northern	316	4.1
SES		
5 (highest)	1503	19.7
4	1456	19.1
3	1446	18.9
2	1623	21.3
1 (lowest)	1597	20.9
Unknown	7	< 0.1
Urban/rural residential status		
Metropolitan (≥ 100,000)	5003	65.6
Large community (99,999 - 50,000)	468	6.1
Small community (49,999 - 10,000)	1164	15.3
Rural (< 10,000)	997	13.1
Chronic disease count		
0	1489	19.5
1	3406	44.6
2	2074	27.2
3-5	663	8.7
Osteoporosis		
No	5983	78.4
Yes	1649	21.6
Previous BMD test (year 2003-2005)		
No	5420	71.0
Yes	2212	29.0
Recent osteoporotic fracture		
No	7249	95.0
Yes	383	5.0
Nursing home residence		
No	7561	99.1
Yes	71	0.9
Age at initial breast cancer diagnosis (years)		
< 50	502	6.6
50-59	1636	21.4
60-69	3243	42.5
≥ 70	2251	29.5

SES socio-economic status, *BMD* bone mineral density

Significantly different BMD testing rates were associated with all identified factors except chronic disease count and stage at initial breast cancer diagnosis (Table 2-3). Interaction terms between osteoporosis diagnosis and other factors were examined but none was found. Significantly higher BMD testing rates were associated with either osteoporosis diagnosis (adjusted prevalence ratio (aPR)=2.39, 95% CI=2.12 to 2.69); or previous BMD tests in 2003-2005 (aPR=3.87, 95% CI=3.46 to 4.32). Significantly lower BMD testing rates were seen among survivors who were aged 75 and over (aPR=0.47); lived in the Fraser Health service region (0.72); lived in the Northern Health service region (0.66); had lower SES (range 0.66 to 0.78); lived in rural areas (0.70); had at least one selected chronic disease (range 0.62 to 0.79); had a recent osteoporotic fracture history (0.21); or were nursing home residents (0.05), compared with corresponding reference groups. BMD testing rates were 20-30% lower in survivors with low SES vs. high SES, in a dose-dependent manner (p <0.01). Among factors associated with breast cancer diagnosis, BMD testing rates were positively associated with the treatment combination of surgery/systemic/radiation (1.23); or tamoxifen treatment (1.29), compared with corresponding reference groups. Compared with survivors diagnosed with initial breast cancer 0-10 years ago, BMD testing rates were higher in survivors diagnosed more than 30 years ago 1.46), but lower in survivors diagnosed 11-20 (0.85) and 20-30 years ago (0.78).

Table 2-3 Associations between factors and bone mineral density testing rates in older female breast cancer survivors during the period 2006-2008

	N =7625 [a]	BMD testing rates [b]	*p* value	aPR [c]	95% CI
Attained age					
65-74	3533	34.4		1.00	--
≥ 75	4092	19.8	***<0.01*** [d]	***0.47***	***0.42, 0.52***
Health service region					
Vancouver Coastal	1791	29.8		1.00	--
Interior	1506	26.5		1.01	0.84, 1.21
Fraser	2303	22.8		***0.72***	***0.62, 0.83***
Vancouver Island	1710	29.5		1.07	0.92, 1.26
Northern	315	20.6	***<0.01***	***0.66***	***0.48, 0.91***
SES					
5 (highest)	1503	32.3		1.00	--
4	1456	26.7		***0.78***	***0.66, 0.92***
3	1446	26.2		***0.78***	***0.67, 0.92***
2	1623	25.1		***0.74***	***0.63, 0.87***
1 (lowest)	1597	22.7	***<0.01*** [d]	***0.66***	***0.56, 0.78***
Urban/rural residential status					
Metropolitan (≥ 100,000)	5000	27.0		1.00	--
Large community (99,999 - 50,000)	468	32.5		1.18	0.94, 1.49
Small community (49,999 - 10,000)	1163	25.4		0.85	0.72, 1.00
Rural (< 10,000)	994	22.8	***<0.01***	***0.70***	***0.58, 0.84***
Chronic disease count					
0	1487	34.9		1.00	--
1	3402	26.9		***0.79***	***0.69, 0.90***
2	2074	21.7		***0.62***	***0.53, 0.72***
3-5	662	21.5	0.28 [d]	***0.64***	***0.51, 0.80***
Osteoporosis					
No	5976	22.8		1.00	--
Yes	1649	40.2	***<0.01***	***2.39***	***2.12, 2.69***
Previous BMD test (2003-2005)					
No	5414	17.9		1.00	--
Yes	2211	47.8	***<0.01***	***3.87***	***3.46, 4.32***
Recent osteoporotic fracture [e]					
No	7242	27.6		1.00	--
Yes	383	6.3	***<0.01***	***0.21***	***0.14, 0.32***
Nursing home residence					
No	7554	26.8		1.00	--
Yes	71	1.4	***<0.01***	***0.05***	***0.01, 0.39***
Age at initial breast cancer diagnosis					
< 50	501	34.9		1.00	--
50-59	1634	30.4		0.82	0.66, 1.02
60-69	3241	29.6		0.91	0.75, 1.12
≥ 70	2249	17.5	***<0.01*** [d]	***0.64***	***0.50, 0.81***

Continued

	N =7625 [a]	BMD testing rates [b]	*p* value	aPR [c]	95% CI
Time since initial breast cancer diagnosis (years)					
0-10	3875	28.7		1.00	--
11-20	2936	24.1		***0.85***	***0.76-0.95***
21-30	678	23.8		***0.78***	***0.65-0.95***
30+	136	33.1	***<0.01*** [d]	1.46	1.00-2.11
Stage at initial breast cancer diagnosis [f]					
I	3443	27.5		1.00	--
II	2109	28.7		1.05	0.93-1.19
III	275	25.1	0.82	0.88	0.66-1.17
Initial breast cancer treatment(s) [g]					
Surgery only	691	24.9		1.00	--
Surgery + Systemic	1026	27.1		1.03	0.82-1.29
Surgery + Radiation	1447	23.6		0.87	0.70-1.08
Surgery + Systemic + Radiation	2201	31.9	***<0.01***	***1.23***	***1.01-1.50***
Initial hormonal treatment(s) [h]					
None	2488	24.9		1.00	--
Tamoxifen only	2881	30.2		***1.29***	***1.14-1.46***
AIs or ovary suppression	19	47.4	***<0.01***	2.46	0.97-6.22

Values in bold and italic indicate statistical significance

BMD bone mineral density, *aPR* adjusted prevalence ratio, *CI* confidence interval, *Ref* reference, *SES* socio-economic status, *AIs* aromatase inhibitors

[a] Survivors with unknown SES status were excluded for the entire analysis

[b] Calculated as portions of survivors with at least one BMD test

[c] PR was adjusted for age, SES, urban/rural status of residence and health service region using a logistic regression model

[d] *p* for trend

[e] Included hip, spine and wrist fracture

[f] Survivors with unknown stage information were not included for this analysis

[g] Systemic treatment, radiation and systemic treatment with radiation were not included for multivariate analysis due to small sample sizes and a lack of clinical meanings

[h] Survivors with unknown hormonal treatment information were not included for this analysis

2.4 Discussion

This is the first population-based study to evaluate utilization of BMD testing among older female breast cancer survivors; namely women aged 65 and over, and diagnosed with breast cancer for three or more years in BC, Canada. Improved survival rates over time lead to a fast-growing group of women diagnosed with breast cancer. In BC alone, the annual estimated number of women surviving breast cancer will increase by 80% from 2,600 in 2000 to 4,675 in 2028 [62]. These survivors are at higher risk of osteoporosis and osteoporotic fractures. BMD tests play a key role in screening for osteoporosis among survivors without osteoporosis diagnosis, and monitoring treatment effectiveness among survivors with osteoporosis diagnosis. Our results showed relatively stable proportions of survivors with ≥1 BMD test for each year from 2005 to 2008. Only 26.5% of survivors aged 65+ received ≥1 BMD test over the three-year period 2006-2008; however, one BMD test at a one- to three-year interval for women aged 65+, regardless of breast cancer diagnosis, was recommended by the Canadian guideline at that time [84, 176]. The utilization of BMD testing is sub-optimal, compared with other disease screening in the BC population [196], in older female breast cancer survivors in BC.

2.4.1 Trend analysis

The osteoporosis prevalence rate in 2008 in our study was 25.6%, based on ICD-9 and ICD-10 codes. This is higher than the rate of 20-25% for women aged 60-69 years in the Canadian community based on actual BMD measurement using the World Health Organization Criteria [78], but lower than the self-reported rates of 33.4% in the US community and 27.7% in women with breast cancer history in the US [143]. For survivors without osteoporosis diagnosis, our study's annual BMD testing rate in 2001 was 5.9%, compared with 13.3% in the US based on a

combination of ICD-9 codes and current procedural terminology [197]. For survivors with osteoporosis diagnosis, no other studies were found for rate comparison. These international differences could be explained by different methodologies in identifying osteoporosis diagnosis, survival time (a range from zero to five years), and measurement time used for rate calculation (a range from one to three years) and time frame used to calculate rates (ranges from one to three years and from 1997 to 2006).

For survivors with osteoporosis diagnosis in our study, we observed that the trends in proportion of survivors with ≥1 BMD test changed from being positive to stable in the year 2002. The positive trend up to 2002 may be due to the 1996 Canadian guideline first recommending repeated BMD measurements to monitor bone loss for women with osteoporosis diagnosis [193]. The stable trend since 2003 could be because the 2002 Canadian guideline suggested a longer monitoring interval between repeated BMD tests to avoid mistaking random fluctuations for real changes [84]. For survivors without osteoporosis diagnosis in our study, we observed that the trends changed from being positive to weak positive in years 2001 and from being weak positive to stable 2005. The positive trend up to 2001 was possibly due to the 1994 WHO report and again, the 1996 Canadian guideline recommending screening of high-risk individuals for osteoporosis using BMD tests [95, 193]. From 2001 to 2005, the trend continued to grow at a slower rate possibly due to two factors. First, high-risk individuals were extended from "peri/postmenopausal women without hormonal therapy" to women with validated risk factors [84, 88, 175, 194]. Second, most fractures happened among individuals with normal BMD measurements [90, 198]. This led to a shift from identifying "high-risk individuals for osteoporosis based on BMD measurements" to "high-risk individuals for fractures using a

combination of BMD measurement and validated risk factors" [88]. Since 2005, the trend became stable due to two possible factors. The first fracture risk calculation tool – Canadian Association of Radiologist and Osteoporosis Canada (CAROC) - was adopted in 2005 [97, 110]. Each individual's fracture risk would be calculated using the combination of BMD measurements and validated risk factors, such as age and gender. Individuals with low fracture risk were suggested to repeat BMD screening test at longer intervals, which could decrease proportions of survivors receiving BMD testing. On the other hand, the Canadian breast cancer follow-up guideline suggested screening breast cancer women treated with AIs for osteoporosis [176]. This should increase proportions of survivors receiving BMD testing.

Several non-guideline factors might also be associated with the trend changes in the proportion of survivors with ≥1 BMD test. The positive trends from 1995 to early 2000s possibly reflected increases in availability of DXA machines, awareness of higher osteoporosis risk associated with systematic adjuvant breast cancer treatments (such as chemotherapy and hormonal treatments) among survivors and physicians, and usage of systemic adjuvant breast cancer treatments in women with early-stage breast cancer. The positive trends might be associated with prioritized access to diagnostic tests for specialists including oncologists over family doctors in Canada [199]. However, our further internal analysis showed that only 12-17% of BMD tests were ordered by specialists. This suggests that specialists' potentially privileged access to diagnostic tests had a minor impact on the usage of BMD tests in survivors in BC.

2.4.2 Association analysis

In our study, multiple factors were associated with different BMD testing rates. Being ≥75 years of age was associated with lower BMD testing rates in our and the Snyder *et al*. study [113]. These survivors aged 75 and over are at significantly higher osteoporotic fracture risk while BMD test screening remains cost-effective up to age 80 [200]. Survivors under age 80 should be encouraged to have BMD tests. A direct relationship between SES and BMD testing rates was observed in survivors in our study. This is consistent with findings in the general population in the province of Manitoba, Canada [114]. Further studies are needed to better understand the nature of these associations. Our results showed urban-rural disparity in BMD testing rates, too. This could be due to lower DXA machine availability in rural BC areas. Chronic disease history was associated with lower BMD testing rates in our study. We observed an insignificant trend between chronic disease count and utilization of BMD testing while a negative trend was found in the Snyder *et al.* study [113]. This could result from different definitions and categories of chronic disease count.

In our study, survivors without osteoporosis diagnosis were less likely to have BMD tests, compared to survivors with osteoporosis diagnosis. Further analysis showed that around 50% of the survivors without osteoporosis did not have any BMD tests for six consecutive years from 2003 to 2008. These survivors may skip BMD tests as they underestimated their personal osteoporosis risk [119].

In our study, survivors residing in nursing homes or with recent osteoporotic fractures were significantly less likely to have BMD tests, while nursing home residence and recent

osteoporotic fractures are associated with significantly higher fracture risk [201, 202]. BMD testing might be skipped for these two groups due to patient or physician factors. For nursing home residents, the common patient factor is limited mobility or cognitive impairment, resulting in difficult transportation from a nursing home to a testing machine, or difficult maintaining a steady position during the test. The common physician factor is that physician may consider BMD tests futile due to unproven cost-benefit effectiveness, polypharmacy and short life expectancy [100]. Patients with recent osteoporotic fractures may be resistant to osteoporosis diagnosis with BMD testing while their physicians may initiate fracture-prevention treatment without BMD measurement, or skip BMD testing for frail patients [123].

In our study, high BMD testing rates were associated with several clinical factors. A higher BMD testing rate was observed among survivors who were diagnosed with breast cancer more than 30 years ago. This is likely because more than half of these survivors (53%) have been diagnosed with osteoporosis, and having an osteoporosis diagnosis is associated with high utilization of BMD testing. Higher BMD testing rates were observed among survivors who were diagnosed with breast cancer at younger ages or received a treatment combination of surgery, adjuvant systemic treatment, and radiation. These survivors were likely to receive aggressive hormonal treatment, such as ovarian suppression. This could also lead to higher utilization of BMD testing.

Although tamoxifen is not approved for treating osteoporosis in the general population or breast cancer survivors by the Food & Drug Administration, this therapy may preserve bone mass in breast cancer survivors[174], which could lessen physicians' likelihood of ordering BMD tests.

However, tamoxifen treatment was associated with higher BMD testing rates in our study. This finding might be explained by our inability to distinguish survivors switching to AIs after tamoxifen from survivors receiving tamoxifen only.

2.4.3 Limitations and future directions

The main limitation of this study is data availability. This prevents us from examining more recent BMD testing rates however is balanced by the completeness of this linked data set. In this study, we evaluated utilization of BMD testing in BC only from 1995 to 2008 due to data availability. Since 2002, we observed stable trends in BMD testing for survivor with or without osteoporosis diagnosis. Since 2008, utilization of BMD testing may have remained stable or changed. Utilization may rise due to greater awareness of the osteoporosis care gap and extending fracture risk assessment to any individuals 50+ [97]. But utilization may drop due to a higher availability of validated fracture risk assessment tools. In 2008, the Canadian version of WHO Fracture Risk Assessment Tool (FRAX) became available in Canada [195]. FRAX assessment without BMD measurements has been used to screen eligibility for DXA BMD tests in BC. This might reduce utilization of BMD testing. Future studies are needed to better understand more recent utilization patterns of BMD testing.

Chronic diseases, osteoporosis diagnosis and diagnostic fractures were identified using diagnostic ICD-9 and ICD-10 codes from outpatient services (*MSP Payment Information File*) and inpatient services (*Discharge Abstracts Database*) in this study. ICD-9 and ICD-10 codes are commonly used to identify diseases in data linkage studies, since the ICD classification is commonly required to document diagnoses in administrative records. Diagnostic codes selected

in this study were not validated but based on other published studies for consistency. Potential bias associated with mis-recording should be considered when interpreting the study results [203].

In this study, we only had a small number of survivors receiving initial hormonal therapy with AIs or ovary suppression to examine associations of factors and BMD testing rates during the period 2006-2008. The study group used here was women diagnosed with breast cancer prior to 1st, January 2003 who had survived three years or more as of 1st, January 2006. AIs were first introduced in BC around 2003 and were first recommended as first-line hormonal treatment for postmenopausal women in 2005 [167]. Postmenopausal survivors diagnosed before 2003 were likely to receive tamoxifen initially and switched to AIs later. These survivors would be identified as the tamoxifen group in this study.

Approximately 7% and 21% of selected survivors in our study were diagnosed with breast cancer before age 50 and at age 50-59 respectively. These survivors were at increased osteoporosis risk if they were pre-menopausal at time of breast cancer diagnosis and became amenorrheic after completing chemotherapy (chemo-induced amenorrhea). We were unable to identify these survivors as the chemo-induced amenorrhea status was not recorded in the data.

Approximately 30% of survivors had unknown initial breast cancer treatment. Those were survivors diagnosed more than 20 years ago; diagnosed at early stages that did not require treatments other than surgery; or receive cancer treatments in a few community clinics outside of BCCA administration.

2.5 Conclusion

BMD testing rates over the three-year period 2006-2008 for breast cancer survivors in BC, Canada are far lower than other disease screening. Lower SES and rural residence were associated with low BMD testing rates. Low BMD testing rates were also associated with other factors, including advanced age, nursing home residence, having recent osteoporotic fractures, or not having previous BMD tests. These survivors with lower SES or in rural areas should be encouraged to have BMD tests as recommended by the Canadian guidelines.

Chapter 3: Promoting Bone Health Management in Women Diagnosed with Breast Cancer: A Pilot Randomized Controlled Trial (study 2)

3.1 Introduction

Osteoporosis affects an estimated 200 million women globally, as osteoporotic fractures occur in one in every three women over age 50 in their lifetime [76, 79, 80]. Osteoporotic fractures lead to excessive mortality, impaired physical function, and more long-term nursing home stays [204-206]. The incidence and economic burden of osteoporotic fractures are increasing over time [207]. It is important to find an intervention to prompt bone health management which prevents osteoporotic fractures. Compared with women without breast cancer, women diagnosed with breast cancer are at higher risk of osteoporosis and osteoporotic fractures [147, 179] due to the negative effects of certain breast cancer treatments [66, 174]. Bone mineral density (BMD) testing, a key to good bone health management, can identify high-risk women before fractures occur. The majority of women, aged 65 and above, and not on osteoporosis medications, have a moderate fracture risk (10-20%) and should have one bone mineral density (BMD) test at a one- to three-year interval per Canadian osteoporosis guidelines [97].

Patient educational material improves BMD testing rates in high-risk patients with recent fractures, or aged ≥65 [128, 129]. It remains unclear whether patient educational material would improve BMD testing rates in another high-risk population – women diagnosed with breast cancer. In the British Columbia (BC) primary care setting, information is primarily delivered to patients by postal mail. With advances in communication technologies, there is a growing interest in conveying information by text messaging or email [208, 209]. Little is known whether a patient's choice of delivery method for educational material – e.g., postal mail, email or

smartphone text messaging - affects patient behavior, such as BMD testing rates, differently, compared with postal mail. A randomized controlled trial (RCT) protocol has been designed to evaluate the effects of educational material and its delivery methods on BMD testing rates. In this study, we assessed the feasibility of the study protocol and pilot-tested the intervention effects.

3.2 Methods

3.2.1 Study protocol

A randomized, unblinded, three-armed (parallel), controlled trial evaluating the effects of interventions, "*educational material delivered by postal mail*" and "*educational material delivered by the patient choice of postal mail, email or smartphone text messaging*", on BMD testing rates in women aged 65 and over, and diagnosed with breast cancer for three or more years in BC, Canada.

3.2.2 Recruitment and randomization

Inclusion criteria were (1) female aged 65-75 on July 1st, 2015 and diagnosed with Stage 0-III breast cancer in 2010-2012, (2) a valid current address in BC, (3) no chemotherapy or radiotherapy for any cancers, (4) fluent English in reading and speaking, (5) no BMD testing with DXA over the three-year period from July 1st, 2012 to June 30th, 2015, (6) no osteoporosis medication in the past 12 months before being recruited, (7) signed consent, and (8) returned their pre-study questionnaire with their choice in delivery methods for educational materials.

We randomly selected 398 survivors fulfilled the inclusion criteria (1)-(3) from the provincial BC Cancer Registry [210], a provincial dataset that includes information of BC residents diagnosed with cancer (Figure 3-1). Each selected survivor's demographic, cancer diagnosis, and family doctor information was also retrieved from the same registry. During the initial screening, survivors were excluded and not invited if they did not have identifiable actively practicing family doctors on the BC Cancer Registry and the College of Physicians and Surgeons of BC website (*www.cpsbc.ca/physician_search*) (n=49), For the 349 survivors with a practicing family doctor, a questionnaire on the potential subjects eligibility was faxed to the physician. The family doctors indicated that 44 survivors were unfit (primarily due to poor health) for our study. An invitation package comprising an invitation letter, duplicated consent forms, and pre-study questionnaires was postal-mailed to each of the remaining 305 survivors. Up to three follow-up phone calls were made at different times of the day, on weekdays and weekends, to the survivors who did not respond within two weeks after their mail out dates. Of the 305 survivor invited, 251 were excluded if they were unable to be reached by both postal mail and phone calls (n=69), were not interested in participating this study (n=84), or were ineligible based on our inclusion criteria (4)-(8) (n=98). The criteria (4) and (5) were confirmed by participants' reports. The criteria (6) was confirmed by medication dispensing records reviewed by a pharmacist through PharmaNet, a province-wide network linking all BC pharmacies that records outpatient prescription medications dispensed to any individual anywhere in BC (*www.bcpharmacists.org/pharmanet*).

From February to May 2015, we successfully recruited 54 participants who were then randomized in a 1:1:1 ratio by blocks of three or six into three groups: control group and two intervention groups. The randomization sequence was computed before the recruitment by statistician (JS) and saved as a hard copy by OT. The research assistant recruiting participants contacted OT by email after each participant was recruited. Both OT and JS were blinded to the participants.

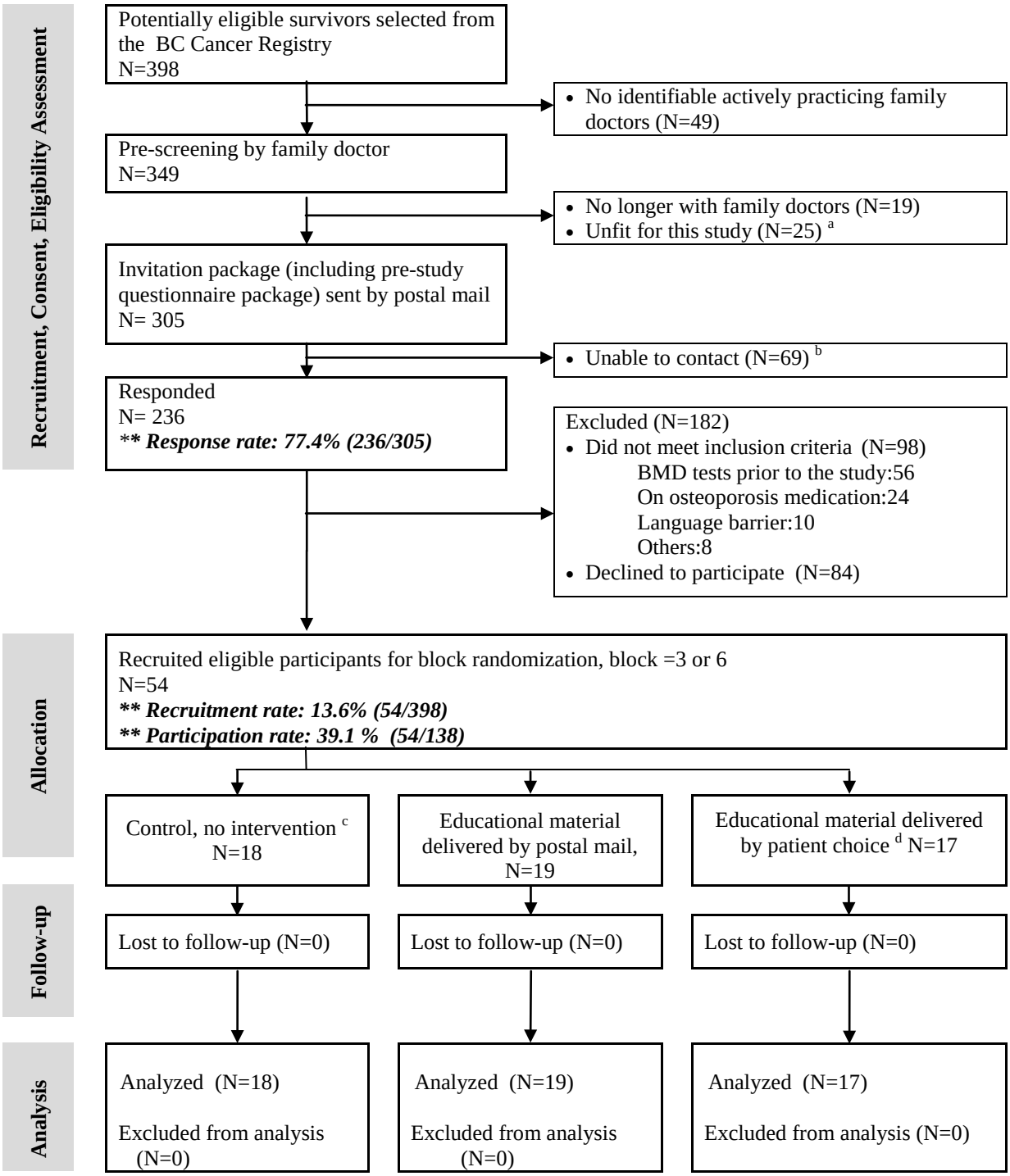


Figure 3-1 Consolidated Standards of Reporting Trails (CONSORT) flow diagram

[a] In poor health condition, nursing home residence, language barrier and other reasons, which were determined by their family doctors

[b] By postal mail or phone call

[c] No intervention during the study period. Educational materials sent after the study's completion

[d] Postal mail, email or smartphone text messaging

3.2.3 Interventions

The two interventions consisted of (1) educational material being delivered by postal mail, and (2) educational material being delivered by patient choice of postal mail, email or smartphone text messaging.

The educational material comprised of two parts: (1) three pages of information on osteoporosis, potential effects of breast cancer treatments on bones, BMD testing, lifestyle advice on exercise, calcium intake, and vitamin D intake, and advice to review osteoporosis risk with her family doctor (Appendix C); and (2) one double-sided page of risk factors based on the 2010 Canadian osteoporosis guidelines and the fracture risk assessment tool (FRAX) developed by the World Health Organization (Appendix D) [97, 195]. Education material was sent to to participants in the intervention groups immediately after being randomized and to control group participants after study completion.

The educational material were created by me, were edited by a material development expert from the Centre of Excellence in Cancer Prevention (*https://cancerprevent.ca/)*, reviewed by three female volunteers aged 65-75 without any breast cancer diagnosis, and then finally reviewed by my committee members.

3.2.4 Self-reported participant questionnaires

Pre-study and post-study questionnaire packages were postal-mailed to collect information from participants during recruitment (baseline) and at six months. The packages included a set of four individual self-report questionnaires: (1) a general or outcome questionnaire, (2) a Godin Leisure-Time Exercise Questionnaire (GLTEQ) [211], (3) a Vitamin D & Sun (VIDSUN)

questionnaire [212], and (4) a Calcium Assessment Tool (CAT) [213]. The general and the outcome questionnaires collected information on demographics, osteoporosis, choice of delivery method for the educational material, and BMD testing with DXA; and were pilot-tested on two volunteers. The GLTEQ, CAT and VIDSUN questionnaire are validated tools. The GLTEQ included four items to assess an individual's exercise habits in a typical week. The GLTEQ is a relative easy-to-use tool and has been recommended for cancer survivor research by the Division of Cancer Epidemiology & Genetics of the National Cancer Institute [214]. The VIDSUN questionnaire incorporated five items to evaluate an individual's risk of vitamin D deficiency. The CAT included 27 items to measure an individual's daily calcium intake in a typical week. The VIDSUN questionnaire and CAT have been validated in this age group [212, 213].

3.2.5 Procedure / intervention outcome measures

The feasibility of the protocol was evaluated by the effectiveness of the recruitment strategy, the representativeness of the recruited participants, and the completeness of outcome measures.

Each participant's outcomes were measured at six months after she was randomized. Outcomes were measured using participant questionnaires, BMD testing reports retrieved from family doctor's office and imaging facilities, and medication dispensing records (Table 3-1).

Our primary intervention outcome was BMD testing rates – the proportion of participants who had BMD tests during their six-month follow-up period based on questionnaire responses and BMD testing reports. Five secondary intervention outcomes were either evaluated once at six months (new osteoporosis diagnosis and initiation of osteoporosis medication from questionnaires, BMD and medication dispensing records) or measured as changes from baseline

(exercise, risk of vitamin D deficiency and calcium intake from questionnaires). Each participant's exercise habits in a typical week were calculated as a leisure score index using the formula [(units of strenuous exercise*9) + (moderate*5) + (light*3)] [211]. VIDSUN questionnaire responses were scored first. Each participant's scores were then tallied and categorized as at high or low risk of vitamin D deficiency [212]. Each participant's daily calcium intake was calculated as mg per day based on the combination of food consumption, the calcium content in that food, and calcium supplements [213].

Table 3-1 Data sources for outcome measures

	Participant questionnaire	**Family doctor**	**BMD imaging facility**	**Medication dispensing record**
Primary outcome				
BMD testing rate	✓	✓		
Secondary outcomes				
Newly diagnosed osteoporosis		✓ BMD reports	✓ BMD reports	
Initiation of osteoporosis medication	✓			✓
Changes in weekly exercise	✓			
Risk of vitamin D deficiency	✓			
Changes in daily calcium intake	✓			

3.2.6 Statistical analysis

The characteristics among the three groups of the participants, non-participants who declined to participate in this study and other non-participants were compared using the chi-square test. The characteristics of the study participants were evaluated using descriptive analysis, either proportions, means with standard deviation (SD) or median with range (for skewed distributions). The changes on leisure score index and daily calcium intake were evaluated for each group using the means of individual differences between baseline and six months with 95% confidence intervals (CI). The effect of the educational material and its delivery method on BMD

testing rates were estimated using rate differences with 95% CI between the control group and the combined intervention groups (postal mail and patient choice groups), and between postal mail group and patient choice group. All analyses were performed Statistical Analysis System version 9.3 (SAS Institute Inc., Cary, NC).

3.2.7 Ethics and clinical trial registration

Ethics was approved by the Clinical Ethics Board of the University of BC (H15-00849). This study protocol has been registered at *www.clinicaltrials.gov* with the registration number NCT02484131.

3.3 Results

3.3.1 Feasibility of the study protocol

The response rate, defined as the proportion of women who responded to our invitation, was 77.4%. The participation rate, defined as the proportion of eligible participants who consented to participate, was 39.1% with an overall recruitment rate, defined as the proportion of participants from the original 398 survivors, of 13% (Figure 3-1). Similar distributions of age at diagnosis, stage of cancer at diagnosis, treatment and region of service were observed among the 54 participants, 84 non-participants who declined to participate in this study, and 260 other non-participants (Table 3-2). The primary and five secondary intervention outcomes were measured for 98% and 78-100% of the 54 recruited participants respectively. One or more missing values were noted in 4-19% of the returned GLTEQ, VIDSUN, and CAT questionnaires at baseline and six months (Table 3-3).

Table 3-2 Representativeness of participants

	Participants	Non-participants		
		Others [a]	Declined to participate	
	(N=54)	(N=260)	(N=84)	*p* value [b]
Age	70.3 ± 3.7	69.6 ± 6.9	70.6 ± 3.1	0.32
Breast cancer stage				
In situ	8 (14.8)	35 (13.5)	9 (10.7)	
I	27 (50.0)	126 (48.5)	50 (59.5)	
II	15 (27.8)	74 (28.5)	20 (23.8)	
III	3 (5.6)	18 (6.9)	5 (6.0)	
Unknown	1 (1.9)	7 (2.7)	0 (0)	0.42
Initial chemotherapy				
Y	12 (22.2)	74 (28.5)	20 (23.8)	
N	39 (72.2)	163 (62.7)	60 (71.4)	
Unknown	3 (5.6)	23 (8.9)	4 (4.8)	0.43
Initial hormonal therapy				
Y	39 (72.2)	167 (64.2)	61 (72.6)	
N	12 (22.2)	69 (26.5)	19 (22.6)	
Unknown	3 (5.6)	24 (9.2)	4 (4.8)	0.47
Health service region				
VCHA	9 (16.7)	54 (20.8)	17 (20.2)	
FHA	14 (25.9)	94 (36.2)	34 (40.5)	
VIHA	12 (22.2)	63 (24.2)	14 (16.7)	
IHA	16 (29.6)	43 (16.5)	16 (19.1)	
NHA	3 (5.6)	6 (2.3)	3 (3.6)	0.28

VCHA Vancouver Coast Health Authority, *FHA* Fraser Health Authority, *VIHA* Vancouver Island Health Authority, *IHA* Interior Health Authority, *NHA* Northern Health Authority

[a] Ineligible for this study, were unable to contact by postal mail or phone calls, or did not have identifiable actively practicing family doctors

[b] Calculated using the chi-square test

Table 3-3 Response patterns in questionnaires

	Items	**Completed both**	**At baseline (pre-study questionnaire)**			**At six-month (post-study questionnaire)**			
Questionnaire	(N)	% (N / total N)	0 missing	1 missing	≥ 2 missing	0 missing	1 missing	≥ 2 missing	No response
GLTEQ [a]	4	91 (49/54)	52	1	1	51	0	1	2
VIDSUN [b]	5	87 (47/54)	52	1	2	48	2	2	2
CAT [c]	27	78 (42/54)	48	3	3	44	2	6	2

GLTEQ Godin Leisure-Time Exercise Questionnaire, *VIDSUN* Vitamin D & Sun Questionnaire, *CAT* Calcium Assessment Tool

[a] GLTEQ evaluated weekly exercise amount

[b] VIDSUN evaluated risk of vitamin D deficiency

[c] CAT measured daily calcium intake

3.3.2 Study participants

Most of the 54 participants self-reported that they were Caucasian (96%), completed secondary school or higher (87%), received hormonal therapy (69%), and had ≤45 minutes of mild exercise (60%) (Table 3-4). The average daily calcium intake was 915 mg per day. The median FRAX risk without BMD measures was 13.5% (range 8.5 to 45%). No major differences were observed across the three treatment groups. Postal mail (69%) was the most popular choice for delivering educational material, followed by email (31%) regardless of the participants' group assignment.

Table 3-4 Characteristics of study participants

	Control group (Total N=18)	Educational material delivered by postal mail (Total N=19)	Educational material delivered by patient choice [a] (Total N=17
	N (%)	N (%)	N (%)
Demographic Factors			
Age (years, mean ± SD)	70.5 ± 3.9	69.8 ± 3.5	71.1 ± 4.0
Ethnicity			
Caucasian	18 (100)	18 (95)	16 (94)
Non-Caucasian	0 (0)	1 (5)	1 (6)
Marital			
Married / common law / living with a partner	11 (61)	12 (63)	15 (88)
Single, widowed, divorced, separated	7 (39)	7 (37)	2 (12)
Education			
Did not complete secondary (high) school	3 (17)	1 (5)	3 (18)
Completed secondary (high) school	15 (83)	18 (95)	14 (82)
Choice for educational material delivery asked before the randomization			
Mail	11 (61)	13 (68)	13 (76)
Email	7 (39)	6 (32)	4 (24)
Cell phone texting	0 (0)	0 (0)	0 (0)
Osteoporosis: risk Factors & previous BMD tests			
FRAX risk [b]			
Median (range)	13.5 (4.8, 45)	14 (5.2, 32)	11.5 (7, 22)
BMI (kg/m^2, mean ± SD)	28.8 ± 6.3	26.7 ± 6.2	27.0 ± 10.7
Smoking			
No	17 (94)	15 (79)	15 (88)
Yes	1 (6)	4 (21)	2 (12)
Drinking			
No	8 (44)	11 (58)	9 (53)
Yes	10 (56)	8 (42)	8 (47)
Weekly exercise (leisure score index, mean ± SD) [c]	24.8 ± 17.0	27.9 ± 23.3	24.0 ± 27.5
Vitamin D deficiency			
Low risk	10 (56)	13 (68)	11 (65)
High risk	7 (39)	6 (32)	5 (29)
Unknown	1 (6)	0 (0)	1 (6)
Calcium intake (mg per day, mean ± SD) [d]	915 ± 370	911 ± 510	920 ± 511

Continued

	Control group (Total N=18)	Educational material delivered by postal mail (Total N=19)	Educational material delivered by patient choice [a] (Total N=17)
	N (%)	N (%)	N (%)
Long term steroid usage			
No	17 (94)	15 (79)	15 (88)
Yes	0 (0)	4 (21)	1 (6)
Unknown	1 (6)	0 (0)	1 (6)
Previous fracture			
No	10 (56)	12 (63)	13 (77)
Yes	7 (39)	7 (37)	4 (24)
Unknown	1 (6)	0 (0)	0 (0)
Parent's fracture			
No	11 (61)	13 (68)	13 (76)
Yes	6 (33)	5 (26)	3 (18)
Unknown	1 (6)	1 (5)	1 (6)
Previous BMD test			
No	7 (39)	3 (16)	4 (24)
Yes	6 (28)	14 (74)	8 (47)
Unknown	5 (33)	2 (11)	5 (29)
Breast Cancer Treatment			
Hormonal therapy			
None	7 (39)	4 (21)	6 (35)
Tamoxifen only	4 (22)	7 (37)	2 (12)
AIs only	3 (17)	5 (26)	5 (29)
Tamoxifen with AIs	4 (22)	3 (16)	4 (24)
Ovarian suppression or ovary removal			
No	17 (94)	19 (100)	17 (100)
Yes	1 (6)	0 (0)	0 (0)

BMI body mass index, *SD* Standard Deviation, *BMD* bone mineral density, *AIs* Aromatase inhibitors

[a] Postal mail, email or smartphone text messaging

[b] Developed by World Health Organization

[c] Two participants who did not complete the exercise section of the pre-study questionnaires were excluded from the analysis

[d] Six participants who did not complete the calcium intake section of the pre-study questionnaires were excluded from the analysis

3.3.3 Primary outcome – bone mineral density testing rates

Although no formal statistical testing was conducted, there was a suggestion of higher BMD testing rates in the groups receiving educational material by mail (26%, 95% CI=10 to 49) and patient choice (18%, 95% CI=5 to 41), compared with the control group (6%, 95% CI=0.3 to 25) (Table 3-5). The BMD testing rate was 17% (95% CI=6 to 33) higher in the groups where educational material was delivered by either postal mail or patient choice compared with the control group. The BMD testing rate was 8.7% (95% CI= -33.9 to 18.9) lower for the patient choice compared with the postal mail group.

3.3.4 Secondary outcomes

Four of the nine participants (44%) who had BMD test were newly diagnosed with osteoporosis. Of the four, two (50%) initiated the osteoporosis medication risedronate which was consistently reported by both the participants' self-reports and medication dispensing records (Table 3-5). Among all 54 participants during the six-month follow-up period, the leisure exercise index increased by 2.8 (95% CI= -13.8 to 19.5) for the educational material delivered by postal mail group, by 4.7 (-2.5 to 11.9) for the educational material delivered by patient choice group, but decreased by 0.9 (-8.3 to 6.5) for the control group. The daily calcium intake increased by 139 mg (-170 to 449) for the postal mail group and by 45 mg (-133 to 224) for the patient choice group, but decreased by 3 mg (-282 to 277) for the control group. The risk for vitamin D deficiency remained unchanged for 39 (72%) of the 54 participants.

Table 3-5 Outcome measures after six month follow-up period

	Control group Total N=18	**Educational material delivered by postal mail [a] Total N=19**	**Educational material delivered by patient choice Total N=17**
	N (%)	N (%)	N (%)
Primary outcome			
Having BMD testing with DXA, N (%)	1 (6)	5 (26)	3 (18)
Reported by study participants	1 (6)	4 (21)	2 (12)
BMD reports retrieved from family doctor or imaging facility	1 (6)	4 (21)	3[b] (18)
Unknown	0 (0)	1 (3)	0 (0)
Secondary Outcomes			
Newly diagnosed osteoporosis, N (%)	1 (6)	3 (16)	0 (0)
Initiating osteoporosis medications, N (%)			
Reported by study participants	1 (6)	1 (5)	0 (0)
Medication dispensing records	1 (6)	1 (5)	0 (0)
Changes in weekly exercise [c]			
- Leisure score index (95% CI)	-0.9 (-8.3, 6.5)	2.8 (-13.8, 19.5)	4.7 (-2.5, 11.9)
Risk of vitamin D deficiency			
Remains low risk	8 (44)	12 (63)	7 (41)
Remains high risk	4 (22)	5 (26)	3 (18)
Low -> High risk	0 (0)	1 (5)	2 (12)
High -> Low risk	3 (17)	1 (5)	1 (6)
Incomplete /unknown	3 (17)	0 (0)	4 (24)
Changes in calcium intake [d] - mg per day (95% CI)	-3 (-282, 277)	139 (-170, 449)	45 (-133, 224)

BMD bone mineral density, *DXA* Dual-energy X-Ray absorptiometry, *CI* Confidence interval

[a] Postal mail, email or smartphone text messaging

[b] One patient reported no DXA test on questionnaire while her BMD testing report was retrieved from her family doctor's office

[c] Five participants who did not complete the Godin Leisure-Time Exercise Questionnaires at either or both baseline and six months were excluded from the analysis

[d] Twelve participants who did not complete the Calcium Assessment Tool at either or both baseline and six months were excluded from the analysis

3.4 Discussion

The feasibility of this RCT protocol was evaluated on participants from throughout the province of BC. This study is the first study to pilot-test the effects of educational material on women diagnosed with breast cancer, a population at higher risk for osteoporotic fractures. The educational material intervention used in this study had a promising positive effect on BMD testing rates (17% increase), weekly exercise, and daily calcium intake in women aged 65 and over, and diagnosed with breast cancer for three or more years in BC. The study protocol is feasible for a future large-scale study. Per the online sample size calculator (*www.stat.ubc.ca*), a minimum of 56 participants per group is required to achieve a statistical power of 0.95 with α=0.05 (one sided test) to detect a 17% increase in BMD testing rates using educational material intervention with a two-parallel-group design in a future large-scale study.

The study participants had a slightly higher average osteoporosis risk (15%, without BMD measurement) compared to the Canadian population at age 70 (around 13%, with BMD measurement) while the negative effects of cancer treatments on bone health are not considered using FRAX [215]. Obesity (body mass index $\geq$30) and infrequent exercise were more prevalent in our study than in BC residents in the same age group [216]. Being obese is associated with higher breast cancer risk [217], and might also be linked with inadequate exercise and reduced metabolism associated with cancer treatment [218]. The potential barriers to exercise include fatigue associated with cancer treatment [219], lack of priority, self-discipline, and procrastination [220]. Inadequate average daily calcium intake was observed for our study participants per the 2010 Canadian Osteoporosis guidelines [97] while the intake was similar compared to BC residents in the same age group. One-third of our study participants were at high

risk of vitamin D deficiency while the assessment tool (VIDSUN questionnaire) has high sensitivity (%) and low specificity (%) [212]. Interventions, such as educational material in this study, should be considered to improve calcium intake and exercise in women diagnosed with breast cancer. Email was the preferred choice for delivering educational material by one-third of participants in this study, which suggests a potential willingness to adopt technology for health-related issues in this specific group.

3.4.1 Educational material

The educational material created for this study included basic information only. There was a focus to make information easy to read and understandable for women from all educational backgrounds. Readers were encouraged to discuss details with relevant health-affiliated professionals, such as family doctors for lifestyle modification, dieticians for calcium or vitamin D rich food, physiotherapists for exercise, and pharmacists for calcium or vitamin D supplements. HealthLink BC URL (*www.healthlinkbc.ca/)* was provided to readers looking for more details on healthy lifestyles. A toll-free 8-1-1 number was provided for a free dietician consultation in BC.

Exercise has shown positive effects on BMD [139]. Moderate-to-vigorous exercise reduces hip fractures by 38-45% [221]. Exercise recommendations vary significantly among different guidelines. Our educational material suggests 10-15 minutes of exercise once or twice a day at least 3-5 times per week, which is higher than the amount suggested by the Canadian Task Force (three times per week, for at least 20-30 minutes each time; for all adults) [175], but lower than the amount suggested in the 2010 Canadian Osteoporosis Guideline (4-7 days per week for 20 to

60 minutes; for all adults) [97] and the 2011 World Health Organization Guideline (≥150 minutes of moderate-intensity aerobic exercise per week or ≥75 minutes of vigorous-intensity aerobic exercise per week; for adults aged ≥65 years) [222].

3.4.2 Bone mineral density testing rate

The absolute increase in BMD testing rate during our six-month follow-up period starting from the delivery of educational material, was lower than the increase seen in high-risk patients with recent fractures (22-51%) [128], but higher than the increase seen in patients aged 65 and over (18%) in primary care settings [129]. This could be explained by differences in sample sizes, interventions (patient reminder, physician reminder, or educational material), medical care settings (emergency department, hospital or primary care clinic), follow-ups ranging from 4 to 16 months, and perceived osteoporotic fracture risk (risk is underestimated in older women) [118, 120].

In this study, the proportion of participants who had BMD tests and who did not during the six-month follow-up period in age, FRAX score, calcium intake, and leisure score index were similar between three groups. Only two of the 14 participants who did not have BMD tests prior to this study, had BMD tests during their six-month follow-up period. This could be because women without fractures tend to underestimate their osteoporosis risk, or women may skip BMD testing due to a potential perceived vulnerability associated with an osteoporosis diagnosis.

3.4.3 Secondary outcome measures

The common questions returning unanswered were associated with supplemental intake of vitamin D and calcium in the CAT and VIDSUN questionnaires. We identified common barriers including poor vision (preventing these participants from reading the small fonts on supplement labels), confusion due to different measurement units of vitamin D (e.g. international units and micrograms), and uncertainty in measurement units of calcium rich food (e.g. cups and cubes). These questions may require modification or clarification in a future large-scale study.

3.4.4 Limitation

The percentage of non-Caucasian participants was low in our study compared to the population proportion of 27% in BC [223]. This could primarily result from language barrier as our educational material was only available in English. The other potential barriers include logistical challenges, cultural barriers, and mistrust of research [224].

The overall recruitment rate in this study was only 13% (54/398). This is primarily because we excluded 190 survivors who were ineligible or their family doctors were not identifiable by the study team. Despite this, the primary outcome measure was obtained for at least 90% of all 54 participants. We did not experience any major events associated with the study protocol. Our approach is a very low cost way to reach a large number of women participants.

3.5 Conclusion

The protocol is feasible for a large-scale study with minor questionnaire modification. There was broad acceptance of the educational material intervention by the study participants. The data suggest that the educational material will increase BMD testing rates. Given the importance of

diagnosing and treating osteoporosis and the low current rates of BMD testing in Canada, this area is a priority for future interventions.

Chapter 4: Aromatase Inhibitors are Associated with a Higher Fracture Risk than Tamoxifen: A Systematic Review and Meta-analysis (study 3)

4.1 Introduction

Adjuvant systemic treatments, such as chemotherapy and hormonal treatment, have been used widely to treat breast cancer [225]. Hormonal treatment is recommended in women with hormone receptor-positive breast cancer, accounting for at least two-thirds of all breast cancer cases [149, 150]. The two most common hormonal treatments are tamoxifen and aromatase inhibitors (AIs).

Tamoxifen, a selective estrogen receptor modulator (SERM), was introduced in the 1970s. Tamoxifen is currently recommended to treat early and advanced stage breast cancer in pre-menopausal women, and post-menopausal women at lower risk of cancer relapse [151]. Tamoxifen is also an optional treatment in women with stage zero (in situ) breast cancer [152]. Tamoxifen reduces the available estrogen to cancer cells by competitively inhibiting the binding of estrogen to estrogen receptors on breast tissues. The effect of tamoxifen on bone tissues is inconsistent across studies and seems to differ by menopausal status. Tamoxifen caused a BMD decrease in healthy pre-menopausal women but a BMD increase in healthy post-menopausal women [155]. In women diagnosed with breast cancer, tamoxifen preserves bone mass in pre-menopausal women, and either slightly increases or decreases BMD in post-menopausal women [156-161]. Tamoxifen may have a beneficial effect on bone health in women diagnosed with breast cancer. However, tamoxifen has not

been approved for the treatment or prevention of osteoporosis in any populations by the US Food & Drug Administration.

AIs were introduced in the early 2000s. AIs are currently recommended to treat early and advanced stage breast cancer in post-menopausal women at higher risk of cancer relapse. AIs reduce the circulating estrogen levels by inhibiting the aromatase enzyme from converting androgen to estrogen in non-ovarian tissues. AIs are suggested for women at higher cancer relapse risk due to its potential negative effect on bone health. AIs significantly increase bone loss [159, 169] and are associated with higher fracture risks in several major trials [170, 171]. However, AI-associated fracture risk has not been reviewed systematically.

The initial goal of this study was to determine whether there are BMD changes and additional fracture risks associated with adjuvant systemic breast cancer treatments, compared with loco-regional treatments (i.e. surgery and radiation therapy) or no breast cancer treatment in women aged 65 and under. Fractures however have a higher clinical impact on healthcare systems than BMD changes. Tamoxifen and AIs are used to treat breast cancer more often than other adjuvant systemic treatments. Hence, we focused our research questions on the differential fracture risks associated with tamoxifen and AIs in younger women aged 65 years and under, and diagnosed with non-metastatic breast cancer.

4.2 Method

This was a systematic review with meta-analysis study using aggregate data from RCTs and cohort studies on fracture risks associated with tamoxifen and AIs in younger women aged 65 years and under, and diagnosed with non-metastatic breast cancer. We registered the review protocol at PROSPERO (registration number CRD42015015604; *www.crd.york.ac.uk/PROSPERO/*). We reported study results using criteria from the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA) [226]. Article search was conducted by the first author. Study selection (NR/OT for title/abstract screening; WH/OT for full-text article review), study quality evaluation (WH/OT), and data extraction (WH/OT) were performed independently by two reviewers using Excel spreadsheets. Disagreements between reviewers were resolved by discussion. Persistent disagreements between reviewers were arbitrated by another designated team member (MD).

4.2.1 Search strategy

We searched PubMed, MEDLINE, CINHAL, EMBASE, and Cancerlit databases for article published from January 1st, 1970 to May 1st, 2015. We included search terms "*breast*" and "wom*n OR female" and "*tumor OR cancer OR neoplasm OR malignanc?*" and "*fracture OR BMD OR densit? OR densitometr? OR absorptiometry?*". Studies were then limited to human studies and English language articles. Review articles were then excluded. The reference lists of the included articles were hand-searched. Approximately 20% of included and excluded articles at each step of the article search were randomly reviewed to ensure proper article search strategies.

4.2.2 Study selection

Articles were initially screened by title and abstract, followed by full article reviews (Figure 4-1). Articles fulfilling the inclusion criteria: (1) RCTs or cohort studies [227], (2) women diagnosed with non-metastatic breast cancer, (3) at least one participant aged 65 years and under at baseline, (4) breast cancer treatments of tamoxifen, AIs or both, and (5) fracture outcomes, were selected. We defined the outcomes in this study as count of fracture events or participants with fractures. Articles reporting pathological fractures or any specific fracture type (e.g. spine fracture only) were excluded.

4.2.3 Study quality assessment

We evaluated the methodological quality of the selected articles using two separate assessment tools suggested by the Cochrane Collaboration Review Group. RCTs were evaluated using the Cochrane risk of bias assessment tool. Each RCT was assessed and rated as “low risk of bias”, “high risk of bias” or “unknown risk of bias” in the seven domains of potential bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases (e.g. funding source, conflict of interest, etc.) [228, 229]. Cohort studies were evaluated using the Newcastle-Ottawa Scale with a range of zero to nine stars. Each cohort study was evaluated in three categories – the selection category with four items, the comparability category with only a single item, and the outcome category with three items. Each cohort study was awarded a maximum of one star per item within the selection and outcome categories, and a maximum of two stars for the single item within the comparability category [230, 231].

4.2.4 Data extraction

Articles reporting data at same follow-up times from the same independent study were collated (ID 5, 16, 18, 21, 30). We extracted data from each included study on method, participant, treatment, fracture outcome, and factors controlled for multivariable regression models as follows:

- *Method:* study design, study period, follow-up duration
- *Participant:* total number, age, breast cancer stage, proportion of post-menopausal women, non-interventional breast cancer treatments
- *Treatment:* dosage, treatment duration, prior tamoxifen treatment
- *Fracture outcome:* definition of fractures, count of fracture events (allowing more than one fracture event per participant), count of participants who developed fractures, and relative measures including odds ratios (ORs), risk ratios (RRs), incidence rate ratios (IRRs), and/or hazard ratios (HR) using Cox regression models
- *Factors controlled for multivariable regression models*

There were two articles (ID 12, 34) each reporting combined data from two independent studies. Data from the Austrian Breast and Colorectal Cancer Study Group trial 8 (ABCSG-8), and Arimidex-Nolvadex-95 (ARNO-95) trial were combined in article 12. Data from the Tamoxifen and Exemestane Trial (TEXT), and Suppression Ovarian Functions (SOFT) trial were combined in article 34 [232, 233]. Extracted data from each independent study, ABCSG-8, ARNO-95, TEXT, and SOFT trial were inadequate for meta-analysis. The authors of both articles were contacted by email but we were unable to obtain additional information on any of these four studies.

4.2.5 Data synthesis

Meta-analyses were undertaken to estimate the differential fracture risks of tamoxifen and AIs, and risks between tamoxifen and AI. Each fracture risk was stratified by three to five factors of menopausal status (pre-menopausal only, mixture of both pre- and post-menopausal, and post-menopausal only), prior tamoxifen treatment (yes vs. no), study design (RCTs vs. cohort study), AI treatment duration (≤48 months vs. 60 months) and AI drug (steroidal vs. non-steroidal vs. any) using subgroup analysis. Menopausal status was determined using age in the two cohort studies with missing menopausal status information (ID 4, 35).

The time effect on differential fracture risk between tamoxifen and AI was evaluated by ranges of follow-up durations (12-36, >36-60, >60-84, >84 months) and treatment period (on- and post-Tam/AI treatment). Meta-analyses were conducted independently for each range of follow-up duration and treatment period. The Tam/AI-treatment period was defined as the time period when women were receiving tamoxifen or AIs during the study period.

For each independent study with serial follow-up data, the article with the longest follow-up duration was included for each individual meta-analysis to avoid double counting of study participants. For studies with multiple treatment arms, the arms were either grouped as a single pair-wise comparison (ID 13, 14) or a three group comparison with each other (ID 35, 36. 37) of tamoxifen, AIs, and control group (no tamoxifen alone, no AIs alone, and no combination of tamoxifen and AIs). Articles with double-zero events (zero-cell counts in both intervention arms) were excluded from meta-analysis [234].

4.2.6 Statistical analysis

Meta-analyses were restricted to studies reporting counts of participants with fractures and not fracture events. For RCTs included in meta-analysis, Relative Risks (RRs) with 95% confidence intervals (CIs) were calculated. For cohort studies included for meta-analysis, published adjusted Hazard Ratios (aHRs) with 95% confidence intervals (CIs) were used first. RRs were calculated for the cohort studies without available aHRs. Adjusted HRs were treated as adjusted RRs due to the low incidence of fracture outcomes. Overall differential fracture risk was pooled as weighted RRs using a generic inverse variance method with random effects models. The weight of each study was based on the inverse of that study's variance. Statistical significance of the pooled RRs was evaluated using Chi-Square tests. Statistical heterogeneity was evaluated using Cochrane's Q statistic and quantified as I^2 measures. Sensitivity tests were conducted when combining RRs and aHRs. All statistical tests were performed using RevMan 5.2 analysis software (The Cochrane Collaboration Copenghagen, Denmark) [235].

4.3 Results

There were 4,004 articles identified, of which 2,078 were duplicate articles (Figure 1). This left 1,926 unique articles for title/abstract screening. Of them, 1,649 were excluded leaving 277 articles for full article review. A total of 43 articles covering 21 independent studies fulfilled our selection criteria and proceeded to methodological quality assessment.

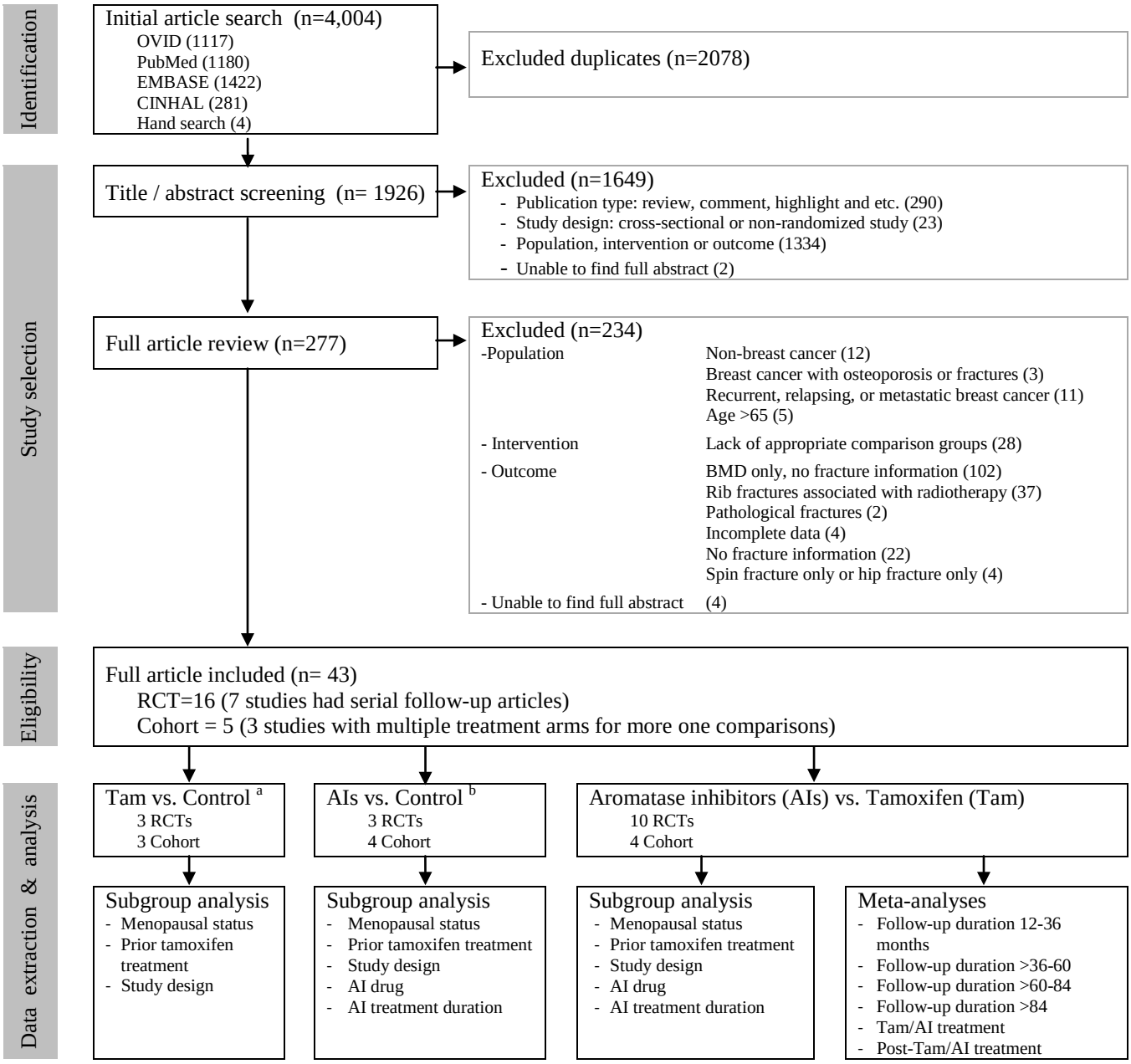


Figure 4-1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) flow diagram for systematic review of the fracture risks associated with breast cancer treatments

AIs aromatase inhibitors, *RCT* randomized controlled trial, *Tam* tamoxifen

[a] No tamoxifen

[b] No AIs

4.3.1 Characteristics of included studies

Sixteen RCTs, four retrospective cohort studies, and one prospective cohort study were included (Table 4-1). All RCTs were designed to evaluate primary outcome of efficacy and secondary outcome of safety including fractures using intent-to-treat analysis with the exception of one study (ID 7). All cohort studies were designed to evaluate fracture outcomes. Seven of the 16 RCTs reported serial follow-up data. Eight of the 16 RCTs involved post-menopausal women only.

Mean or median age ranged from 43 to 67 years. Treatment dose was unknown in four cohort studies (ID 4, 11, 35, 36). Doses of tamoxifen were 20 mg per day in almost all studies, but one (ID1) of 30 mg per day and two of 20-30mg per day (ID 12, 15). Doses of AIs were consistent across all studies as follows: anastrozole (1 mg per day), letrozole (2.5 mg per day), and exemestane (25 mg per day). Treatment duration ranged from 12 to 72 months while follow-up duration ranged from 12 to 128 months. About 17-25% crossover was reported in a few studies (ID 25, 26). Fracture outcomes were measured as any self-reported fracture (15 studies), self-reported osteoporotic/minimal-trauma fracture (ID 1, 36), self-reported hospitalized fracture (ID 32), any fracture event in medical records (ID 11), or any fracture using data linkage (ID 4, 35).

Table 4-1 Summary of studies

Study Information						Study participants (safety population)				Treatment		Published fracture outcomes - fracture				Meta-analysis	Factors
ID	Study name Author, year (ref)	Design	Country	Data source	Median follow-up duration	Age (Years) [a]	Post-menopausal (%)	Prior tamoxifen [b] (duration)	No.	Arms	Duration	Type	Participants with fractures No.	Fracture events per 1000 PY	Risk measure (95% CI)	Risk Measure used in meta-analysis (95% CI)	Adjusted
Tamoxifen vs. Control / placebo (reference)																	
1	Kristense, 1994 [162]	RCT	Denmark	Self-report	44 M	57 (NR, 65)	100	N	20 23	Tam Control	24 M	Osteo-porotic	0 / -- 0 / --	--	--	--	--
2	Love, 1994 [163]	RCT	USA	Self-report	Mean 60.5 M	58 ± 4	100	N	70 70	Tam Placebo	24 M	Any	6 / 7 8 / 10	--	--	Calculated RR 0.75 (0.27, 2.05)	--
3	Sacco, 2003 [236]	RCT	Italy	Self-report	52 M	61 ± 6	95	Y (24 M)	943 958	Tam Control	36 M	Any	8 / -- 10 / --	--	--	Calculated RR 0.81 (0.32, 2.05)	-
Aromatase inhibitors (AIs) vs. Control / placebo (reference)																	
4	Mincey, 2006 [237]	Cohort	US	Data-linkage	Range 1998- 2005	66 ± 11 64 ± 13	<100 [c]	N	1354 11,014	AIs Control	--	Any	183 / -- 1132 / --	86 / -- 63.6 / --	aHR 1.21 (1.03, 1.43) IRR 1.35 (1.16, 1.58)	Published aHR 1.21 (1.03, 1.43)	Age, 1, 2, 3, 4
5	***MA 17*** Goss, 2003 [238]; DeGrendele, 2003 [239]	RCT	Multiple , 9	Self-report	2.4 Y	62 (NR)	100	Y (60 M)	2154 2145	AIs (Let) Placebo	60 M	Any	77 / -- 63 / --	--	--	--	--
6	***MA 17*** Goss, 2005 [240]				30 M				2572 2577	AIs (Let) Placebo			137 / -- 119 / --	--	--	Calculated RR 1.15 (0.94, 1.41)	--
7	***MA 17*** Goss, 2008 [241]				1.1 Y [d] (after unblinding)				1579 [e] 804	AIs (Let) Placebo			82 / -- 25 / --	--	--	--	--
8	***Norwegian*** Lonning, 2005 [242]	RCT	Norway	Self-report	24 M	59 (46-73)	100	N	73 74	AIs (Exe) Placebo	24 M	Any	4 / -- 5 / --	--	--	--	--
9	***Norwegian*** Geisler, 2006 [243]				36 M				73 74	AIs (Exe) Placebo			4 / -- 5 / -	--	--	Calculated RR 0.81 (0.23, 2.90)	--
10	***NSABP (B-33)*** Mamounas, 2008 [244]	RCT	USA / Canada	Self-report	Till April 2004	60 (NR)	100	Y (57-66 M)	783 779	AIs (Exe) Placebo	60 M	Any	28 / -- 20 / --	--	--	Calculated RR 1.39 (0.79, 2.45)	--
Aromatase inhibitors (AIs) vs. Tamoxifen (reference)																	
11	Koopal, 2015 [245]	Cohort	Netherland	Charts + X-ray	Post-Tam/AI (3.1 Y)	52 ± 7 (pre-m) 71 ± 10 (post-m)	0	N	39 92	AIs Tam	5.7 - 6 Y	Any	4 / -- 24 / --	--	--	Calculated RR 0.39 (0.15, 1.06)	--
12	***ABCSG – 8 / ARNO 95*** Jakesz, 2005 [232]	RCT	Germany / Austria,	Self-report	28 M	62 (41-80)	100	Y (24 M)	1602 1597	AIs (Ana) Tam	36 M	Any	34 / -- 16 / --	--	OR 2.14 (1.14, 4.17)		--
13	***ABCSG-12*** Grant, 2009 [246]	RCT	Austria	Self-report	47.8 M	45 (26-57)	0	N	903 900	AIs (Ana) Tam	36 M	Any	12 / -- 12 / --	--	--	Calculated RR 1.00 (0.45, 2.21)	--
14	***ABCSG-12*** Grant, 2011 [247]				62 M				903 900	AIs (Ana) Tam			13 / -- 12 / --	--	--	Calculated RR 1.08 (0.50-2.35)	--

Continued

Study Information						Study participants (safety population)				Treatment		Published fracture outcomes - fracture				Meta-analysis	Factors
ID	Study name Author, year (ref)	Design	Country	Data source	Median follow-up duration	Age (Years) [a]	Post-menopausal (%)	Prior tamoxifen [b] (duration)	No.	Arms	Duration	Type	Participants with fractures No.	Fracture events per 1000 PY	Risk measure (95% CI)	Risk Measure used in meta-analysis (95% CI)	Adjusted
Aromatase inhibitors (AIs) vs. Tamoxifen (reference)																	
15	***ARNO 95*** Kaufmann, 2007 [248]	RCT	Germany	Self-report	30.1 M	61 (46-74)	100	Y (24 M)	445 452	AIs (Ana) Tam	36 M	Any	10 / -- 10 / --	--	--	Calculated RR 1.02 (0.43, 2.42)	--
16	***ATAC*** Buzdar, 2002 [249]; Fisher, 2002 [250]; Baum, 2002[251]	RCT	Multiple, 21	Self-report	33.3 M	64 ± 9	100	N	3092 3094	AIs (Ana) Tam	60 M	Any	183 / -- 115 / --	--	--	Calculated RR 1.59 (1.27,2.00)	--
17	***ATAC*** Baum, 2003 [252]				42 M				3092 3093	AIs (Ana) Tam			219 / -- 137 / --	--	--	Calculated RR 1.60 (1.30, 1.97)	--
18	***ATAC*** Howell, 2005 [253]; Cuzick, 2007 [254]				68 M				3092 3094	AIs (Ana) Tam			340 / -- 237 / --	22.6 / -- 15.6 / --	OR 1.49 (1.25, 1.77) HR 1.44 (1.21, 1.68)	Calculated RR 1.44 (1.23, 1.68)	--
19	***ATAC*** Arimidex, 2008 [255]				100 M				3092 3094	AIs (Ana) Tam			--	--	--	--	--
					On Tam/AI				3092 3094	AIs (Ana) Tam			-- / 375 -- / 234	-- / 29.3 -- / 19	IRR 1.55 (1.31-1.83)	--	--
					Post Tam/AI				2496 2419	AIs (Ana) Tam			-- / 146 -- / 143	-- / 15.6 -- / 15.1	IRR 1.03 (0.81, 1.31)	--	--
20	***ATAC*** Cuzick, 2010 [170]				120 M				3092 3094	AIs (Ana) Tam			--	--	--	--	--
					On Tam/AI				3092 3094				451 / -- 351 / --	--	--	Calculated RR 1.29 (1.13, 1.46)	--
					Post-Tam/AI				2223 2246				110 / -- 112 / --	--	--	Calculated RR 0.99 (0.77, 1.28)	--
21	***BIG 1-98*** Thurlimann, 2005 [256]; Monnier, 2005 [257]	RCT	Multiple, 27	Self-report	25.8 M	61 (38-90)	100	N	3975 3988	AIs (Let) Tam	60 M	Any	225 / -- 159 / --	22 / -- 15 / --	OR 1.44	Calculated RR 1.42 (1.16, 1.73)	--
22	***BIG 1-98*** Crivellari, 2008 [258]				40.4 M				2448 2447	AIs (Let) Tam			196 / -- 132 / --	--	--	--	--
23	***BIG 1-98*** Coates, 2007 [259]				51 M				2448 2447	AIs (Let) Tam			211 / -- 141 / --	--	--	Calculated RR 1.50 (1.22, 1.84)	--
24	***BIG 1-98*** Rabaglio, 2009, [171]				On Tam/AI 60.3 M [f]				2448 2447	AIs (Let) Tam			228 / -- 160 / --	25.2 / 27.1 18.1 / 18.7	HR 1.38 (1.13, 1.69) aHR 1.40 (1.14, 1.71)	Calculated RR 1.42 (1.17, 1.73)	Age, 5, 6, 7, 8, 9, 10

Continued

Study Information						Study participants (safety population)				Treatment		Published fracture outcomes - fracture				Meta-analysis	Factors
ID	Study name Author, year (ref)	Design	Country	Data source	Median follow-up duration	Age (Years) [a]	Post-menopausal (%)	Prior tamoxifen [b] (duration)	No.	Arms	Duration	Type	Participants with fractures No.	Fracture events per 1000 PY	Risk measure (95% CI)	Risk Measure used in meta-analysis (95% CI)	Adjusted
Aromatase inhibitors (AIs) vs. Tamoxifen (reference)																	
25	***BIG 1-98*** Mouridsen, 2009 [260]				71 M				1540 1534	AIs (Let) Tam			--	--	--	--	--
					on Tam/AI (Y1-2)				1540 1534	AIs (Let) Tam			65 / -- 50 / --	--	--	--	--
					on Tam/AI (Y 3-5) [g]				1540 1534	AIs (Let) Tam			90 / -- 67 / --	--	--	--	--
					on Tam/AI (Y 1-5)				1540 1534	AIs (Let) Tam			150 / -- 112 / --	--	--	--	--
26	***BIG 1-98*** Colleoni, 2011 [261]				74 M				2448 2447	AIs (Let) Tam			244 / -- 165 / --	--	--	Calculated RR 1.48 (1.22, 1.79)	--
27	***HOBOE*** Nuzzo, 2012 [262]	RCT	Italy	Self-report	12 M	50 (29-80)	46	N	148 152	AIs (Let) Tam	60 M	Any	0 / 0 0 / 0	--	--	--	--
28	***IES*** Coombes, 2004 [263]	RCT	Multiple, 37	Self-report	30.6 M	64 ± 8	100	Y (2.4 Y)	2305 2329	AIs (Exe) Tam	2-3 Y	Any	72 / -- 53 / --	--	--	Calculated RR 1.37 (0.97, 1.95)	--
29	***IES*** Coleman, 2007 [264]				58 M				2320 2338	AIs (Exe) Tam			162 / 188 115 / 143	17.6 / 20.1 13.2 / 16.0	OR 1.45 (1.13-1.87)	Calculated RR 1.42 (1.13, 1.79)	--
30	***IES*** Bliss, 2012 [265]; Clomean, 2010 [158]				91 M				2319 2338	AIs (Exe) Tam			249 / 280 190 / 214	--	OR [h] 1.36 (1.04, 1.76)	Calculated RR 1.32 (1.10, 1.58)	--
					On Tam/AI				2319 2338	AIs (Exe) Tam			113 / 117 86 / 83	-- / 21 -- / 12.3	OR [h] 1.39 (0.94, 2.06) HR [h] 1.39 (0.96, 2.01)	Calculated RR 1.37 (1.04, 1.81)	--
					Post Tam/AI				2105 2036	AIs (Exe) Tam			144 / 163 117 / 128	-- / 20.3 -- / 20.6	OR [h] 1.20 (0.86, 1.69) HR [h] 1.20 (0.89, 1.63)	Calculated RR 1.19 (0.94, 1.51)	--
31	***ITA*** Boccardo. 2005 [266]	RCT	Italy	Self-report	36 M	63 (38-77)	100	Y (28 M)	223 225	AIs (Ana) Tam	2-3 Y	Any	2 / -- 2 / --	--	--	Calculated RR 1.01 (0.14, 7.10)	--
32	***ITA*** Boccardo, 2013 [267]				128 M				223 225	AIs (Ana) Tam		Hospital events,	4 / -- 4 / --	--	--	Calculated RR 1.01 (0.26, 3.98)	--
33	***N-SAS BC03*** Aihara, 2010 [268]	RCT	Japan	Self-report	42 M	60 ± 7	100	Y (1-4 Y)	347 349	AIs (Ana) Tam	1-4 Y	Any	5 / -- 9 / --	--	--	Calculated RR 0.56 (0.19, 1.65)	--

Continued

Study Information						Study participants (safety population)				Treatment		Published fracture outcomes - fracture				Meta-analysis	Factors
ID	Study name Author, year (ref)	Design	Country	Data source	Median follow-up duration	Age (Years) [a]	Post-menopausal (%)	Prior tamoxifen [b] (duration)	No.	Arms	Duration	Type	Participants with fractures No.	Fracture events per 1000 PY	Risk measure (95% CI)	Risk Measure used in meta-analysis (95% CI)	Adjusted
Aromatase inhibitors (AIs) vs. Tamoxifen (reference)																	
34	***TEXT / SOFT (IBCSG)*** Pagani, 2014 [233]	RCT	Multiple	Self-report	68 M	43 ± NR	0	N	2318 2325	AIs (Exe) Tam	60 M	Any	158 / -- 120 / --	--	--	--	--
Multiple treatment arms																	
35	Ligibel, 2012 [269]	Cohort	US	Data linkage	30 M	67 ± NR	<100 [c]	N	Total 44,026	Tam Control	--	Any	--	26.8 / -- 38.1 / --	aHR 0.93 (0.82-1.06)	Published aHR 0.93 (0.82-1.06)	Age, 1, 2, 3, 11, 12, 13, 14, 15
									Total 44,026	AIs Control				33.3 / -- 38.1 / --	aHR 1.13 (1.02-1.25)	Published aHR 1.13 (1.02-1.25)	
									Total 44,026	AIs Tam				33.3 / -- 26.8 / --		--	
36	Robinson, 2014 [270]	Cohort	Australia	Self-report	Mean 5.7 Y	57 (27-87)	35	N	393 252	Tam Control	--	Minimal trauma	56 / -- 30 / --	--	--	Calculated RR 1.20 (0.79-1.81)	--
									306 252	AIs Control			46 / -- 30 / --		OR 1.31 (0.80, 2.14)	Calculated RR 1.26 (0.82-1.94)	--
									306 393	AIs Tam			46 / -- 56 / --			Calculated RR 1.05 (0.74, 1.51)	--
37	Xu, 2014 [271]	Cohort	China	Self-report	32.5 M	56 ± 8 61 ± 9	76-88	N	52 89	Tam Control	--	Any	1 / -- 1 / --	--	aHR 2.64 (0.14, 48.73)	Published aHR 2.64 (0.14, 48.73)	10, 16, 17
						61 ± 7 61 ± 9			70 89	AIs Control			9 / -- 1 / --		aHR 20.08 (1.7, 234.1)	Published aHR 20.08 (1.7, 234.1)	
						61 ± 7 56 ± 8			70 52	AIs Tam			9 / -- 1 / --		--	Calculated RR 6.69 (0.87, 51.14)	

[a] Mean ± SD or median (range)

[b] Tamoxifen treatment prior to the study

[c] Menopausal status was determined based on age range

[d] Information of fracture outcome was collected for 1.1 years after unblinding on October 2003

[e] 1579 participants crossed over from placebo group after unblinding

[f] Fracture data obtained from participants on medications only

[g] 25.2% crossover

[h] 99% confidence intervals

Abbreviations: *aHR* adjusted hazard ratio, *AIs* Aromatase inhibitors, *Ana* anatrozole, *CI* confidence interval, *Exe* Exemestane, *HR* hazard ratio, *IRR* incidence ratio, *Let* letrozole, *M* month, *No* number, *NR* not recorded, *OR* odds ratio, *pre-m* pre-menopausal, *post-m* post-menopausal, *ref* reference, *RCT* randomized controlled trail, *RR* risk ratio, *SD* Standardized deviation, T*am* Tamoxifen, *Y* year,

Study abbreviations: *ABCSG* Austrian Breast & Colorectal Cancer Study Group, *ARNO* Arimidex-Nolvadex, *ATAC* Arimidex, Tamoxifen, Alone or in Combination, *BIG* Breast International Group, *HOBOE* Hormonal Bone Effects, *IES* Intergroup Exemestane Study, *ITA* Italian Tamoxifen Anastrozole, *NSABP* National Surgical Adjuvant Breast and Bowel Project, *SOFT* Suppression of Ovarian Function Trial, *TEXT* Tamoxifen and Exemestane

Adjusted factor: 1 Charlson comorbidity index, 2 residential regions, 3 health plan, 4 income, 5 body mass index, 6 smoking, 7 osteoporosis, 8 fracture history, 9 hormonal replacement therapy, 10 bisphosphonates, 11 index year, 12 urban/rural status, 13 drug class, 14 education, 15 % of black, 16 age of diagnosis, 17 age of menopause

4.3.2 Study quality assessment

Study quality assessment was summarized in Table 4-2 and Table 4-3. High risk of bias was observed primarily in domains of blinding of participants, blinding of outcome assessors, incomplete data, and other biases (e.g. funding) among RCTs. Unblinding of participants and their outcome assessment was observed in at least half of the RCTs that were either open RCTs or unblinded during their study periods. Financial support from pharmaceutical companies was noted in at least 80% of the RCTs. High percentages of incomplete data were observed in studies with longer follow-up durations. The quality of all cohort studies was consistently high with either seven or nine out of a maximum of nine stars.

Table 4-2 Summary of risk of bias assessment for the included randomized controlled trials

A Random sequence generation (selection bias)
B Allocation concealment (selecitn bias)
C Blinding of participants and personnel (performance bias)
D Blinding of outcome asessment (detection bias)
E Incomplete outcome data (attrition bias)
F Selective reporting (reporting bias)
G Other bias

Low risk of bias
Unknown risk of bias
High risk of bias

Table 4-3 Summary of Newcastle-Ottawa Scale assessment for the included cohort studies

Study	Selection (maximum 4 stars)				Comparability (maximum 2 stars)	Outcome (maximum 3 stars)			Total score (out of 9)
	1	2	3	4	5	6	7	8	
Xu, 2014	--	★	★	★	★★	--	★	★	7
Robinson, 2014	★	★	--	★	★★	--	★	★	7
Koopal, 2015	★	★	★	★	--	★	★	★	7
Mincey, 2006	★	★	★	★	★★	★	★	★	9
Ligibel, 2012	★	★	★	★	★★	★	★	★	9

MAX Maximum
1. Representativeness of exposed cohort
2. Selection of non-exposed cohort
3. Ascertainment of exposure
4. Outcome not present at start of study
5. Comparability of cohorts on the basis of the design or analysis
6. Assessment of outcome
7. Was follow-up long enough for outcomes to occur
8. Adequacy of follow up of cohort

4.3.3 Tamoxifen

Three RCTs and three cohort studies compared fracture outcomes between women treated and not treated with tamoxifen (Table 4-4 and Figure 4-2). One RCT with double-zero events was excluded from this meta-analysis. This analysis included 37,783 participants. Fracture risk did not differ between tamoxifen and no-tamoxifen groups (pooled RR=0.95, 95% CI=0.84 to 1.07). The statistical heterogeneity was low with an I^2 measure of 0% (p=0.72). No statistical significance was reported in subgroup analyses by menopausal status (p=0.65), prior tamoxifen treatment (p=0.74) or study design (p=0.58).

4.3.4 Aromatase inhibitors

Three RCTs and four cohort studies compared fracture outcomes between women treated and not treated with AIs. All seven studies were included in this meta-analysis (Table 4-4, Figure 4-3). Data from the longest follow-up durations were selected for the two included studies (ID 6, 9).

This analysis included 59,258 participants. A 17% (95% CI =1.07 to 1.28) higher fracture risk was observed in the AI group than the no-AI group. Statistical heterogeneity was low with an I^2 measure of 8% (p=0.37). No statistical significance was noted in subgroup analyses by menopausal status (p=0.88), prior tamoxifen treatment (p=0.99), study design (p=0.88), AI treatment duration (p=0.57), or AI drug (p=0.93). Sensitivity analyses excluding the Xu *et.al.* study (ID 37) resulted in a similar estimate of 16% RR increase with a zero I^2 measure across all analyses.

4.3.5 Comparison of aromatase inhibitors and tamoxifen

Ten RCTs and four cohort studies compared fracture outcomes between women treated with AIs and treated with tamoxifen (Table 4-4, Figure 4-4). Four studies (ID 12, 27, 34, 35) were excluded due to either missing data, double-zero events, or reporting combined data from more than one independent study. Data from the longest follow-up duration was selected for the five included studies (ID 14, 18, 26, 30, 32). This analysis included 20,403 participants. A 35% (95% CI=1.21 to 1.51) higher fracture risk was observed in the AI group compared with the tamoxifen group. The statistical heterogeneity was low with an I^2 measure of 12% (p=0.43). No statistical significance was observed in subgroup analysis by menopausal status (p=0.75), prior tamoxifen treatment (p=0.5), study design (p=0.68), AI drug (p=0.83), or AI treatment duration (p=0.19) (Table 4-4). Sensitivity analyses excluding the Xu *et.al.* study (ID 37) resulted in a similar estimate of 36% RR increase with a low I^2 measure (range 0-7) across all analyses.

Table 4-4 Meta-analysis including subgroup analysis of aromatase inhibitors, tamoxifen, and control groups on fractures

Treatment arms	Study (N)	Participant (N)	Pooled RR (95%CI)	*p* for effect	I^2 (%) [a]	*p* for subgroup differences	ID of article included
Tam vs. control (no-Tam) [b]							
Total effect	5	37,783	0.95 (0.84, 1.07)	0.39	0	0	2, 3, 35, 36, 37
Subgroup analysis							
Menopausal status						0.65	
Pre-menopausal	0		--	--	--		--
Pre- / post-menopausal	4		0.95 (0.84, 1.08)	0.42	0		3, 35, 36, 367
Post-menopausal	1		0.75 (0.27, 2.05)	0.57	--		2
Prior tamoxifen treatment						0.74	
No	4		0.95 (0.84, 1.07)	0.41	0		2, 35, 36, 37
Yes	1		0.81 (0.32, 2.05)	0.66	--		3
Study design						0.58	
RCT	2		0.78 (0.40, 1.55)	0.48	0		2, 3
Cohort	3		0.95 (0.84, 1.08)	0.45	0		35, 36, 37
AIs vs. control (no-AIs) [b]							
Total effect	7	59,258	***1.17 (1.07, 1.28)***	***<0.01***	8		4, 6, 9, 10, 35, 36, 37
Subgroup analysis							
Menopausal status						0.88	
Pre-menopausal	0		--	--	--		--
Pre- / post-menopausal	4		***1.19 (1.01, 1.41)***	***0.04***	49		4, 35, 36, 37
Post-menopausal	3		1.17 (0.97, 1.41)	0.10	0		6, 9, 10
Prior tamoxifen treatment						0.99	
No	5		***1.18 (1.02, 1.37)***	***0.03***	35		4, 9, 35, 36, 37
Yes	2		***1.18 (0.97. 1.42)***	***0.09***	0		6, 10
Study design						0.88	
RCT	3		1.17 (0.97. 1.41)	0.10	0		6, 9, 10
Cohort	4		***1.19 (1.01, 1.41)***	***0.04***	49		4, 35, 36, 37
AI treatment duration						0.57	
≤48 months	2		1.18 (0.97, 1.42)	0.09	0		6, 10
60 months	1		0.81 (0.23, 2.90)	0.75	--		9

Continued

Treatment arms	Study (N)	Participant (N)	Pooled RR (95% CI)	*p* for effect	I^2 (%) [a]	*p* for subgroup differences	ID of article included
AIs vs. control (no-AIs) [b]							
AI drug						0.93	
Non-steroidal (letrozole and anastrozole)	1		1.15 (0.94, 1.41)	0.16	--		6
Steroidal (exemestane)	2		1.27 (0.76, 2.14)	0.36	0		9, 10
Any AI	4		***1.19 (1.01, 1.41)***	***0.04***	49		35, 36, 37
AIs vs. Tam [b]							
Total effect	9	20,403	***1.35 (1.21, 1.51)***	***<0.01***	12		14, 15, 18, 26, 30, 32, 33, 36, 37
Subgroup analysis							
Menopausal status						0.75	
Pre-menopausal	1		1.08 (0.5, 2.35)	0.85	--		14
Pre- / post-menopausal	2		2.00 (0.36, 11.21)	0.43	67		36, 37
Post-menopausal	6		***1.39 (1.26, 1.54)***	***<0.01***	0		15, 18, 26, 30, 32, 33
Prior tamoxifen treatment						0.5	
No	5		***1.38 (1.18, 1.62)***	***<0.01***	27		13, 18, 26, 36, 37
Yes	4		***1.27 (1.07, 1.51)***	***<0.01***	0		15, 30, 32, 33
Study design						0.68	
RCT	7		***1.39 (1.26, 1.53)***	***<0.01***	0		14, 15, 18, 26, 30, 32, 33
Cohort	2		2.00 (0.36, 11.21)	0.43	67		36, 37
AI treatment duration						0.19	
≤48 months	5		***1.26 (1.07, 1.50)***	***<0.01***	0		14, 15, 30, 32, 33
60 months	2		***1.45 (1.29, 1.64)***	***<0.01***	0		18, 26
AI drug						0.76	
Non-steroidal (letrozole and anastrozole)	6		***1.41 (1.26, 1.59)***	***<0.01***	0		14, 15, 18, 26, 32, 33
Steroidal (exemestane)	1		***1.32 (1.10, 1.58)***	***<0.01***	--		30
Any AI	2		2.00 (0.36, 11.21)	0.43	67		36, 37

Values in bold and italic indicate statistical significance

Tam tamoxifen, *AI* aromatase inhibitor, *RR* risk ratio

[a] For heterogeneity

[b] Reference group

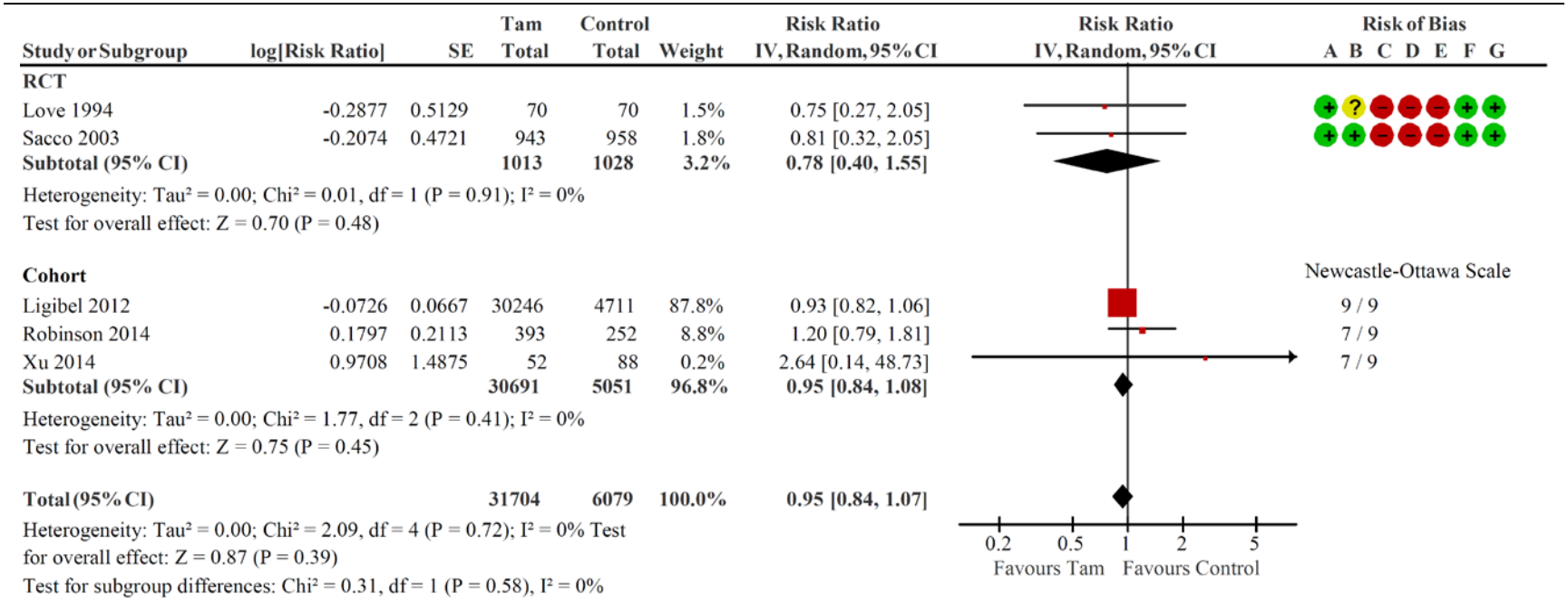


Figure 4-2 Forest plot of comparison for fracture risk between women treated with tamoxifen and not treated with tamoxifen (control) by study design subgroups

Tam tamoxifen, *IV* inverse variance, *CI* confidence interval, *SE* standard error, *RCT* randomized controlled trial

The large diamond at the bottle of the table represents the pooled risk ratio of all studies. The width of the diamond represents with 95% CI. Results of study quality assessment were included.

Risk of bias: A Random sequence generation (selection bias), B Allocation concealment (selecitn bias), C Blinding of participants and personnel (performance bias), D Blinding of outcome asessment (detection bias), E Incomplete outcome data (attrition bias), F Selective reporting (reporting bias), G Other bias

+ Low risk of bias ? Unknown risk of bias − High risk of bias

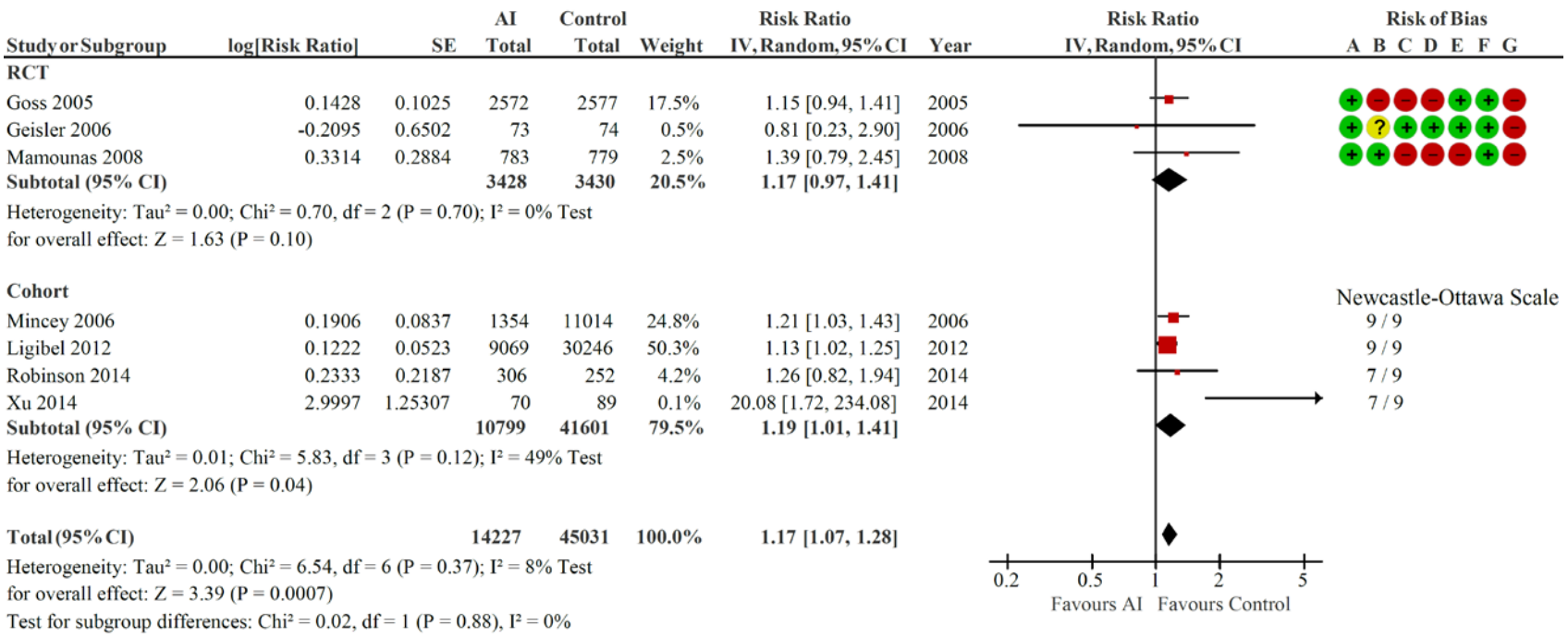


Figure 4-3 Forest plot of comparison for fracture risk between women treated with AIs and not treated with AIs (control) by study design subgroups

AI aromatase inhibitor, *IV* inverse variance, *CI* confidence intervals, *SE* standard error, *RCT* randomized controlled trial

The large diamond at the bottle of the table represents the pooled risk ratio of all studies. The width of the diamond represents with 95% CI. Results of study quality assessment were included.

Risk of bias: A Random sequence generation (selection bias), B Allocation concealment (selecitn bias), C Blinding of participants and personnel (performance bias), D Blinding of outcome asessment (detection bias), E Incomplete outcome data (attrition bias), F Selective reporting (reporting bias), G Other bias

+ Low risk of bias ? Unknown risk of bias − High risk of bias

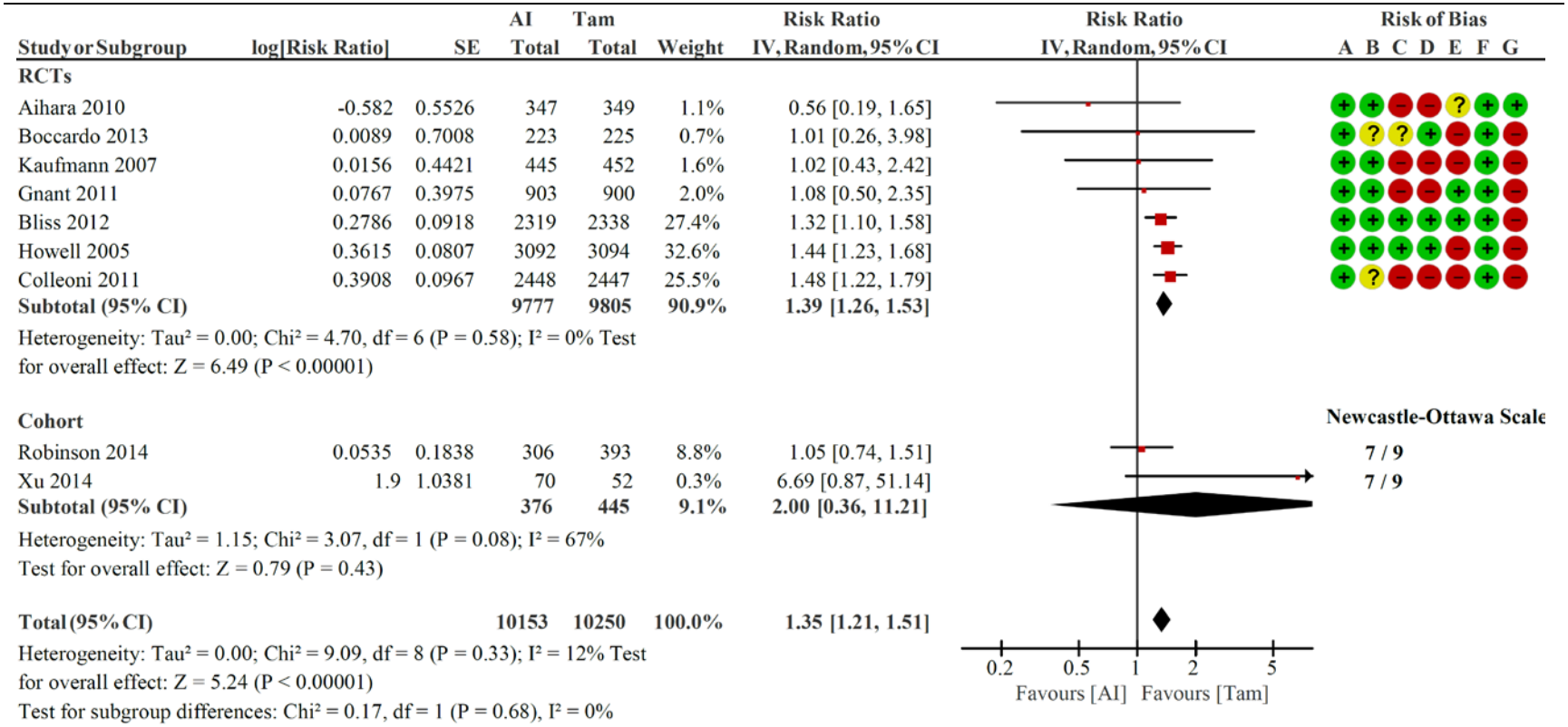


Figure 4-4 Forest plot of comparison for fracture risk between women treated with AIs and treated with tamoxifen by study design subgroups

AI aromatase inhibitor, *Tam* tamoxifen, *IV* inverse variance, *CI* confidence intervals, *SE* standard error, *RCT* randomized controlled trial

The large diamond at the bottle of the table represents the pooled risk ratio of all studies. The width of the diamond represents with 95% CI. Results of study quality assessment were included.

Risk of bias: A Random sequence generation (selection bias), B Allocation concealment (selecitn bias), C Blinding of participants and personnel (performance bias), D Blinding of outcome asessment (detection bias), E Incomplete outcome data (attrition bias), F Selective reporting (reporting bias), G Other bias

+ Low risk of bias ? Unknown risk of bias − High risk of bias

4.3.6 Comparison of aromatase inhibitors and tamoxifen – time effect

Twenty articles from ten independent studies were included for these meta-analyses (Table 4-5, Figure 4-5, Figure 4-6). Compared with the tamoxifen group, increased AI-associated fracture risk showed a downward trend from 47% (pooled RR=1.47, 95% CI=1.28 to 1.68) to 32% (pooled RR=1.32, 95% CI=1.1 to 1.57) when the range of follow-up duration increased from 12-36 months to > 84 months. Compared with the tamoxifen group, AI-associated fracture risk increased by 33% (pooled RR=1.33, 95% CI=1.21 to 1.47) during the Tam/AI treatment period, but did not increase (pooled RR=0.99; 95% CI=0.72 to 1.37) during the post-Tam/AI treatment period. Sensitivity analysis excluding the Koopal *et. al.* study (ID 11) resulted in a similar RR estimate (pooled RR=1.09, 95% CI=0.92 to 1.31) with a reduction of I^2 measure by 56% for the post-Tam/AI treatment period.

Table 4-5 Meta-analysis of aromatase inhibitors and tamoxifen on fractures at different ranges of follow-up duration and treatment phases

	Study (N)	**Participant (N)**	**Pooled RR (95% CI)**	***p* for effect**	**I^2 (%) [a]**	**ID of included articles**
Aromatase inhibitors (AIs) vs. Tamoxifen [b]						
Range of follow-up duration (months)						
12-36	6	20,250	1.47 (1.28, 1.68)	<0.01	0	15, 16, 21, 28, 31, 37
> 36-60	5	18,237	1.46 (1.27, 1.68)	<0.01	15	13, 17, 23, 29, 33
> 60-84	4	13,583	1.39 (1.23, 1.57)	<0.01	7	14, 18, 26, 36
> 84	2	5,105	1.32 (1.10, 1.57)	<0.01	0	30, 32
Treatment period						
Tam/AI treatment	3	13,917	1.33 (1.21, 1.47)	<0.01	0	20, 25, 30
Post-Tam/AI treatment	3	8,741	0.99 (0.72, 1.37)	0.96	60	11, 20, 30

[a] For heterogeneity
[b] Reference group

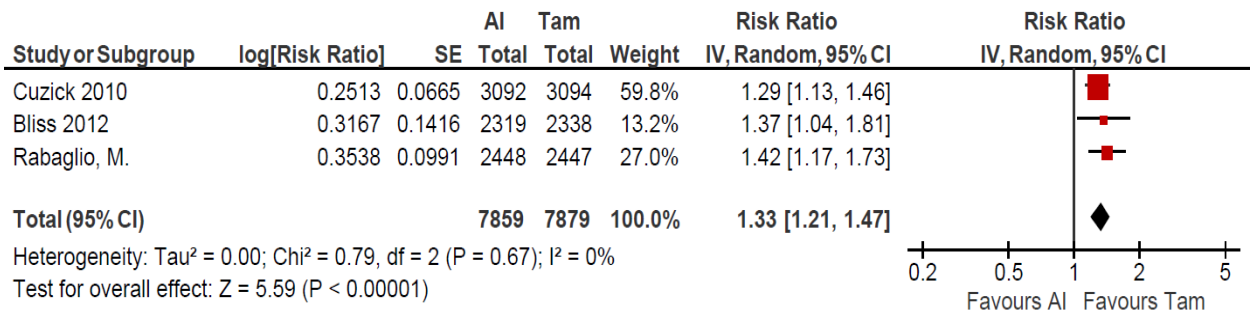


Figure 4-5 Forest plot of comparison for fracture risk between women treated with aromatase inhibitors and tamoxifen (during treatment period)

Tam tamoxifen, *IV* inverse variance, *CI* confidence interval, *SE* standard error, *RCT* randomized controlled trial
The large diamond at the bottle of the table represents the pooled risk ratio of all studies. The width of the diamond represents with 95% CI. Results of study quality assessment were included.

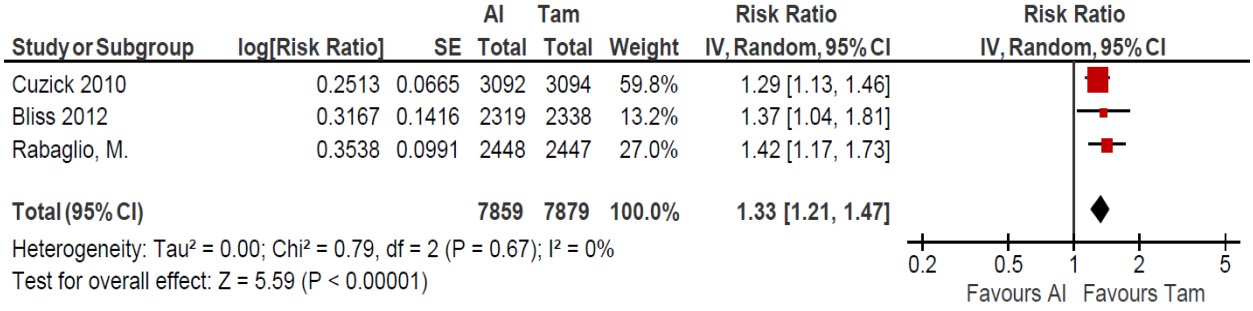


Figure 4-6 Forest plot of comparison for fracture risk between women treated with aromatase inhibitors and tamoxifen (during treatment period)

Tam tamoxifen, *IV* inverse variance, *CI* confidence interval, *SE* standard error, *RCT* randomized controlled trial
The large diamond at the bottle of the table represents the pooled risk ratio of all studies. The width of the diamond represents with 95% CI. Results of study quality assessment were included.

4.4 Discussion

Osteoporosis is a significant global health issue. Osteoporotic fractures are associated with excessive mortality, impaired physical function, and more long term nursing home stays [204-206]. The impact of osteoporosis is higher on women diagnosed with breast cancer than women without breast cancer. Most adjuvant systemic breast cancer treatments result in faster bone loss and a consequential higher fracture rate in women diagnosed with breast cancer [147, 174]. The study data showed that fracture risk did not differ between women treated and not treated with tamoxifen. AI-associated fracture risk was 17% and 35% higher than the risks in the no-AI group and tamoxifen group respectively. Compared with the tamoxifen group, increased AI-associated fracture risk trended down when the range of follow-up duration increased. AI-associated fracture risk increased by 30% during the Tam/AI treatment period but did not increase during the post-Tam/AI treatment period when compared with the tamoxifen group.

4.4.1 Tamoxifen

Our results showed that fracture risk did not differ between the tamoxifen and no-tamoxifen groups. This finding is consistent with the fact that tamoxifen has no effect on reducing vertebral or hip fractures in general populations [141, 164]. By contrast, tamoxifen treatment for one-year increased the risk of trochanteric fractures (HR=2.12, 95% CI=1.12 to 4.01) among 1,716 post-menopausal women with non-metastatic breast cancer during the 12-year follow-up in the Danish Breast Cancer Cooperative Group (DBCG) trial [272]. While evidence shows that tamoxifen may preserve BMD, tamoxifen has not been approved for the treatment or prevention of osteoporosis in any population by the US Food and Drug Administration. Women, who

receive tamoxifen breast cancer treatment, should still receive BMD testing recommended for women diagnosed with breast cancer.

Our results showed that menopausal status did not affect fracture risk between women treated and not treated with tamoxifen. However, 80% of articles included in our analysis involved a mixture of pre- and post-menopausal women. There was only one article available for the post-menopausal subgroup and none for the pre-menopausal subgroups.

4.4.2 Aromatase inhibitors

AIs are more effective than tamoxifen (Tam) at reducing mortality, reducing cancer recurrences, and prolonging disease-free survival [273, 274]. AIs are given alone for 5 years to patients at higher cancer relapse risk, or in sequence for 2-3 years before or after tamoxifen (sequential AI-Tam or sequential Tam-AI) for patients at lower cancer relapse risk [275]. Sequential treatments, compared with either tamoxifen or AIs alone, reduce the exposure times of both tamoxifen and AIs, which may reduce the long-term side effects associated with either tamoxifen or AIs, such as fracture risk.

Our analysis showed that AI-associated fracture risk increased by 17 and 35% when compared with the no-AI and tamoxifen groups respectively. This finding is consistent with higher fracture risks observed in major trials with an AI intervention.

When comparing AI with tamoxifen groups, differential fracture risks were higher without a statistical difference in the prior tamoxifen treatment subgroup (pooled RR=1.38, 95% CI=1.18

to 1.62) than the no prior tamoxifen treatment subgroup (pooled RR=1.27, 95% CI=1.07 to 1.51). This might be because prior tamoxifen treatment may reduce AI-associated fracture risk. Or it may be because follow-up time was longer in the prior tamoxifen subgroup (30-128 months) than the no prior tamoxifen subgroup (32-74 months), and fracture risk decreased when follow-up duration increased.

We did not include or compare fracture risk between sequential AI-Tam and sequential Tam-AI treatments in this study due to limited available data. However, the BIG-98 trial showed sequential AI-Tam treatment reducing fracture risk by 22% (calculated RR=0.78, 95% CI=0.62 to 0.99) compared with the sequential Tam-AI treatment in approximately 3,000 participants during the 45-month follow-up [260].

Longer AI treatment duration did not affect fracture risk in our study, but increased fracture risk by 47% in the Amir *et. al. study* in 2011 [276]. This could be explained primary by different data synthesis methods. Our study evaluated the effect of AI treatment duration on differential fracture risk between AIs and tamoxifen. The Amir *el. al*. study evaluated differential fracture risk of AI treatment duration [276].

A steroid AI (exemestane) with irreversible binding properties may affect bone health differently than non-steroidal AIs (letrozole and anastrozole) with reversible binding properties [277]. Our results showed no difference between steroidal and non-steroidal AI subgroups when evaluating differential fracture risks of AIs, and between AIs and tamoxifen. This finding is consistent with findings from two other major trials; a bone sub-study of the Tamoxifen Exemestane Adjuvant

Multinational (TEAM) in Japan [278] and MA.27 [279] comparing non-steroidal anastrozole with steroidal exemestane.

Management of AI-associated bone loss is inconsistent to screen for bone loss. A baseline BMD test before initiating AI treatment and follow-up BMD tests at one- to three-year intervals have been suggested [97, 280]. However, an optimal interval for serial BMD testing remains uncertain. Is a shorter screening interval, such as annually, more helpful in identifying women at high fracture risk associated with AIs? Current risk assessment tools, such as the World Health Organization Fracture Risk Assessment tool, do not take AI-associated fracture risk into consideration, which can lead to underestimated fracture risk for women diagnosed with breast cancer and treated with AIs. Should AIs be considered for any fracture risk assessment tool?

4.4.3 Aromatase inhibitors vs. tamoxifen, time effect

While extracting and synthesizing data, we noted that fracture risk was not consistent over time. The RR decreased from 1.60 to 1.44 when the follow-up duration increased from 42 to 68 months in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [252, 253]. The IRRs decreased significantly from 1.55 during the Tam/AI treatment period to 1.03 during the post-tam/AI treatment period in The ATAC trial [255]. In response to this we evaluated the time effect on fracture risk by conducting four individual meta-analyses for four ranges of follow-up duration (12-36, >36-60, >60-84, and >84 months) and two individual meta-analyses for Tam/AI treatment and post-Tam/AI treatment periods.

Our results showed that the increased AI-associated fracture risk decreased from 47% (95% CI=1.28 to 1.68) to 32% (95% CI=1.10 to 1.57), when compared with the tamoxifen group and the range of follow-up duration increased from 12-36 to > 85 months. AI-associated fracture risk increased by 33% (95% CI=1.21 to 1.47) during the Tam/AI treatment period but did not increase during the post-Tam/AI treatment period, when compared with tamoxifen. These two findings were consistent as fracture risk decreased over time when more participants entered their post-Tam/AI treatment periods. However, it remains unclear what caused the differences in fracture risks between the treatment and post-treatment periods. It may be due to the independent effect of AI on fracture risk, the independent effect of tamoxifen on fracture risk or both effects combined. The fracture incidence rates (per 1,000 person-years) in the AI group decreased significantly from 29.3 (95% CI=26.5 to 32.4) during the treatment period to 15.6 (95% CI=13.2 to 18.3) during the post-treatment period while rates in the tamoxifen group were stable (treatment period: 19.0, 95% CI=16.7 to 21.5; post-treatment period: 15.1, 95% CI=12.8 to 17.8) in the ATAC trial (ID 19). Contrasting this, the fracture incidence rates (per 1,000 person-years) in the AI group were stable during both treatment period (21.0, 95% CI=14.5 to 27.5) and post-treatment period (20.3, 95% CI=13.7 to 26.9), while rates in the tamoxifen group increased from 12.3 (95% CI=7.3 to 17.3) during the treatment period to 20.6 (95% CI=13.8 to 27.4) during the post- treatment period in the Intergroup Exemestane Study (IES) [158, 170].

4.4.4 Study methodology

Similar estimates between RCTs and cohort subgroups were observed for fracture risk in our study and for effects of other non-cancer drugs in other studies [281, 282]. This is likely because both RCTs and cohort studies included in this study had large participant populations, sufficient

follow-up time, and low risk of bias [283]. Most included cohort studies reported relative measures adjusted for confounders, which further reduced selection bias. While at least 50% of included RCTs were unblinded to outcome assessment, this had a minimal effect on assessing objective outcomes including fractures.

Risk differences, defined as differences in proportions of participants with fractures, between two treatments were not analyzed in this study due to significant variation in fracture rates (10 times), heterogeneous participant groups, and baseline risk between studies. Number needed to treat, the average number of participants who need to be treated to prevent one fracture, was not estimated for the same reason.

All selected RCTs and cohort studies in this study reported relative measures as ORs, HRs or IRRs. RRs were selected to estimate effect sizes for several reasons. RRs are more appropriate measures and easier to interpret than ORs. ORs could exaggerate effect sizes, especially for common events or being misinterpreted as RRs [284, 285]. RRs were favored over HRs and IRRs as RRs could be recalculated for almost all included articles except one. HRs were not re-calculable at aggregate data level. IRRs could be recalculated while incidence rates were only available from one-third of the included articles. Published aHRs instead of calculated RRs were selected from three included cohort studies (ID 4, 35, 36) for our meta-analysis. This was because adjusted ratios provide a better effect size estimate with less bias, when compared with unadjusted ratios. Both RRs and aHRs were pooled using a generic inverse variance method.

A generic inverse variance method with random effects model was selected in this study to account for different risk measures and heterogeneity across the included studies. The generic inverse variance method is able to pool different relative measures when only ratios with CIs were available. Although we chose random effects models in this study, statistical heterogeneity was low (<15%) in the majority of our analyses except the analysis for post-Tam/AI treatment period and some subgroup analyses. Effect sizes were almost identical using either random or fixed effects models based on our internal analysis.

Heterogeneity is inevitable in meta-analysis. Clinical heterogeneity involving study participant, treatment, and outcome was evaluated by reviewing study methods and assessing clinical relevance. Methodological heterogeneity involving study design and risk of bias was evaluated using Cochrane's *Q* statistic and qualified as I^2 measures. I^2 measures (%) indicate proportions of variability across studies. Mild to moderate statistical heterogeneity (27-67%) was noted in our meta-analyses. This statistical heterogeneity decreased significantly to 0-7% after excluding the Xu *et. al.* study (ID 37) or the Koopal *et. al.* study (ID 11). This statistical heterogeneity associated with the Xu *et. al*. study and the Koopal *et. al.* study could be explained primarily by uncontrolled confounders due to a lack of reported adjusted relative measures.

There was clinical heterogeneity in age of diagnosis, age of menopause, and proportion bisphosphonate usage especially in the Xu *et. al* study (ID 37). Age at cancer diagnosis was four years younger in the tamoxifen group than the AI and control treatment groups. Proportions of participants on bisphosphonates was 18% in the AIs group but <1% in the control and tamoxifen groups. Other differences in the Xu *et. al.* study, compared with the most of the included studies

in this review, were setting (one hospital vs. national / multi-national), sample size (211 vs. 2000-44,000), and ethnicity (Chinese vs. Caucasians).

While distributions in characteristics in each treatment group were missing in the Koopal *et. al.* study, there were significant variations between the pre-menopausal and post-menopausal groups in average age of cessation of hormonal treatments (52 vs.72), follow-up time (2.5 vs. 3.4 years), proportion of chemotherapy (88 vs. 20%), and proportion of bisphosphonate usage (36% vs. 24%). These significant variations were likely to confound fracture risk estimates. Other differences in the Koopal *et. al*. study, compared with most selected studies in this review, were setting (one medical center vs. national/multi-national) and sample size (300 vs. 2000-44,000).

High risk of bias was noted in open or unblinded RCTs, which accounted for at least 50% of the selected RCTs, and could impact outcome assessment. Unblinding to outcome assessment is likely to affect subjective outcomes including pain and fatigue, but not objective outcomes like fractures. The high risk of bias associated in open or unblinded RCTs has minimal effects on our findings.

The numbers of study participants were identical or the same across serial follow-up articles of each independent study with the exception of the Breast International Group (BIG) 1-98 trial. This was primarily associated with its protocol involving two-arm and four-arm options (Figure 4-7 There were 1,835 participants recruited for the two-arm option (tamoxifen and AIs) in 1998-2000 and 6,193 participants recruited for the four-arm option (tamoxifen only, AIs only, sequential tamoxifen-AI, and sequential AI-tamoxifen) in 1999-2003. The first article (ID 21)

published in 2005, included participants from all six arms including sequential treatment groups still on their first treatments only. The participants receiving sequential treatments were excluded in the following four articles (ID 22, 23, 24, 26). The fifth article (ID 25) published in 2009, only involved participants from the tamoxifen and AI groups of the four-arm option.

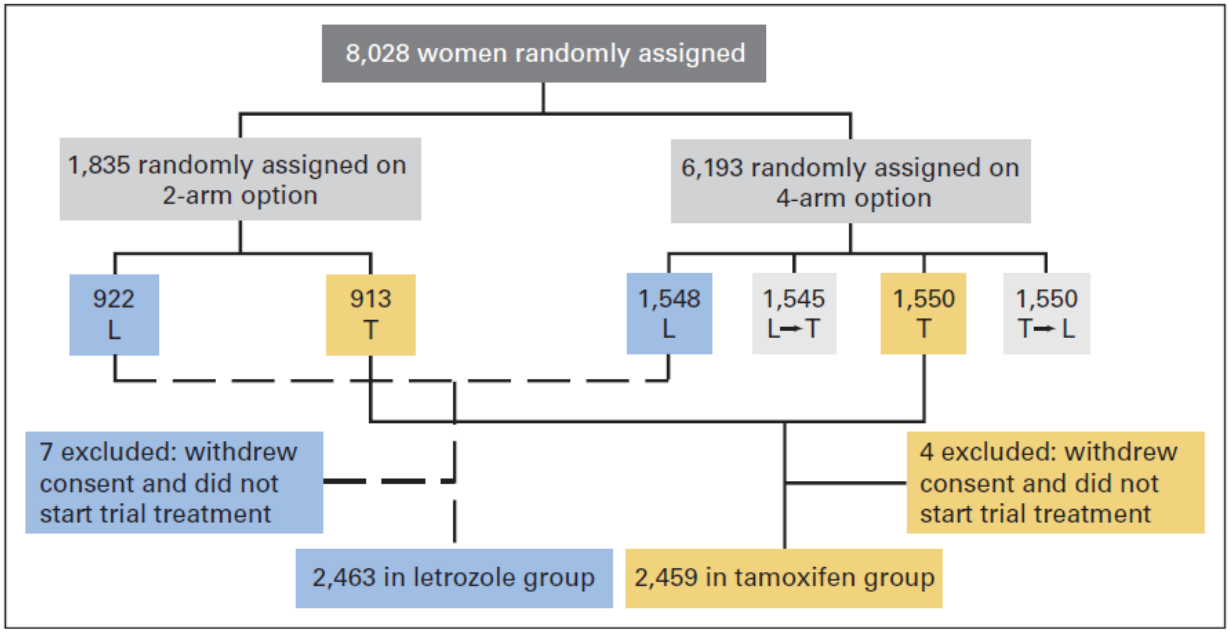


Figure 4-7 Consort diagram of Breast International Group 1-98 trial

Reprinted with permission. *L* letrozole, *T* tamoxifen

4.4.5 Limitation

This review was limited by the relative low numbers of available articles on certain subgroups, especially pre-menopausal groups. When comparing AIs with tamoxifen, fracture risks did not differ among subgroups of pre-menopausal, a mixture of pre- and post-menopausal, and post-menopausal women. Only two included studies (ID 13, 34) involved 100% pre-menopausal women. However, the TEXT/SOFT study (ID 34) was not included in our reported meta-analysis as it reported combined data from two independent studies TEXT and SOFT. An internal

analysis including data from the TEXT/SOFT study was conducted. It resulted in a similar RR estimate with a slightly narrower 95% CI of 1.24 to 1.48.

4.5 Conclusion

Fracture risk is significantly higher in women treated with AIs, especially during the treatment period. While tamoxifen may preserve BMD, tamoxifen is not associated with fracture risk reduction. Women who receive tamoxifen or AI breast cancer treatment should receive BMD tests as recommended for women diagnosed with breast cancer. Optimal osteoporosis management programs, especially during the treatment period, are needed for this group of women.

Chapter 5: Discussion and Conclusion

The primary goal of this thesis is to provide a better understanding of osteoporosis, specifically bone mineral density (BMD) testing and the effects of breast cancer treatments on fracture risk, in women diagnosed with breast cancer. This thesis was developed on two main concepts. First, women diagnosed with breast cancer are at higher fracture risk compared with women without breast cancer. Second, BMD testing is recommended to high risk populations – by age (old women aged ≥65) or risk factors (younger women aged <65 with risk factors; breast cancer treatment is not consistently considered a risk factor for BMD testing eligibility). Studies were designed to understand (1) utilization BMD testing in older women who should receive BMD testing as recommended; and (2) the effects of breast cancer treatments on fracture risk in younger women as these women will only receive BMD testing when risk factors exist.

This thesis is the first study to evaluate BMD testing and pilot-test the effect of patient educational material to improve BMD testing rates at a population level - in women aged ≥65 and diagnosed with breast cancer for three or more years in British Columbia, Canada. This thesis also systematically reviewed the effects of the two most common hormonal treatments, tamoxifen and aromatase inhibitors (AIs), in women aged ≤65 and diagnosed with non-metastatic breast cancer.

5.1 Key Findings

5.1.1 Utilization of bone, mineral density testing among women diagnosed with breast cancer in British Columbia, Canada

The goal of study 1 was to evaluate the trends in proportion of women with at least one BMD per calendar year from 1995 to 2008 and identify factors associated with different BMD testing rates, using a cross-sectional methodology and population based data-linkage in older female breast cancer survivors; namely women aged 65 years and over, and diagnosed with breast cancer for three or more years in British Columbia (BC), Canada.

During the period from 1995 to 2008, the number of survivors almost doubled from 4,974 to 9,662, prevalence of osteoporosis diagnosis increased from 6% to 25.6%, and proportions of women with at least one BMD test increased from 1.0% to 10.1%. The proportions were increasing annually from 1995 to 2005 and became relatively stable from 2005 to 2008.

Associations between socio-demographic, clinical factors, and BMD testing rates over the three-year period 2006-2008 were estimated as adjusted prevalence ratios (aPR) using log-binomial models in 7,625 survivors. Lower SES (aPR=0.66 to 0.78) or rural residency (aPR=0.70) were associated with a 20-30% lower utilization of BMD testing, compared with the highest SES or urban residency respectively. There was a significantly lower likelihood of having a BMD test observed in survivors who were aged 75 years and over (aPR=0.47, 95% CI=0.42 to 0.52), were nursing home residents (aPR=0.05, 95% CI=0.01 to 0.39), had recent osteoporotic fractures (aPR=0.21, 95% CI=0.14 to 0.32), or did not have previous BMD tests (aPR=0.26, 95% CI=0.23 to 0.29).

5.1.2 Promoting bone health management in women diagnosed with breast cancer: a pilot randomized controlled trial

The goal of study 2 was to test a randomized controlled trial (RCT) study protocol designed to (1) improve bone health management, especially BMD testing rates during a six-month follow-up period, with educational material; and (2) assess whether delivery methods (postal mail vs. patient's choice of postal mail, email or smartphone text messaging) of educational material affect bone health management differently in the 54 recruited women aged ≥65 and diagnosed with breast cancer for three or more years in BC, Canada.

The feasibility of the study protocol was evaluated. The recruitment strategy worked well. The response rate, defined as the proportion of women who responded to our invitation, was 77.4%. The participation rate, defined as the proportion of eligible participants who consented to participate, was 39.1%. Representativeness of the recruited group was high based on similar distributions of five factors among the 54 participants, 84 non-participants who declined to participate in this study, and 260 other non-participants. Outcome measures were obtained for at least 90% of the 54 participants. No major issues associated with the study protocol were identified.

Although no formal statistical testing was conducted, there was a suggestion of higher BMD testing rates in the groups receiving educational material by mail (26%, 95% CI=10 to 49) and patient choice (18%, 95% CI=5 to 41), compared with the control group (6%, 95% CI=0.3 to 25). BMD testing rate was 17% (95% CI=6 to 33) higher in the groups where educational material was delivered by either postal mail or patient choice compared with the control group.

BMD testing rate was 8.7% (95% CI= -33.9 to 18.9) lower in the patient choice group compared with the postal mail group.

5.1.3 Aromatase inhibitors are associated with a higher fracture risk than tamoxifen: a systematic review and meta-analysis

The objectives of study 3 was to systematically evaluate published evidence of bone fracture risks associated with the two most common adjuvant systemic breast cancer treatments, tamoxifen and aromatase inhibitors (AIs).

A total of 43 articles covering 21 independent studies were included in our evaluation. Fracture risk did not differ between women treated and not treated with tamoxifen (pooled RR=0.95, 95% CI=0.84 to 1.07). AI-associated fracture risk was 17% and 35% higher than the risk in the no-AI (pooled RR=1.17, 95% CI=1.07 to 1.28) and tamoxifen (pooled RR=1.35, 95% CI=1.21 to 1.51) groups respectively. No statistical significance was reported in subgroup analyses by menopausal status, prior tamoxifen treatment, study design, AI drug, or AI treatment duration for comparisons of tamoxifen vs. no-tamoxifen, AIs vs. no-AIs, and AIs vs. tamoxifen. Different time effects on fracture risk were observed when comparing AIs with tamoxifen. Compared with the tamoxifen group, the increased AI-associated fracture risk dropped from 47% to 32% when the range of follow-up duration increased from 12-36 months to >85 months. Compared with the tamoxifen group, AI-associated fracture risk was significantly higher (RR=1.33, 95% CI=1.21 to 1.47) during the treatment period but not (pooled RR=1.09, 95% CI=0.91 to 1.31) during the post-Tam/AI treatment period.

5.2 Strengths and Limitations

5.2.1 Strengths

A major strength of this thesis is that the three study research questions were developed based on the eligibility criteria for BMD testing. Three different study methodologies were then selected based on what was best suited for each of the research questions.

Older women aged 65 and over are eligible for BMD testing regardless of other non-age risk factors. Study 1 provided in-depth knowledge on the utilization of BMD testing in older women diagnosed with breast cancer. Utilization of BMD was well evaluated from 1995 when dual energy X-ray absorptiometry (DXA) became a billable medical service in BC, to 2008 using secondary data-linkage. The advantage of using provincial data include (1) a larger sample size than other studies using non-data-linkage methods; (2) high representativeness of study group with low selection bias; (3) relative low cost as the data has been recorded for administrative purposes; (4) no recall bias that is commonly associated with self-reported data; (5) data was available for more than 10 years which permitted trend analysis. Proportions of women with at least one BMD test were evaluated by calendar year for 13 consecutive years instead of a one-time measurement. This provided a better understanding on how the proportions changed with time in BC. The proportions were stratified by osteoporosis diagnosis as BMD testing is used for osteoporosis screening in women without osteoporosis diagnosis and for treatment effectiveness monitoring in women with osteoporosis. This information was important for health service planning as different strategies are required to improve utilization for each group. Relevant guidelines and historical non-guideline local factors, which might influence the utilization of BMD testing, were integrated into the discussion section. These provided an exhaustive review

and a more complete picture of the utilization of BMD testing over a decade period in BC. The study results showed low BMD testing rates while BMD testing is an important tool to identify women at high fracture risk before fractures occur. This led to the development of study 2.

Study 2 evaluated the feasibility of a study protocol and pilot-tested a potential educational material intervention to improve BMD testing rates with a pilot randomized controlled trial (RCT) design. The pilot study design provided valuable information and identified potential issues before conducting a large-scale study. These findings can be applied to a future study protocol to enhance the likelihood of success in a large-scale study. Potential eligible women for this study were selected from the provincial BC Cancer Agency registry. This allowed me to conduct this population-based study and evaluate participants from throughout the province of BC. This approach is a low-cost technique to reach a large number of women. This easy, relatively inexpensive, centralized approach also supported the potential to develop a province-wide bone health management plan for women diagnosed with breast cancer, similar to other province-wide programs we have, such as the cervical cancer screening program and breast cancer screening program. Educational material was edited specifically for this unique population. A strength of educational material is its ability to promote knowledge and awareness of osteoporosis and osteoporotic fracture, which can lead to permanent lifestyle changes. With the positive effects of educational material on BMD testing, it should be considered for future bone health management. Email and text messaging were available options for delivering educational materials. Surprisingly, almost one-third of study participants preferred receiving educational material by email over traditional postal mail. This suggests a potential willingness to adopt technology for health-related issue in this older women group. Other technologies,

especially ones with easy access and the ability to deliver a large amount of information, to deliver educational material can be considered in the future. These would include online learning models.

Study 3 systematically synthesized differential fracture risks associated with hormonal treatment of tamoxifen and AIs, and risks between tamoxifen and AIs using a meta-analysis methodology. Systematic review and meta-analysis were selected as it can (1) review all published studies using vigorous methodological assessment tools; (2) pool data from multiple high-quality independent studies which increase statistical power of outcome measures; and (3) provide the highest strength of evidence compared with other study types, such as cohort study or randomized controlled trials. The two breast cancer treatments, tamoxifen and AIs, reviewed in this study have a higher impact than other breast cancer treatments. Both are given to almost two-thirds of women diagnosed with breast cancer. Each of these two mediations is the alternative to the other when one is not well tolerated by patients or contraindicated in post-menopausal women. To well evaluate the effects of tamoxifen and AIs on differential fracture risk, three comparison groups were selected: (1) tamoxifen vs. no-tamoxifen (2) AIs vs. no-AI, and (3) tamoxifen vs. AIs. Different studies were included in each comparison which allowed me to cross-examine the effects between tamoxifen and AI. Moreover, the time effects on differential fracture risk between tamoxifen and AIs were evaluated by two time factors – follow-up duration and treatment period. Results were consistent with randomized controlled trial as the fracture risk decreased with time. To be more specific, the differential fracture risk between tamoxifen and AIs became insignificant when treatment discontinued. The study results

are generalizable to all younger women diagnosed with breast cancer and take hormonal treatment, and likely to influence clinical practice guidelines.

5.2.2 Limitations

This thesis was limited by two factors. First, the link between study 1 and study 2 was weak due to a seven-year gap. Study 2 was developed based on the findings from study 1 in 2015 which analyzed data from 1995 to 2008. Second, the phases of cancer care differed between studies. Both study 1, evaluating utilization of BMD testing and study 2, pilot-testing interventions to improve BMD testing rates were conducted in women who have already completed their initial breast cancer treatments (diagnosed with breast cancer for three or more years), while study 3 showed a significantly higher AI-associated fracture risk during the treatment period. This inconsistency in cancer treatment phases came about because study 2 and study 3 were developed concurrently.

Study 1 was significantly limited by the fact that the data was old, and the lack of availability of data on treatment factors that might have affected BMD testing rates. The data was only available till year 2008, which was almost ten years old as of this publication. Results from study 1 may not reflect the current utilization of BMD testing, and therefore may not be as relevant to the development of strategies for current care improvement. While the proportions of women with at least one BMD test per calendar year had been relatively stable from 2005 to 2008, utilization of BMD testing after 2008 may be influenced by several factors. Utilization of BMD testing after 2008 may increase due to the increasing usage of AIs and the increasing awareness of fracture risk associated with systemic adjuvant breast cancer treatments. On the contrary,

utilization of BMD testing after 2008 may decrease due to the increasing use of validated fracture risk assessment tools, such as the Canadian version of the World Health Organization Fracture Risk Assessment Tool released in 2008. Developing study 2 based on the results from study 1 with a seven-year gap weakened the link between study 1 and study 2.

Some important factors that could affect BMD testing utilization or identification of risk groups, such as AI usage and chemo-induced amenorrhea were also not available in the data of study 1. The Breast Cancer Outcome Unit (BCOU) data only includes information on initial hormonal treatments. We were unable to identify women who switched from initial tamoxifen treatment to subsequent AI treatment. The BCOU data records menstrual status at initial diagnosis of breast cancer but not changes in menstrual status after the completion of chemotherapy. Women with chemo-induced amenorrhea were at higher fracture risk but were not identifiable in this study. Five selected non-cancer chronic diseases, osteoporosis and osteoporotic fractures were identified using International Classification of Disease, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes. All codes were commonly used in data-linkage studies. Lack of accurate recording could lead to potential bias due to misclassification [203]. Also, osteoporotic fractures were measured at different time periods for women who had BMD tests (within six-month of a BMD test) or not had BMD tests (three year study period). This could lead to a potential estimation bias. However, the impact would be expected to be low due to the low fracture rate of 6.3%.

Study 2 was subject to potential bias due to low representativeness of the study group and a low overall recruitment rate. The proportion of non-Caucasian participants was less than 5% in our

study compared to the population proportion of 27% in BC [223]. This could be primarily explained by the exclusion of potential participants due to language barriers, as educational material was available in English only. The other potential causes of a non-representative study group are logistical challenges, cultural barriers, and mistrust of research [224]. The overall recruitment rate in this study was only 13% (54/398). However, only three-quarters of the original 398 women were invited to participate in this study. Of all women invited, about one-third were ineligible for this study.

Study 3 was limited by low numbers of studies available for subgroup analyses, such as factors of menopausal status, AI treatment duration and AI drug. No studies reporting 100% pre-menopausal women were available for estimating differential fracture risks of tamoxifen and AIs. Only one study reporting 100% pre-menopausal women was available for estimating different fracture risk between tamoxifen and AIs. Another study involving 100% pre-menopausal women, The Tamoxifen and Exemestane Trial (TEXT)/Suppression Ovarian Functions (SOFT) study (ID 34), was not included in our reported meta-analysis as it reported combined data from two independent studies TEXT and SOFT. Potential bias should be considered when interpreting subgroup analyses with low numbers of studies.

5.3 Conclusion

Increased risk of fractures is reported in women diagnosed with breast cancer and treated with aromatase inhibitors, while screening for osteoporosis with bone mineral density testing is sub-optimal. There is a need for better bone health management programs which should include educational materials.

5.4 Implications, Applications and Future Research

Women diagnosed with breast cancer are at higher risk of osteoporosis and osteoporotic fractures because most adjuvant breast cancer treatments cause estrogen deficiency while estrogen plays a key role in bone heath. Osteoporosis is a major public health issue with significant care gaps while breast cancer is the most common female cancer worldwide. Osteoporosis has a significant impact with more deaths, physical disabilities, and economic burdens [132-134]. The disability burden of osteoporotic fractures is higher than most common cancers with the exception of lung cancer [88]. Costs of hospital care for osteoporotic fractures are higher than for breast cancer, myocardial infarction, and stroke [286]. Osteoporosis has become a more critical issue in women diagnosed with breast cancer than the female general population. A better understanding of bone health management is urgently needed for future care planning, which is the main objective of this thesis.

5.4.1 Older women aged 65 years and over who were diagnosed with breast cancer

In older women (aged 65 years and over) who were diagnosed with breast cancer, BMD tests at one- to three-year intervals are recommended. BMD testing plays a key role in identifying women at higher fracture risk before fractures occur. Study 1 (Chapter Two) showed that utilization of BMD testing remains sub-optimal, especially in women with lower SES or living in rural areas. The proportions of women with at least one BMD test per calendar year were under 15% over the period from 1995 to 2008. This is significantly lower than screening rates for other common chronic diseases, such as diabetes (73-80%) or cholesterol (82.4%) in Ontario, another Canadian province [287]. Study 2 suggested that educational material has a great potential to improve bone health management, especially BMD testing rates.

All findings imply that this group of older women should be encouraged to receive BMD testing as recommended by the most current Canadian guidelines. Patient educational material could potentially improve bone health management, especially BMD testing rates and physical activity in this group of women.

The patient educational material developed for this thesis, comprised of two parts: (1) three pages of information on osteoporosis, potential effects of breast cancer treatments on bones, BMD testing, lifestyle advice to promote bone health, and advice to review osteoporosis risk with one's family doctor (Appendix C); and (2) one double-sided page of risk factors based on the 2010 Canadian osteoporosis guidelines and fracture risk assessment tool (FRAX) developed by the World Health Organization (Appendix D) [97, 195]. This educational material targets primarily patient barriers, especially underestimated personal perceived risk of osteoporosis [118-120]. The double-sided page of risk factors could prompt family doctors' knowledge on osteoporosis risk factors. While it is important to prompt patients' awareness in bone health management, physicians should be encouraged to recommend BMD testing, FRAX evaluation and healthy lifestyles based on the relevant guidelines. Healthy lifestyles include exercise, adequate calcium and vitamin D intake, avoid excessive alcohol drinking and fall prevention. Among lifestyles, exercise should be recommended per the World Health Organization Guidelines ((≥150 minutes of moderate-intensity aerobic exercise per week or ≥75 minutes of vigorous-intensity aerobic exercise per week; for adults aged ≥65 years) for all adults aged ≥65, regardless to their chronic disease history [222].

This thesis identified a significant care gap in utilization of BMD testing, factors associated with low BMD testing rates, and a potential educational material intervention to improve BMD testing rates and bone health-associated lifestyles. Several important questions still need to be answered in future studies. While the pilot RCT suggested that patient educational material developed for this thesis had positive effects on bone health management, the question of the most effective way to deliver this material, especially with newer communication technologies and targeting disparate subgroups with lower BMD testing rates, needs further investigation. Newer communication technologies, such as internet communication, with high availability and relative low-cost should be considered in disparate subgroups, including but not limited to women with lower SES, living in rural areas, or with previous osteoporotic fracture.

5.4.2 Younger women aged 65 years and under who were diagnosed with breast cancer

In younger women aged 65 and under, and diagnosed with breast cancer, BMD testing is only recommended to high-risk individuals. The definitions of high risk vary between guidelines. While most adjuvant systemic breast cancer treatments cause estrogen deficiency and accelerated bone loss, BMD testing is not universally indicated for women who receive these treatments. For example, BMD testing is not indicated for a 60-year-old woman who receives AIs without additional osteoporosis risk factors based on the most current guidelines in BC in 2011 [178]. A better understanding of fracture risks associated with adjuvant systemic breast cancer treatments can potentially alter BMD eligibility criteria for younger women. Study 3 demonstrated from current literature that tamoxifen has no effect on fracture risk while AIs increase fracture risk. AIs increased fracture risk over tamoxifen. This increased AI-associated fracture risk, compared with tamoxifen, decreases over time and is primarily seen only while women are receiving their AI treatment.

These findings have several implications. First, while tamoxifen may preserve BMD, tamoxifen does not reduce fracture risk; therefore, younger women who receive tamoxifen as part of breast cancer treatment should still receive BMD testing as recommended by guidelines. Second, increased AI-associated fracture risk should be taken into consideration for fracture risk assessment and BMD testing eligibility. Third, increased AI-associated fracture risk, compared with tamoxifen, is significantly higher during the treatment period but not the post-treatment period. Better bone health management programs, especially during the treatment period are needed for women who received AI breast cancer treatment.

Future research is needed to (1) evaluate fracture risk associated with sequential treatments of both tamoxifen and AIs; (2) to identify an optimized bone health management plan for women who are receiving AI treatment. First, AIs could be given alone for five years or in sequence for 2-3 years before or after tamoxifen (sequential AI-tamoxifen or sequential tamoxifen-AI). Sequential treatments, compared with either tamoxifen or AIs alone, reduce the exposure times of both tamoxifen and AIs, which may reduce the long-term side effects associated with either tamoxifen or AIs, such as fracture risk. This lead to two important questions: “do fracture risks differ between sequential tamoxifen-AI and AI-tamoxifen treatments?” and “is sequential treatment (either tamoxifen-AI or AI-tamoxifen) associated with lower fracture risk than an AI treatment alone?” Second, women who receive AI treatment are at higher fracture risk, especially during the treatment period. A BMD testing at one- to three-year intervals is recommended for this group by the Canadian guideline [97]. The optimal interval for BMD testing for this particular group remains unclear. Is a shorter screening interval, such as annual BMD testing as suggested for cancer populations by some international guidelines [174], better

than a two- or three-year interval for screening this special population for osteoporosis before fractures occur? Also, should AI be considered in any fracture risk assessment tools such as the World Health Organization Fracture Risk Assessment tool?

5.4.3 Women diagnosed with breast cancer

Most adjuvant systemic breast cancer treatments accelerate bone loss and increase fracture risks in women diagnosed with breast cancer. Optimal bone health management could potentially prevent fractures from occurring. Bone health management should include lifestyle advice, screening with BMD testing, pharmacological treatment, and monitoring. Bone health management, especially for women who receive breast cancer treatments with negative effects on bones, should be initiated when breast cancer diagnosis is made and continue through to end of life. To achieve optimal bone health care through the breast cancer diagnosis, treatment and post-treatment phases, requires coordination and share of care between oncologists and family doctors [288-290]. While multiple shared care models between oncologists and family doctors have been proposed [288], it remains unclear which model is more suitable for women diagnosed with breast cancer in BC. Future research is needed to (1) understand current care-share patterns on bone health between oncologists and family doctors; and (2) identify potential barriers associated with care-share or care coordination between oncologists and family doctors.

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Appendices

Appendix A Summary of datasets in this study

Database	Data range for this study	Population coverage	Data Description	Information obtained for this study
BC Cancer Registry [21]	1986 – 2011	BC residents diagnosed with cancer since 1985 (95%)	All cancers diagnosed for BC residents	• Gender • Birth dates • Death dates • Cancer diagnosis
Breast Cancer Outcome Unit (BCOU)	1989 - 2011	BC residents diagnosed with breast cancer and referred to one of the provincial treatment centers operated by BCCA since year 1989	Breast cancer treatment	• Breast cancer treatment
Consolidation file [*Medical Service Registration & Premium Billing]* [23]	1986 – 2011	All Canadians and legal immigrants who have been living in BC for at least 6 months	Demographic information	• Gender • Birth dates • Residential regions • Postal codes for urban/rural status • Socioeconomic status • Active registration status for alive follow-up status
MSP Payment Information File [22]	1986 – 2011	All Canadians and legal immigrants who have been living in BC for at least 6 months.	Medically necessary services	• BMD tests • Osteoporosis diagnosis • Bone fracture diagnosis • Chronic disease diagnosis
Discharge Abstracts Database [Hospital Separation] [26]	1986 – 2011	All BC residents	Hospital admissions and day surgeries	• Osteoporosis diagnosis • Bone fracture diagnosis • Chronic disease diagnosis
BCCA British Columbia Cancer Agency, *MSP* Medical Service Payment				

Appendix B Summary of codes for variables

Variable	Diagnostic Codes		Fee code [b]
	ICD 9 code [a]	ICD 10 code	
Nursing home			00115, 13334
Osteoporosis	733	M80, M81	
Osteoporotic fracture			
Hip	820	S72	
Spine	805	S22, S32	
Forearm	813	S62	
Chronic disease [189]			
Myocardial infarction and coronary heart disease	410, 412	I21, I22, I25.2	
Cerebrovascular disease	430-438	G45, G46, H34.0, I60-I69	
Dementia	290	F00-F03, G30, F05.1, G30, G31.1	
Chronic pulmonary disease	490-505	I27.8, I27.9, I40 –I47, J60-J67, J68.4, J70.1, J70.3	
Diabetes	250	E10.0–E10.9, E11.0-E11.9, E12.0-E12.9, E13.0-E13.9, E14.0-E14.9	

ICD -9 International Classification of Diseases, Ninth Revision, ICD-10 International Classification of Diseases, Tenth Revision

[a] fee codes are specific for the province of British Columbia only

Appendix C Educational Material

Bone health management study:

Osteoporosis information
for women over age 65 who have had breast cancer

Do you know your risk for osteoporosis and bone fractures?

Find out how to get tested and reduce your risk.

Complete the enclosed osteoporosis and bone fracture risk assessments and review the results with your family doctor. Ask your family doctor whether getting a bone mineral density test is right for you.

The content in this package is not intended as a substitute for medical advice and diagnosis. Always seek the advice of your family doctor regarding your risk and concerns with your bone health.

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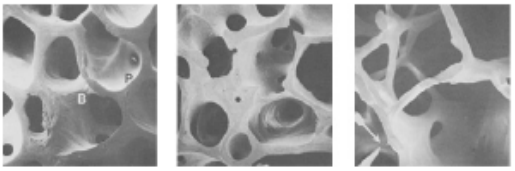
What is osteoporosis?



Healthy bone | Osteopenia | Osteoporosis

Bone is a living tissue, and bone mass naturally changes at different life stages. When women enter menopause, bone mass loss accelerates due to a drop in estrogen levels. This can increase the risk of osteoporosis, which is a disease of the bones. It is characteristic of low bone mass, which makes your bone thinner and more brittle. Osteopenia is the stage when bone mass is below normal, but not low enough for osteoporosis. Both conditions can increase your risk of broken bones, particularly of the hip, spine, wrist, and shoulder. Anyone can develop osteoporosis, but it is more common in older women. Almost half of women will experience broken bones due to falls or minor trauma in their lifetime, and these fractures can be disabling and may make it hard to live independently.

How does breast cancer treatment affect bone health?

Certain breast cancer treatments are associated with bone loss. The fastest bone loss happens in the first year of cancer treatment, but it may continue to drop beyond the first year. This bone loss makes bone thinner and more brittle, leading to osteoporosis or fractures. **Women who have had breast cancer treatment may be at increased risk of osteoporosis or fractures.**

Am I at risk?

Osteoporosis is a silent disease, and it is possible to have broken bones without knowing it. In addition to breast cancer treatment, several factors can further increase your risk of developing osteoporosis or broken bones due to osteoporosis. These risk factors are listed in the two assessments on the enclosed insert. **Please complete these two assessments. Then, take the assessments to your family doctor and discuss your risk factors and concerns about your bone health. Ask if you are eligible for a bone mineral density test (also called a bone density test).**

What is a bone mineral density test?

This test measures the amount of calcium and minerals in bones. The test involves lying on a table for 10-20 minutes while a low dose x-ray beam scans the spine, hip, or both. **This test is free if you are at risk for osteoporosis.** The test involves no pain and has no known risk other than minimal radiation exposure. The measurement is then compared to the range of measurements in healthy young adults. Based on this comparison, bone mass will be categorized as normal, osteopenia (low bone mass), or osteoporosis. The results will be sent to your family doctor.

You can reduce your risk of developing osteoporosis and bone fractures due to osteoporosis by modifying your lifestyle.

1. Don't smoke, and avoid exposure to second hand smoke.

If you do smoke, consider discussing with your family doctor how to quit. You can also visit the QuitNow website at www.quitnow.ca or call the QuitNow office at 1-877-455-2233 (toll-free) for free resources and support.

2. Limit daily alcohol to two drinks or less.

3. Eat calcium rich foods. Consider taking a calcium supplement.

Women aged 50 and above need 1,000-2,000 mg of elemental calcium per day. Calcium in food and supplement pills is in compound form, such as calcium carbonate, calcium citrate, or calcium lactate. During digestion, the elemental calcium is released from the food or pills, and becomes available for the body to absorb. Supplements should be considered if you are unable to get enough calcium from food alone.

Examples of calcium rich foods

- 8 oz of low fat yogurt (plain or fruit) or milk (all types), 250-450 mg elemental calcium
- ½ can of salmon or sardines, 250-300 mg
- 1 cup of cooked broccoli, kidney beans, lima beans, lentils, chickpeas, baked beans, soy beans, or white beans, 50-150 mg
- Some cereals, milk, orange juice, and other foods may be fortified with calcium. Please read product nutrition labels for details.

For more information on portion sizes or alternative food sources of calcium, please contact a HealthLinkBC Registered Dietician by calling 8-1-1 (toll-free) or visit www.healthlinkbc.ca/healthyeating.

Calcium supplements

- **Check with your family doctor or pharmacist if you take other any medications or are at high risk for kidney stones.**
- Talk with a pharmacist to ensure you will be getting the appropriate daily amount of elemental calcium (1,000-2,000 mg).
- Get the most absorption of any calcium supplements by dividing doses through the day, but do not take more than 500 mg of elemental calcium at one time.
- Avoid calcium supplements made from oyster shells, bone meal, or dolomite as they may contain toxic metals.

4. Eat foods rich in vitamin D. Consider taking a vitamin D supplement.

The recommended daily vitamin D intake for women aged 50 and above is 800-1,000 IU. Vitamin D can be obtained from sun exposure in the skin, food, or supplements. In Canada, it is hard to get enough vitamin D from sun exposure without increasing the risk of skin cancer.

Examples of vitamin D rich foods

- 3 oz of cooked or canned fish (salmon, swordfish, or tuna), 150-650 IU
- 1 cup of raw diced mushrooms (chanterelle or morel), 100-200 IU
- 1 cooked egg, 50-100 IU
- Some cereals, milk, orange juice, and other foods may be fortified with vitamin D. Please read product nutrition labels for details.

For more information on portion sizes or alternative food sources of vitamin D, please contact a HealthLinkBC Registered Dietician by calling 8-1-1 (toll-free) or visit www.healthlinkbc.ca/healthyeating.

5. Be physically active, and do weight-bearing (muscle strengthening) exercises.

Weight-bearing and muscle-strengthening exercises reduce the risk of osteoporosis, help build strong bones, and reduce the risk of falls and fractures. Weight-bearing exercises are performed while you stay upright so that your feet and legs support your weight. Check with your family doctor or physiotherapist before starting or changing any exercise program.

Some general guidelines

- **Try to exercise for 10 to 15 minutes once or twice a day at least 3-5 times per week.**
- Examples of exercises include: walking, jogging, hiking, aerobics, dancing, using a stair-step machine, sports where you stay on your feet, and lifting weights (using dumbbells or weight machines).
- If you have osteoporosis, consider taking an Osteofit class in your community. You can find information on Osteofit classes at www.osteofit.org.
- Contact your local gyms, community centres, or senior's centres for information on other exercise classes and facilities.

Do you have more questions about this study or about osteoporosis?

Please contact Dr. Olivia Tseng by calling 604-675-8000 extension 7637 or by sending an email to otseng@bccrc.ca.

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Appendix D List of risk factors

Osteoporosis risk assessments for women over age 65 who have had breast cancer

Certain breast cancer treatments are associated with bone loss. If you have been treated for breast cancer you may be at increased risk for osteoporosis and broken bones due to osteoporosis. In addition, several other factors can further increase your risk of developing these conditions. The following two tables will identify your risks.

Please circle yes (Y) or no (N), or provide the indicated information, for each risk factor. Review your risk factors with your family doctor to determine whether you need a bone mineral density test. You are at higher risk of osteoporosis and/or broken bones if you have circled one (Y) in Table 1 or two (Y) in Table 2.

Table 1: Risk factors for broken bones due to osteoporosis

Risk factors	Explanation			
Older age	The risk of osteoporotic fractures increases with age		Age:	
Gender			F	M
BMI ≤ 19	Body mass index, calculated from height and weight, which is 19 or less	Unsure	19 or less	Greater than 19
History of low trauma fracture	A fracture in any bone due to falling from standing height		Y	N
History of hip fracture in mother or father	Either biological father or mother had a broken hip in the past		Y	N
Smoking			Y	N
Taking Cortisone or Prednisone for more than 3 months			Y	N
Rheumatoid arthritis	Having a diagnosis of a disease causing chronic inflammation of the joints, especially hand and wrist joints		Y	N
Secondary osteoporosis	Having a diagnosis of osteoporosis resulting from other diseases, such as type I diabetes, chronic malnutrition, chronic malabsorption, and untreated long-standing hyperthyroidism		Y	N
Drinking ≥ 3 units of alcohol per day	Drinking 3 or more units of alcohol (in any combination) per day. 1 unit of alcohol = 1 single spirit shot, ½ a can or bottle of beer, or ½ a glass of wine		Y	N

Doctors: The reference for this assessment is http://www.shef.ac.uk/FRAX/tool.aspx?country=19.

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Table 2: Risk factors for osteoporosis

Major risk factors	Explanation		
Age ≥ 65	Being age 65 or older	Y	N
Low trauma vertebral compression fracture	A fracture of a spinal vertebrae due to falling from standing height or less	Y	N
Low trauma fracture at any site after age 40	A fracture in any bone due to falling from standing height or less after age 40	Y	N
Family history of osteoporotic fractures	Any close family members who had fractures due to osteoporosis	Y	N
Taking Cortisone or Prednisone for more than 3 months		Y	N
Malabsorption syndrome (i.e., Crohn's disease, Celiac disease)	Having a diagnosis of a condition of ineffective nutrient absorption through the bowels	Y	N
Primary hyperparathyroidism	Having a diagnosis of a disease causing excess production of parathyroid hormones due to an overactive parathyroid gland	Y	N
Hypogonadism	Having a diagnosis of a disease causing in the reduction or absence of hormone secretion from the ovaries	Y	N
Early menopause	Entering menopause before age 45	Y	N
Minor risk factors	**Explanation**		
Past history of clinical hyperparathyroidism	A disease causing excess production of parathyroid hormone due to an overactive parathyroid gland, kidney failure, vitamin D deficiency, or kidney transplant	Y	N
Long term use of anticonvulsants	Anti-seizure medications which can prevent or control seizures/convulsions	Y	N
Low calcium intake	Daily calcium intake less than 400 mg (approximately 8 oz of yogurt)	Y	N
Smoking		Y	N
Drinking ≥ 3 units of alcohol per day	Drinking 3 or more units of alcohol (in any combination) per day. 1 unit of alcohol = 1 single spirit shot, ½ a can or bottle of beer, or ½ a glass of wine	Y	N
Excessive caffeine	Drinking 4 or more cups of coffee or tea per day	Y	N
Weight < 125 lbs (57 kg)	Weighing less than 125 lbs or 57 kg	Y	N
Weight loss	Current weight is less than 90% of weight at age 25	Y	N
Long term use of heparin	Taking the medication heparin for more than 3 months	Y	N
Rheumatoid arthritis	Having a diagnosis of a disease causing chronic inflammation of the joints, especially hand and wrist joints	Y	N

For more information about the bone health management study or these risk assessments, please contact Dr. Olivia Tseng by calling 604-675-8000 extension 7637 or by sending an email to otseng@bccrc.ca.