Breast Cancer Screening Behaviours and Outcomes in Women with a Family History of Breast and/or Ovarian Cancer in Ontario

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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Abstract

Having a family history of breast and/or ovarian cancer is one of the most important risk factors for developing breast cancer. It is unknown if the survival benefit from mammography screening extends to women with a family history, and if prognostic features differ by level of familial risk. The relationship between perceived breast cancer risk and breast screening has been widely studied in women with familial risk; however, most studies are cross-sectional, precluding insight into the directionality of this relationship. The objectives of this thesis were to: examine the impact of mammography screening and familial risk on diagnoses and prognostic features of breast cancer and benign breast disease (BBD); and examine the effect of perceived risk on breast screening. An additional methodological objective was to evaluate the validity of self-reported mammogram data. The data source for this thesis was the Family History Study (FHS), a prospective cohort study of women from the Ontario site of the Breast Cancer Family Registry with a family history of breast/ovarian cancer. Women with high familial risk were more likely to be diagnosed with breast cancer (OR = 2.84; 95% CI:1.50-5.38), or BBD (OR = 1.94; 95% CI:1.03-3.66), than women with low/moderate risk. No significant differences were detected in prognostic features by level of risk; however,
symptomatic cancers were larger (OR = 9.72; 95% CI:1.01-93.61) and diagnosed at a later stage (OR = 7.80; 95% CI:1.18-51.50) than screen-detected cancers. In low risk women, women who perceived their risk as >50% were more likely to have a mammogram (OR = 1.13; 95% CI:0.59-2.16), and clinical breast examination (CBE (OR = 1.11; 95% CI:0.63-1.95) than women who perceived their risk as 50%. In moderate/high risk women, women who perceived their risk as >50% were less likely to have a mammogram (OR = 0.70; 95% CI:0.40-1.20), and CBE (OR = 0.52; 95% CI:0.30-0.91) than women who perceived their risk as 50%. Over 90% of women in the FHS accurately reported their mammogram use in the previous year. Together, these studies make an important contribution to understanding the effectiveness and use of breast screening in women with familial risk.
For Ernest Sinclair, who instilled in me the importance of education
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<th>Description</th>
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<tbody>
<tr>
<td>ATM</td>
<td>ataxia telangiectasia mutated</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>BBD</td>
<td>benign breast disease</td>
</tr>
<tr>
<td>BCFR</td>
<td>Breast Cancer Family Registry</td>
</tr>
<tr>
<td>BI-RADS</td>
<td>Breast Imaging - Reporting and Data System</td>
</tr>
<tr>
<td>BOADICEA</td>
<td>Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm</td>
</tr>
<tr>
<td>BRCA1</td>
<td>breast cancer 1 gene</td>
</tr>
<tr>
<td>BRCA2</td>
<td>breast cancer 2 gene</td>
</tr>
<tr>
<td>BRIP1</td>
<td>BRCA1 interacting protein C-terminal helicase 1</td>
</tr>
<tr>
<td>BSE</td>
<td>breast self-examination</td>
</tr>
<tr>
<td>CBE</td>
<td>clinical breast examination</td>
</tr>
<tr>
<td>CCHS</td>
<td>Canadian Community Health Survey</td>
</tr>
<tr>
<td>CCS</td>
<td>Canadian Cancer Society’s Advisory Committee on Cancer Statistics</td>
</tr>
<tr>
<td>CHEK2</td>
<td>checkpoint kinase 2</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CPAC</td>
<td>Canadian Partnership Against Cancer</td>
</tr>
<tr>
<td>CR</td>
<td>computed radiography</td>
</tr>
<tr>
<td>DCIS</td>
<td>ductal carcinoma in situ</td>
</tr>
<tr>
<td>DR</td>
<td>direct radiography</td>
</tr>
<tr>
<td>ER</td>
<td>estrogen receptor</td>
</tr>
<tr>
<td>ERBB2</td>
<td>v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2</td>
</tr>
<tr>
<td>FHQ</td>
<td>Family History Questionnaire</td>
</tr>
<tr>
<td>FHS</td>
<td>Family History Study</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in situ hybridization</td>
</tr>
<tr>
<td>GWAS</td>
<td>genome-wide association study</td>
</tr>
<tr>
<td>HBM</td>
<td>Health Belief Model</td>
</tr>
<tr>
<td>HER-2/neu</td>
<td>human epidermal growth factor receptor 2</td>
</tr>
<tr>
<td>HRT</td>
<td>hormone replacement therapy</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>IBIS</td>
<td>International Breast Intervention Study</td>
</tr>
<tr>
<td>IHC</td>
<td>immunohistochemistry</td>
</tr>
<tr>
<td>IHF</td>
<td>independent health facility</td>
</tr>
<tr>
<td>LCIS</td>
<td>lobular carcinoma in situ</td>
</tr>
<tr>
<td>MAR</td>
<td>missing at random</td>
</tr>
<tr>
<td>MARIBS</td>
<td>MRI breast imaging screening study</td>
</tr>
<tr>
<td>MCAR</td>
<td>missing completely at random</td>
</tr>
<tr>
<td>MNAR</td>
<td>missing not at random</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Care and Excellence</td>
</tr>
<tr>
<td>NNS</td>
<td>number needed to screen</td>
</tr>
<tr>
<td>NST</td>
<td>no special type</td>
</tr>
<tr>
<td>OBSP</td>
<td>Ontario Breast Screening Program</td>
</tr>
<tr>
<td>OCR</td>
<td>Ontario Cancer Registry</td>
</tr>
<tr>
<td>OHIP</td>
<td>Ontario Health Insurance Plan</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PALB2</td>
<td>partner and localizer of BRCA2</td>
</tr>
<tr>
<td>PHQ</td>
<td>Personal History Questionnaire</td>
</tr>
<tr>
<td>PHSQ</td>
<td>Personal History and Screening Questionnaire</td>
</tr>
<tr>
<td>PR</td>
<td>progesterone receptor</td>
</tr>
<tr>
<td>PTEN</td>
<td>phosphatase and tensin homolog</td>
</tr>
<tr>
<td>PTNM</td>
<td>pathological classification system of staging tumors</td>
</tr>
<tr>
<td>RAD51C</td>
<td>RAD51 paralog C</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating characteristic</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>TNM</td>
<td>classification system of staging tumors</td>
</tr>
<tr>
<td>TP53</td>
<td>tumor protein 53</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
Chapter 1
Introduction and Objectives

1.1 Introduction

Breast cancer is the leading incident cancer and second-leading cause of cancer death among Canadian women (Canadian Cancer Society’s Advisory Committee on Cancer Statistics [CCS], 2014). Having a family history of breast cancer has been established as one of the most important risk factors for developing breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2001; Pharoah et al., 1997). A mortality benefit from screening mammography in women at average risk of developing breast cancer has been established (Nelson et al., 2009; Canadian Task Force on Preventive Health Care, 2011); however, the mortality benefit for women with a family history of breast and/or ovarian remains unknown. Several studies have found that women with a family history may benefit from regular breast cancer screening, reporting higher cancer detection rates (Halapy et al., 2004; Kerlikowske et al, 2000) and favourable prognostic features of screen-detected cancers (Randall et al., 2009; Møller et al., 1998; Tilanus-Linthorst et al., 2000). The impact of level of familial risk on breast cancer prognosis has not been previously examined.

Women with a family history of breast cancer are recommended to be screened for breast cancer annually with mammography, clinical breast examination (CBE), and/or magnetic resonance imaging (MRI) starting prior to age 50 years (Eccles et al., 2000; Warner et al., 1999a; Chart & Franssen, 1997). North-American studies have demonstrated that many (45-64%) women with familial risk do not undergo annual screening mammography (Campitelli et al., 2011, Madlensky et al., 2005). The relationship between perceived risk of breast cancer and breast cancer screening has been widely studied in women with a family history of breast cancer. Most of these previous studies have been cross-sectional. As it is likely that women’s recent
breast cancer screening histories could influence perceived breast cancer risk, reverse causation is an important concern. While four prospective studies have been conducted (Price et al., 2010; Somers et al., 2009; Lemon et al., 2006; Diefenbach et al., 1999), their generalizability and validity is limited. Somers et al. (2009) did not account for confounders, Difenbach et al. (1999) included only women with very strong family histories from a high-risk clinical setting, and Lemon et al. (2009) examined screening behaviours in the year following relative’s diagnosis of breast cancer.

Self-reported mammogram data are often relied on in epidemiologic research evaluating the use of breast cancer screening. Only two studies (Pijpe et al., 2011; Larouche et al., 2012) have validated self-reported mammogram dates in women with a family history of breast cancer, both including only women with confirmed or suspected mutations in the breast cancer 1 gene (BRCA1) or breast cancer 2 gene (BRCA2). These women likely differ in their breast cancer screening behaviours, and ability to recall screening episodes compared with women in the general population with familial risk.

The objectives of this thesis were developed to address identified gaps and methodological limitations in the breast cancer screening literature. The overall aims of the thesis were to: (i) develop a better understanding of the effectiveness of mammography screening, and impact of level of familial risk on diagnoses and prognostic features of breast cancer and benign breast disease; (ii) assess the effect of perceived risk on breast cancer screening use; and (iii) evaluate the validity of self-reported screening mammogram data, in women with varying levels of familial breast cancer risk.
1.2 Study Objectives

Objective 1. Examine the effect of mammography screening and familial risk on diagnoses and prognostic features of breast outcomes in women with varying levels of familial breast cancer risk

(i) Estimate associations between screening mammography and diagnoses of breast outcomes (invasive and in-situ cancers, and benign breast disease).

(ii) Estimate associations between screening mammography and prognostic features of cases of invasive breast cancer and benign breast disease.

(iii) Estimate associations between level of familial breast cancer risk and diagnoses of breast outcomes (invasive and in-situ cancers, and benign breast disease).

(iv) Estimate associations between level of familial breast cancer risk and prognostic features of cases of invasive breast cancer and benign breast disease.

Objective 2. Examine the effect of perceived breast cancer risk on participation in breast cancer screening in women with varying levels of familial breast cancer risk

(i) Examine the association between perceived breast cancer risk and breast cancer screening use in women with a family history of breast cancer through a systematic review of published observational studies, and evaluate the quality of previous literature.

(ii) Estimate associations between perceived lifetime breast cancer risk and subsequent use of screening mammography, CBE, and genetic testing.

(iii) Examine whether the level of familial breast cancer risk modifies the association between perceived breast cancer risk and breast cancer screening/genetic test use.
Objective 3. Examine the accuracy of self-reported screening mammogram dates in women with varying levels of familial breast cancer risk

(i) Validate self-reported mammogram dates against dates abstracted from imaging reports, and estimate the magnitude and direction of inaccurate recall of mammogram dates.

(ii) Identify factors (socio-demographic characteristics, health and breast cancer screening behaviours) associated with the accuracy of self-report.
Chapter 2
Background and Literature Review

2.1 Epidemiology of Breast Cancer

2.1.1 Anatomy

The female breast is composed of both epithelial elements, which include milk-producing glands (lobules) and ducts, and stromal elements, which include adipose tissue, connective tissue, and blood and lymphatic vessels (Colditz et al., 2006; Canadian Breast Cancer Foundation, 2013). Breast development is regulated by hormones and growth factors; responding selectively to hormonal stimuli with either cell proliferation or differentiation (Russo & Russo, 2002). Estrogens are known to play a significant role in promoting proliferation of both normal and neoplastic breast cells (Russo & Russo, 2002). Breast cancer is a disease in which malignant cells form in the breast tissue. Nearly all breast cancers (>95%) are epithelial in origin, and are classified as adenocarcinomas (Colditz et al., 2006). Cancers of the breast are classified as in situ (cancers which are contained within the breast lobule or duct) or invasive (cancers which are not contained by the lobular or ductal walls and have invaded the breast stroma) (Colditz et al., 2006). Lobular carcinoma in situ (LCIS) is not clinically detectable, as it rarely produces abnormalities which present during mammography. Instead, LCIS is typically detected incidentally during histologic examination of other breast lesions (Goldschmidt & Victor, 1996; Vainio & Bianchini, 2002). LCIS increases the risk for subsequent invasive breast cancer in either breast approximately 10-fold (Vainio & Bianchini, 2002; Page et al., 1991). Ductal carcinoma in situ (DCIS) is characterized from low- to high-grade, and subtypes may have different risks of subsequent invasive breast cancer (Vainio & Bianchini, 2002). Unlike LCIS,
invasive tumors subsequent to a diagnosis of DCIS often occur in the quadrant of the breast where the DCIS lesion was initially located (Page et al., 1995).

Breast cancers are further subtyped based on their histopathology, molecular pathology, genetic analysis or gene expression profiling. This is done to obtain detailed clinical and prognostic information regarding tumor behaviour, for the prediction of tumor response to specific therapeutic strategies, as well as prediction of overall outcome (Colditz et al., 2006; Sims et al., 2008).

2.1.2 Tumor Features

Tumor size has long been recognized to be one of the most important prognostic indicators. Larger breast cancer tumors are associated with poorer rates of survival compared with tumors smaller in size (Soerjomataram et al., 2008; Fitzgibbons et al., 2000), and a dose-response trend has been demonstrated (Soerjomataram et al., 2008). The absence or presence of metastases to the regional lymph nodes is also of prognostic importance with regard to disease-free and overall survival. While regional metastasis is partially a function of time (invasive breast cancers are more likely to become node-positive the longer they exist in the preclinical phase), nodal involvement is also considered to indicate a more biologically aggressive breast cancer phenotype (Jatoi et al., 1999, Nassar et al., 2001). One previous study found average 10-year survival for patients with node-negative breast cancers was 75%, but only 25-30% for patients with node-positive disease (Rampaul et al., 2001). A similar trend is apparent with regard to disease recurrence; one previous study found that while only 20-30% of node-negative patients experienced recurrence of their breast cancer within 10 years, recurrence occurred for approximately 70% of patients with node-positive breast cancers (Fitzgibbons et al., 2000). Rates of survival have also been found to be poorer with increasing numbers of affected lymph nodes.
For example, previous studies have demonstrated that cases with four or more positive nodes have poorer rates of 5-year (Jatoi et al., 1999; Fitzgibbons et al., 2000) and 10-year (Weiss et al., 2003) survival compared with patients with 3 or fewer positive nodes. Survival of patients with lymph node-positive breast cancer has improved with the revision of staging systems, and systemic treatment approaches (Soerjomataram et al., 2008).

Staging of cancers is a method of determining the anatomic extent of a cancer based on its natural history, which is relevant to therapeutic decision-making and determining overall prognosis (Edge et al., 2010). TNM staging is determined by the combined score on three components, including: tumor size (T), involvement of the regional lymph nodes (N) and presence of distant metastasis (M) (Edge et al., 2010). The clinical TNM classification system is based on evidence acquired from non-invasive diagnostic methods such as physical examination or imaging, or more invasive methods such as biopsy (Beahrs, 1988). The clinical classification system is prone to unreliability; there is clinical-pathological agreement on tumor size in only 54% of cases (Yorkshire Breast Cancer Group, 1980), and clinical assessment of lymph nodes is not always accurate (i.e. positive nodes may be impalpable or negative nodes may be enlarged due to benign changes) (Pinder et al., 2008). As such, the pathological TNM (pTNM) staging system is recommended, which incorporates pathologic measurement of both tumor size and lymph node status following surgical resection of the primary tumor and lymph nodes (Pinder et al., 2008). The presence of metastatic disease is not typically assessed histologically, and thus the clinical classification of distant metastasis is usually given by the “M” component (Pinder et al., 2008). Breast cancers diagnosed at a later stage are associated with poorer prognosis. For example, one population-based study of all cases of breast cancer in British Columbia in 2002 found that 10-year breast cancer survival rates by stage were above 99% for stage 0, 95% for stage I, 81% for stage II, 55% for stage III, and 4% for stage IV (Davidson et al., 2013).
Histologic grade is also strongly associated with breast cancer survival and recurrence, though not included in formal staging criteria due to concerns about its value for small tumors (Rakha et al., 2008). The Elston-Ellis modification to the Scarff-Bloom-Richardson grading system (Nottingham grading system) is the most commonly used histologic grading system; it is recommended by the United Kingdom, the European Breast Screening Pathology Groups, the United States Directors of Anatomic and Surgical Pathology, the Union for International Cancer Control, and the World Health Organization (WHO) (Pinder et al., 2008). Histologic grading takes into account three morphological features, including: tubule formation, nuclear pleomorphism and mitotic count, each of which is assigned a score from 1 to 3 (Elston & Ellis, 1991). Tumors are considered well-differentiated if the overall score is 3 to 5 (histologic grade I), moderately-differentiated if the score was 6 to 7 (histologic grade II) or poorly-differentiated if the score was 8 to 9 (histologic grade III). A study by Rakha et al (2008) examined the association between histologic grade and survival, finding survival was significantly decreased for cancers with a histologic grade of II vs. 1 and III vs. 1. Rates of disease-free survival were also poorer for breast cancers with higher histological grade, though this association only reached statistical significance for grade III vs. 1 (Rakha et al., 2008). High mitotic activity index has also been demonstrated to be associated with poorer prognosis (van Diest et al., 2004).

Lymphovascular invasion refers to the presence of tumor emboli within blood vessels or lymphatic vessels. While not currently included in most staging systems, prognostic indices or treatment guidelines, some studies have demonstrated that lymphovascular invasion is strongly associated with survival (Rakha et al., 2012; Lee et al., 2006; Schoppmann et al., 2004), and presence of distant metastases (Ragage et al., 2010). It has been suggested that lymphovascular invasion may be as predictively important as lymph node involvement with regard to survival (Pinder et al., 2008).
2.1.3 Histological Type

Breast cancer is a heterogeneous disease, demonstrating marked variability in its clinical presentation and behaviour. Histologic typing may confer biological and prognostically meaningful information (Ellis, 1992), in addition to that inferred by tumor morphology alone. Invasive ductal carcinoma of no special type (NST) is the most common carcinoma of the breast, accounting for 40% to 75% of invasive breast cancers (Ellis et al., 2003). NST is a diagnosis of exclusion, referring to adenocarcinomas that do not exhibit characteristics to warrant classification as a special type. Special types account for approximately 25% of all breast cancers, and 18 special types are currently recognized by the WHO (Ellis et al., 2003). Some special types, including tubular, mucinous, invasive cribriform, medullary, infiltrating lobular and tubulo-lobular breast cancers have demonstrated more favourable prognoses compared with NST (Vainio & Bianchini, 2002; Pereira et al., 1995). These cancers are typically diagnosed at grade 1 and demonstrate rates of 10-year survival that generally exceed 80% (Pereira et al., 1995). Alternatively, other special types, such as mixed or solid lobular, mixed ductal and lobular, or ductal/NST have substantially lower rates of 10-year survival (Pereira et al., 1995). Ten-year survival from inflammatory breast cancer is approximately 30% (Tai et al., 2005).

2.1.4 Molecular Factors

Breast cancers are further classified by their expression levels of steroid hormone receptors (estrogen-receptors (ER) and progesterone-receptors (PR)) assessed with immunohistochemistry (IHC), as well as expression of human epidermal growth factor receptor 2/neu (HER-2), assessed with IHC and fluorescence in situ hybridization (FISH) (Colditz et al., 2006; Sims et al., 2008). ER is expressed in 60-80% of invasive breast tumors (Vainio & Bianchini, 2002), and over half of ER+ tumors are also PR+ (Ghayad & Cohen, 2008). Less than
10% of tumors are ER-/PR+ (Ghayad & Cohen, 2008). The v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2) or human epidermal growth factor receptor 2 (HER-2/neu) oncogene is amplified in an estimated 20% of invasive breast tumors, leading to HER-2 overexpression (Vainio & Bianchini, 2002). Compared with ER+/PR+/HER-2- tumors, ER-/PR-/HER-2+ and ER-/PR-/HER-2-(triple-negative) tumors are significantly more likely to be diagnosed at a later stage and higher histologic grade, after adjusting for age (Ontitilo, 2009). Triple negative tumors also have low rates of overall survival, and disease-free survival (Ontitilo, 2009; O’Brien, 2010; Bauer et al., 2007). Expression status for ER, PR and HER-2 receptors indicate which molecular pathways affect a tumor, and is used to determine the type of endocrine therapy. ER+/PR+ (early-stage and metastatic) breast cancers are treated with anti-estrogenic endocrine therapies such as adjuvant tamoxifen or anastrozole (Early Breast Cancer Trialists’ Collaborative Group, 2005; Budzar, 2003), and have a response rate of 60 to 70%, while ER-/PR- tumors have a response rate of less than 10% to hormone therapy (Vainio & Bianchini, 2002). ER+/PR- tumors have an intermediate response rate of 40%. Tumors that have receptor overexpression or gene amplification of HER2 are treated with anti-HER2 therapies, such as trastuzumab, which improves chemotherapy response in HER2+ breast cancers (Kelly & Buzdar, 2013). To date, no specific drug therapy has been identified for triple negative tumors, and thus chemotherapy remains the mainstay in treatment of these cancers (Kelly & Buzdar, 2013).

2.1.5 Benign Breast Disease

Benign breast disease (BBD) represents small changes in normal breast tissue that can indicate an increased risk of invasive breast cancer, or may behave as a non-obligate precursor lesion (Bodian, 1993; Lakhani, 2003; Page et al., 2003). Specific histologic abnormalities based on pathologic examination have a range of relative risks for subsequent invasive breast cancer (Colditz et al., 2006; Schnitt & Connelly, 2004). BBD is generally sub-classified into three types.
of lesions, based on their severity and associated risk for subsequent breast cancer, including: (i) non-proliferative disease, (ii) proliferative disease without atypia, and (iii) proliferative disease with atypia (Dupont & Page, 1985). Non-proliferative breast lesions (i.e. mastitis, cysts, apocrine metaplasia and mild hyperplasia) are not associated with increased risk of breast cancer (Hartmann et al., 2005; Fitzgibbons et al., 1998). Proliferative breast disease without atypia (i.e. fibroadenoma with complex features, intraductral papilloma, sclerosing adenosis) is associated with moderately increased risk (1.5- to 2-fold) of subsequent breast cancer (Shnitt & Connelly, 2004), while breast cancer risk is increased 3.5- to 6-fold when atypical hyperplasia (ductal or lobular) is present (Shnitt & Connelly, 2004; Fitzgibbons et al., 1998). While many studies have demonstrated that a higher proportion of breast cancers subsequent to a diagnosis of BBD develop in the ipsilateral breast, lesions with atypia also confer increased risk of breast cancer in the contralateral breast (Collins et al., 2007; Hartmann et al., 2005).

2.1.6 Descriptive Epidemiology

While breast cancer can occur in both men and women, male breast cancer is rare; less than 1% of all breast cancer cases occur in men (Bove, 2008; Hankinson et al., 2008). Breast cancer is both the leading incident cancer and leading cause of cancer-related mortality among women worldwide (Youlden et al., 2012). It is estimated that in 2008, 1,384,000 women were diagnosed with breast cancer and 450,000 women died from breast cancer globally (Youlden et al., 2012). Within Canada, breast cancer is the most commonly diagnosed malignancy among women, with an estimated 24,400 new diagnoses in 2014, representing 26.1% of all newly diagnosed female cancers (CCS, 2014). In Canada, breast cancer incidence rose through the early 1990s, likely due to the rising use of mammography screening (CCS, 2014). From 1988 to 2004, breast cancer incidence rates have fluctuated, likely a result of shifts in hormonal factors (i.e. age at menarche, pregnancy, and menopause, breastfeeding practices, and use of oral contraceptives
and hormone replacement therapy [HRT]) (Holford et al., 2006). Since 2004, breast cancer incidence has stabilized in Canada (CCS, 2014). The lifetime probability of developing breast cancer for Canadian women of all ages is 11.5% (CCS, 2014). In 2014, 9500 new breast cancer diagnoses and 1950 breast cancer deaths are expected to occur in the province of Ontario (CCS, 2014). The prevalence of breast cancer is just below 1.0%; approximately 63,000 women in Ontario had been diagnosed with breast cancer in the previous 10 years by the beginning of 2010 (Cancer Care Ontario, 2013).

Breast cancer ranks second (following lung cancer) in female cancer mortality in Canada; there will be an estimated 5000 deaths from breast cancer in 2014, representing 13.8% of all female cancer deaths (CCS, 2014). Age-standardized mortality rates for female breast cancer in Canada have been declining since the mid-1980s, demonstrating a relative reduction of 43% from 32.0 per 100,000 women in 1986, to a projected 18.4 deaths per 100,000 women in 2014 (CCS, 2014). This is thought to be the direct result of increased participation in breast cancer screening (namely mammography), combined with the use of targeted adjuvant therapies following breast cancer surgery (CCS, 2014). Similar declines in rates of breast cancer mortality have been observed in the United States, United Kingdom and Australia (Bray et al., 2004).

2.1.7 Familial Breast Cancer

Family history of breast cancer is likely the most important risk factor for the development of breast cancer, aside from age. Women with one affected first-degree relative are approximately twice as likely to develop breast cancer in their lifetime compared with women who have no affected relatives, and risks are higher when more than one first-degree relative is affected or the relative is younger in age at diagnosis (Collaborative Group on Hormonal Factors in Breast Cancer, 2001; Pharoah et al., 1997; Bevier et al., 2012). For example, women with both
an affected mother and sister have approximately three times the risk of developing breast cancer relative to women without a family history, and women with three or more affected first-degree female relatives have nearly four times the risk of developing breast cancer (Pharoah et al., 1997; Collaborative Group on Hormonal Factors in Breast Cancer, 2001). While rare, a first-degree family history of male breast cancer may further increase this risk (Bevier et al., 2012). The risk associated with a family history of breast cancer in female second-degree relatives is lower (RR = 1.5, 95% CI: 1.4-1.6) than the risk conferred by having a first degree family history (Pharoah et al., 1997). A woman with a first-degree relative diagnosed with ovarian cancer is also approximately twice as likely to develop breast cancer compared with women with no affected relatives (Ziogas et al., 2000).

Studies conducted in the United States have estimated that approximately 7% to 11% of women in the general population have a first-degree family history of breast cancer (Hughes et al., 2003; Mai et al., 2011; Ramsey et al., 2006). Extrapolated to the female populations of Canada and Ontario aged 20 to 79 years as of July 1, 2013 (Statistics Canada, 2013), an estimated 911,102 to 1,431,731 Canadian women, and 353,704 to 555,820 Ontarian women have a first-degree family history of breast cancer, respectively.

Many studies that have examined differences in prognostic features of breast cancers between women with a first- or second-degree family history of breast cancer and women without a family history have noted no significant differences (Figueiredo et al., 2007; Margolin et al., 2006; Israeli et al., 1994; Jobsen et al., 2000; Russo et al., 2002; Thalib et al., 2004). However, a few studies have reported that tumors in women with familial risk are smaller (Malone et al., 2011; Molino et al., 2004), and more often node-negative (Fukutomi et al., 1993; Mohammed et al., 1998) and ER+ (Molino et al., 2004) than tumors in women without a family
history. These results may explain why some studies have observed a survival benefit in women with familial risk (Malone et al., 2011; Fukutomi et al., 1993; Mohammed et al., 1998).

Two high-risk breast cancer disposing genes,\textit{BRCA1} and \textit{BRCA2}, have been identified. A meta-analysis by Antoniou et al. (2003) demonstrated that \textit{BRCA1} mutation carriers have a 65\% (95\% CI: 44-78\%) lifetime risk of breast cancer and 39\% lifetime risk of ovarian cancer (95\% CI: 18-54\%), while \textit{BRCA2} mutation carriers have a 45\% (95\% CI: 31-56\%) lifetime risk of breast cancer and 11\% (95\% CI: 2-19\%) lifetime risk of ovarian cancer, though a range of estimates have been reported. \textit{BRCA2} mutations are also associated with significantly increased risk of pancreatic, gastric, bone, prostate and laryngeal cancers, as well as melanoma (Breast Cancer Linkage Consortium, 1999; Risch et al., 2006; Bennett et al., 1999; van Asperen et al., 2005; Moran et al., 2012). Numerous studies have investigated mutation penetrance, and some lifetime risk estimates for carriers of either \textit{BRCA} mutation have exceeded 80\% (Ford et al., 1994; Ford et al., 1998; Easton et al., 1993). Penetrance estimates differ by method of case ascertainment; family studies tend to produce higher estimates than studies based on cases unselected for family history (Narod, 2002). While penetrance of \textit{BRCA1/2} mutations is high, they are rare. In the general population, the estimated carrier rate is 1 in 345 to 1 in 1000 (Ford et al., 1995; Whittemore et al., 1997; Peto et al., 1999). Prevalence of \textit{BRCA1/2} mutations is higher among specific geographic and ethnic sub-populations; the combined population frequency of \textit{BRCA1} and \textit{BRCA2} mutations in Ashkenazi Jewish men and women is 2.0\% to 2.5\% (Struwing et al., 1995; Roa et al., 1996; Warner et al., 1999b), and clusters of \textit{BRCA} mutations have also been identified in the Netherlands (Peelen et al., 1997), Iceland (Thorlacius et al., 1996; Arason et al., 1998), Sweden (Einbeigi et al., 2001), and the Bahamas (Donenberg et al., 2011).

Mutation carrier status is also linked to breast cancer outcomes. Numerous studies have investigated prognosis in \textit{BRCA}-associated breast cancers. Some early studies demonstrated that
prognosis may be more favourable in BRCA-associated breast cancer compared with sporadic cancer (Porter et al., 1994; Marcus et al., 1996; Gaffney et al., 1998; Verhoog et al., 1998). Later studies with more rigorous methodologies (i.e. larger samples, inclusion of important prognostic factors, adjusting for treatment type) have demonstrated BRCA-associated cancers have poorer prognosis (Robson et al., 2004; Goodwin et al., 2012; Brekelmans et al., 2007; Kriege et al., 2008; Bonadona et al., 2007; Budroni et al., 2009). A review of this evidence suggests the overall prognosis of BRCA-associated breast cancer does not differ from that of sporadic breast cancer (Bordeleau et al., 2010). However, risk of contralateral breast cancer is higher in BRCA-associated breast cancers (Metcalfe et al., 2004; Brekelmans et al., 2007), and survival may depend on whether adjuvant chemotherapy was administered (Goodwin et al., 2012; Robson et al., 2004).

Family linkage studies have identified several additional high-penetrance genetic mutations, on tumor suppressor genes phosphatase and tensin homolog (PTEN) and tumor protein 53 (TP53) (Filippini & Vega, 2013). Breast cancer risk in female TP53 mutation carriers is approximately 30% by age 30 years (Lalloo & Evans, 2012), and 50% by age 50 years (Li et al., 1988). Mutations on checkpoint kinase 2 (CHEK2), ataxia telangiectasia mutated (ATM), BRCA1 interacting protein C-terminal helicase 1 (BRIP1), RAD51 paralog C (RAD51C), and partner and localizer of BRCA2 (PALB2) are also associated with a moderate increase (20% to 40%) in lifetime breast cancer risk (Filippini & Bega, 2013; Lalloo & Evans, 2012). Genome-wide association studies (GWAS) have identified numerous common low-penetrance alleles that are associated with slightly increased or decreased breast cancer risk (Filippini & Vega, 2013; Lalloo & Evans, 2012). Only 5% to 10% of all cases of breast cancer are thought to be the direct result of genetic mutations, with BRCA1 and BRCA2 mutations accounting for the largest proportion (2% to 5%) (Hankinson et al., 2008).
Women with a family history of breast cancer are more likely to be diagnosed with benign breast disease, and are also at increased risk for developing high-risk types of BBD such as atypical hyperplasia (Webb et al., 2002). This increase in risk is more pronounced in younger women (Bertelson et al., 2008; Webb et al., 2002; Berkowitz et al., 1985). Women with both a family history of breast cancer and diagnosed with a severe type of BBD (i.e. proliferative lesions without atypia, or atypical hyperplasia) have a greater risk of developing breast cancer compared with women with corresponding BBD severity who do not have a family history of breast cancer (Dupont and Page, 1985; Collins et al., 2006).

2.2 Screening for Breast Cancer

The overarching goal of screening is the detection of disease at an early stage, which facilitates treatment and the potential for improvements in prognosis that would not have been afforded if the disease were detected at a later stage. The disease must have an asymptomatic period (preclinical phase), during which the disease can be detected by a screening test. Breast cancer is known to have a detectable asymptomatic phase (referred to as sojourn time), wherein breast tumors can be detected by a screening test prior to exhibiting symptoms (clinical phase).

2.2.1 Evidence for the Effectiveness of Breast Cancer Screening

Mammography

Mammography is an X-ray technique developed for imaging the soft tissue of the breast (Vainio & Bianchini, 2002). Currently, mammography is the gold standard of screening for breast cancer, but it is also used for diagnostic imaging in symptomatic patients (Vainio & Bianchini, 2002). Two types of mammography are currently available, including screen-film mammography and more recently, digital mammography. Digital mammography captures an
electronic image of the breast. Digital detectors have a wider dynamic range, which results in increased contrast resolution than is available with film; thus, digital mammography facilitates the detection of more cancers that may be hidden by dense breast tissue (Dershaw, 2006; Vainio & Bianchini, 2002). Other advantages of digital mammography include the potential for providing images with lower doses of radiation to the breast compared with screen-film mammography, and the ability to transmit image files electronically (Vainio & Bianchini, 2002). There are two types of digital mammography technology, including direct radiography (DR) and computed radiography (CR). With DR, the detector is integrated into the mammographic unit and the digital image is processed and displayed almost instantaneously (Health Canada, 2013), while with CR, the detector is cassette-based and removable, and the image is generated by an external reading device (Fischer et al., 2006).

A wide range of estimates (52% to over 90%) of the sensitivity of screen-film mammography have been reported by randomized controlled trials (RCT) and population-based breast cancer screening programs, varying by the method of calculation (i.e. length of the screening interval) (Vainio & Bianchini, 2002). A meta-analysis by Humphrey et al. (2002), demonstrated high rates of sensitivity (71% to 98%) for a screening interval of 1 year, while sensitivity ranged from 53% to 86% for a 2-year interval, based on high quality evidence. Test sensitivity of screen-film mammography is affected by a number of host characteristics; it is lower for women who are less than 50 years of age (Humphrey et al., 2002; Carney et al., 2003; Kerlikowske et al., 1996), who have breasts with a greater amount of fibroglandular tissue (high mammographic density) (Kerlikoswke et al., 1996; Chiarelli et al., 2006a; Mandelson et al., 2000; Sala et al., 1998; van Gils et al., 1998), and are current users of HRT (Chiarelli et al., 2006a; Banks 2001; Kavanagh et al., 2000).
Studies have demonstrated that digital mammography has higher cancer detection rates in women who are more likely to have their cancer missed by screen-film mammography (Burrell et al., 1996; D’Orsi & Newell, 2007; Ikeda et al., 1992; Rosenberg et al., 1998), and higher diagnostic accuracy in women who are younger than 50 years of age, women with high breast density, and women who are pre- or peri-menopausal (Pisano et al., 2005). However, a recent study evaluating the performance of both CR and DR technology relative to screen-film mammography (Chiarelli et al., 2013), found important differences between the two types of digital mammography. Chiarelli et al. (2013) demonstrated that while the cancer detection rate for digital DR (4.9 per 1000; 95% CI: 4.7-5.2) and screen-film mammography (4.8 per 1000; 95% CI: 4.7-5.0) are approximately equivalent, the cancer detection rate for digital CR is significantly lower (3.4 per 1000; 95% CI: 3.0-3.9) than cancer detection rates for DR and screen-film mammography. This 21% reduction in performance would result in the detection of approximately 10 fewer breast cancers per 10,000 women screened with CR, compared with screen-film mammography (Chiarelli et al., 2013).

The first RCT to investigate the effect of mammography in reducing breast cancer mortality, The Health Insurance Plan Study, was initiated in 1963 (Shapiro et al., 1982), and followed by numerous other studies in Canada (Miller et al., 1992a, Miller et al., 1992b), Scotland (Roberts et al., 1990) and Sweden (Andersson et al., 1988; Tabar et al., 1985; Bjurstam et al., 1997; Frissell et al., 1986), over the next twenty years. RCTs have demonstrated a reduction in breast cancer mortality that is directly attributable to screening with mammography (Humphrey et al., 2002; Nelson et al., 2009). A 2002 meta-analysis from the U.S. Preventive Health Services Task Force provided a pooled-estimate from 7 trials, demonstrating a 22% reduction in mortality (relative risk [RR] = 0.78, 95% CI: 0.70-0.87) for women aged 50 to 74 years from mammography screening (Humphrey et al., 2002). An update was released in 2009,
providing age-stratified estimates; pooled-estimates from 6 trials demonstrated that mammography screening reduces breast cancer mortality by 14% (RR = 0.86, 95% CI: 0.75-0.99) for women aged 50 to 59 years, and a pooled-estimate from 2 trials demonstrated a greater mortality benefit in women aged 60 to 69 years of 32% (RR = 0.68, 95% CI: 0.54-0.87) (Nelson et al., 2009). A summary of evidence from the Canadian Task Force on Preventive Health Care in 2011 demonstrated results largely in line with those of the U.S. Preventive Health Services Task Force, showing an overall mortality reduction of 21% (RR = 0.79, 95% CI: 0.68-0.90) from screening mammography in women aged 50 to 69 years.

A mortality benefit of 15% (RR = 0.85, 95% CI: 0.75-0.96) was also demonstrated for screening women aged 39 to 49 years with mammography by both the U.S. Preventive Health Services Task Force and Canadian Task Force on Preventive Health Care (Nelson et al., 2009; Canadian Task Force on Preventive Health Care, 2011). While the mortality benefit for screening women aged 39 to 49 years with mammography is significant, the number needed to screen (NNS), number of false-positive results and subsequently unnecessary diagnostic procedures are higher among this younger age group in comparison to women aged 50 to 69 years (Canadian Task Force on Preventive Health Care, 2011). Specifically, the NNS (defined as the number of women who would need to be screened biennially over a median of approximately 11 years to prevent a single death from breast cancer) for women aged 50 to 69 years is 721, compared with 2108 for women aged 40 to 49 years (Canadian Task Force on Preventive Health Care, 2011). Additionally, due to the higher likelihood of false-positive results in women younger than 50 years of age, it is estimated that screening approximately 2100 women biennially for 11 years would result in about 690 women having a false-positive result, and 75 women undergoing unnecessary breast biopsy (Canadian Task Force on Preventive Health Care, 2011). For women 70 years of age and above, the U.S. Preventive Health Services Task Force reported results from
only one trial (precluding meta-analysis), indicating a RR for breast cancer mortality of 1.12
(95% CI: 0.73-1.72). The Canadian Task Force on Preventive Health care pooled estimates from
two trials for women aged 70 years and above, demonstrating a similar point estimate (RR = 0.68; 95% CI: 0.45-1.01) to the pooled estimate reported by Nelson et al. (2009) for women aged 60 to 69, however this reduction in mortality was statistically non-significant.

A few studies have demonstrated higher rates of cancer detection with mammography in
women with a family history of breast cancer compared to women without a family history
(Halapy et al., 2004; Kerlikowske et al., 2000). Kerlikowske et al. (2000) compared women with
a first-degree family history of breast cancer to women without a family history, and found a
significantly higher positive predictive value, and significantly lower specificity for screening
mammography in women with a family history compared to family history negative women.
Several other studies in women with a family history of breast cancer have demonstrated screen-
detected breast tumors are smaller in size (Randall et al., 2009), less likely to demonstrate nodal
or distant metastases (Randall et al., 2009; Møller et al., 1999a; Møller et al., 1998; Tilanus-
Linthorst et al., 2000), and diagnosed at an earlier stage (Tilanus-Linthorst et al., 2000) compared
with symptomatic cancers. Few previous studies have examined screening outcomes among
women with a family history of breast cancer by varying levels of familial risk. One study by
Gui et al. (2001) found that women with moderate or high familial risk had proportionally fewer
tumors larger than 20mm in diameter compared to women with low familial risk, however these
findings were unadjusted and statistical significance was not reported. Halapy et al. (2004) found
that women with moderate or strong family history of breast and/or ovarian cancer had a similar
proportion of tumors larger than 20mm in diameter as women without a family history, but
women with a strong family history had the lowest proportion of node-negative breast tumors. A
subsequent study by Halapy et al. (2005) also demonstrated increased rates of interval cancers in
women with familial risk, with women with a strong family history demonstrating the highest rates. The impact of screening mammography on reducing mortality specifically in women with familial breast cancer risk remains unknown.

Clinical breast examination

Clinical breast examination (CBE) is a technique used to examine the breasts, which includes visual examination and palpation. CBE is conducted by a trained health professional, typically a physician or nurse. While there is no ‘gold standard’ in CBE technique, it typically includes examination of the breast in several standing, seated and supine positions (Vainio & Bianchini, 2002). Test sensitivity of CBE ranges from 40% to 59% (Barton et al., 1999). No trials have investigated the effect of screening with CBE alone on breast cancer mortality, relative to no screening. A study by Chiarelli et al. (2009) found that screening women with CBE in addition to mammography resulted in higher cancer detection rates, and higher sensitivity compared with screening with mammography alone. However, screening with combined mammography and CBE increased the likelihood of having a false-positive test compared with mammography alone; for each additional cancer detected by CBE per 10,000 women screened, there were an additional 55 false-positive screens (Chiarelli et al., 2009). Bancej et al. (2003) demonstrated that invasive cancers detected by both mammography and CBE were larger in size and more often node-positive than tumors detected by mammography alone. Two meta-analyses of RCTs have been published to date, demonstrating that screening with CBE in addition to mammography is not associated with reduced breast cancer mortality beyond that achievable by mammography alone (Humphrey et al., 2002; Kerlikowske et al., 1995). Similar to mammography, higher cancer detection rates for CBE have been found in women with moderate to strong familial risk relative to women with no family history of breast and/or ovarian cancer (Halapy et al., 2005).
Breast self-examination

Similar to CBE, breast self-examination (BSE) is a technique used to examine the breast and axilla using visual examination and palpation. While CBE is performed by a physician or nurse, BSE is performed by the woman herself. Evidence from clinical trials investigating the efficacy of BSE is limited. Overall test sensitivity of BSE is approximately 26% in screened women, but ranges with age from 41% in women aged 35-39 years to 21% in women aged 60-74 years (Woolf, 1992; Baker, 1982). Two reviews have demonstrated that regular BSE results in a slight increase in rates of cancer detection; however, there is no observable reduction in breast cancer mortality (Baxter, 2001; Hackshaw & Paul, 2003). None of the trials reviewed by Hackshaw & Paul (2003) found lower mortality in women who practiced BSE (pooled RR = 1.01, 95% CI: 0.92-1.12), compared with women who did not perform BSE. There is also evidence that BSE education leads to an increase in benign biopsy rates (Baxter, 2001; Hackshaw & Paul, 2003). Nevertheless, BSE is still advocated by some groups as a means of promoting breast health awareness.

Breast ultrasonography

Ultrasound is an imaging technique that produces images from reflected high-frequency sound waves in real time (Vainio & Bianchini, 2002), and can be used to visualize the internal structures of the breast. Breast ultrasonography is non-invasive and does not confer exposure to ionizing radiation. Doppler ultrasound may also be used to evaluate local tissue changes related to tumor angiogenesis (i.e. blood flow) in an identified breast mass, which aids in distinguishing malignant tumors from benign lesions and surrounding tissues (Mehta et al., 2000; Warner et al., 2001). Breast ultrasound is primarily used as an adjunct to mammography, for the evaluation of suspected breast lesions and/or to guide needle biopsy (Vainio & Bianchini, 2002). Ultrasound is
more sensitive than mammography for screening mammographically dense breast tissue (Kolb et al., 1998; Warner et al., 2001), and thus may be particularly useful for younger women who are at high risk of breast cancer. Recently, a study examined the use of breast ultrasound in combination with screen-film mammography in women with elevated breast cancer risk and dense breasts, finding that the breast cancer detection rate was raised from 8.2 per 1000 for mammography alone to 11.4 per 1000, with sensitivity increasing from 31.3% to 43.8% (Berg et al., 2012). However, the specificity of mammography alone was 92.1%, and reduced to 84.4% when ultrasound was also performed (Berg et al., 2012).

Breast magnetic resonance imaging

Magnetic resonance imaging (MRI) involves the use of rapidly fluctuating, high magnetic fields to produce cross-sectional images of internal structures (Vainio & Bianchini, 2002). Like breast ultrasound, breast MRI does not confer exposure to ionizing radiation, however a contrast agent must be intravenously infused to be able to reliably detect abnormalities (Vainio & Bianchini, 2002; Saslow et al., 2007; Warner et al., 2001). Breast MRI has traditionally been used in the characterization of breast abnormalities identified during mammography, and evaluation of patients diagnosed with breast cancer; however, it is also indicated for screening women at increased risk of breast cancer, and women with breast augmentation mammoplasty (Kuhl, 2007). The sensitivity of breast MRI is not influenced by breast density (Warner et al., 2001), thus is beneficial in screening young women. The overall test sensitivity of breast MRI is estimated to be 94% to 100% (Harms et al., 1993; Orel et al., 1994). Some studies have demonstrated that mammography has superior specificity to MRI in women with familial breast cancer risk. For example, results of the Magnetic Resonance Imaging Breast Screening (MARIBS) study in the United Kingdom demonstrated that while sensitivity was significantly higher (p = 0.01) for breast MRI (77%; 95% CI: 60-90) than mammography (40%; 95% CI: 24-
58), specificity was significantly lower (p <0.0001) for breast MRI (81%; 95% CI: 80-83) than for mammography (93%; 95% CI: 92-95) (Leach et al., 2005). Screening with combined mammography and breast MRI resulted in a sensitivity of 94% (95% CI: 81-99) and specificity of 77% (95% CI: 75-79) (Leach et al., 2005). A study that compared breast MRI with breast ultrasound, mammography, and clinical breast examination in a population of BRCA1 and BRCA2 mutation carriers in Ontario also found lower specificity for MRI; sensitivity of MRI was 100% compared with 33% for mammography, while specificity was 91% for MRI and 99.5% for mammography (Warner et al., 2001). A large multicenter study of participants from the American College of Radiology Imaging Network also demonstrated significantly lower specificity for MRI (Berg et al., 2012). After three annual screens, sensitivity for MRI was 87.5% (95% CI: 61.7-98.4) and 31.3% (95% CI: 11.0-58.7) for mammography, while specificity for MRI was 75.7% (95% CI: 72.0-79.1) and 92.1% (95% CI: 89.7-94.1) for mammography (Berg et al., 2012). Combined screening with mammography and MRI resulted in a sensitivity of 100% (95% CI: 79.4-100.00) and specificity of 70.6% (95% CI: 66.8-74.3) (Berg et al., 2012). In contrast, a few studies have found similar specificity for both mammography and MRI in populations of women with familial risk (Warner et al., 2004; Kuhl et al., 2005).

2.2.2 Potential Harms of Breast Cancer Screening

While there is strong evidence of a reduction in mortality attributable to mammography screening in women aged 40 to 49 years, and 50 to 74 years, the potential harms associated with screening for breast cancer must also be addressed. In recent years, the balance between the benefit and potential harms of breast cancer screening has been the topic of much controversy and debate. The issue of overdetection, or overdiagnosis is central to this debate. Overdiagnosis of breast cancer refers to cancers detected by a screening test, which would never have become clinically apparent during a woman’s lifetime without the intervention of screening. Because
there is no method to distinguish between cancers that would never progress to become symptomatic and cancers which would lead to death if left untreated, both types are treated similarly. Thus, treatment of an overdiagnosed cancer subjects a woman to the harms of cancer treatment without therapeutic benefit (Pace & Keating, 2014). Quantifying the magnitude of overdiagnosis is difficult; estimates have ranged from 0% to more than 50%, as a result of major differences in the populations, types of cancers included, and methods of estimation used across studies (Pace & Keating, 2014; Marmot et al., 2013). The most robust method to estimate overdiagnosis is to compare cumulative incidence of breast cancer in the screened and unscreened groups of a RCT, with adequate years of follow-up after screening ends, and where the control group was never screened (Biesheuvel et al., 2007). Two recent reviews (Pace & Keating, 2014; Marmot et al., 2013) suggest the best evidence comes from long-term follow-up from three RCTs which never invited the control group to screening, including the Malmö I trial (Zackrisson et al., 2006), and the Canadian National Breast Screening Study trials (Miller et al., 2002; Miller et al., 2000). A meta-analysis of estimates of overdetection from these trials estimates that 10.7% of breast cancers were overdiagnosed in women invited for screening mammography (Independent UK Panel on Breast Cancer Screening, 2012).

Within the context of breast cancer screening, a false-positive result refers to a positive or abnormal result on a screening test, which is subsequently found not to be cancer during recall for further assessment. False-positive results are more common in women younger than age 50 years (Canadian Task Force on Preventive Health Care et al., 2011). Harms from receiving a false-positive result include undergoing unnecessary diagnostic procedures (additional mammograms or other imaging tests, fine-needle aspiration, or open biopsy), and psychological distress. A recent systematic review demonstrated that having a false-positive mammogram led to psychological distress that endured for up to three years, that distress increased with the level
of invasiveness of the diagnostic procedure, and that women were significantly less likely to return for the next round of screening (Bond et al., 2013).

Moderate- and high-dose chest irradiation is an established risk factor for both breast cancer incidence and mortality, with the highest risk observed for exposures that occur prior to age 20 years (Preston et al., 2002; Ronckers et al., 2005). Radiation dose from a standard two-view mammogram is very low. While it has been estimated that risks of radiation-induced breast cancer are outweighed by the reduction in mortality achievable with annual or biennial screening mammography for women age 40 years or above (Yaffe & Mainprize, 2011), there are concerns that regular exposure to low-dose chest irradiation starting at a young age could increase lifetime breast cancer risk. This is particularly important for women with a first-degree family history of breast and/or ovarian cancer and BRCA mutation carriers, who are often recommended to begin screening with mammography as young as age 25 years. Additionally, it has been hypothesized that carriers of BRCA mutations have increased radiosensitivity due to impaired response to double strand DNA breaks, which can be caused by ionizing radiation (Powell & Kachnic, 2003). Millikan et al. (2005) found a significant positive association between breast cancer and number of lifetime mammograms in women with a genetic predisposition, and results reported by Pijpe et al (2012) suggest that mammogram use prior to age 30 years is associated with increased risk of breast cancer in BRCA1 and BRCA2 mutation carriers. Other studies have not observed increased risk of breast cancer from mammography in women with BRCA1 and BRCA2 mutations, and early age at first mammogram (before age 30 or 40 years) did not appear to increase this risk (Giannakeas et al., 2012; Narod et al., 2006; Goldfrank et al., 2006). It is worthy of note that much of the evidence regarding the risk of breast cancer from diagnostic and screening mammography come from studies that include screen-film mammography. The average radiation dose from digital mammography is approximately 20% lower than that from
screen-film mammography (4.7 mGy for a standard two-view screen-film mammogram vs. 3.7 mGy for a digital mammogram) (Hendrick et al., 2010). Given the increasing use of digital mammography, the risks of mammography-induced breast cancer in future will likely be slightly lower than those reported by previous studies.

2.2.3 Breast Cancer Screening Recommendations in Canada

In its 1994 report, the Canadian Task Force on the Periodic Health Examination (now the Canadian Task Force on Preventive Health Care) recommended all women aged 50 to 69 years undergo screening for breast cancer by mammography and CBE every 1 to 2 years (Morrison, 1994). The 1994 report also recommended against screening women aged 40 to 49 years (Morrison, 1994). In 2001, the Task Force performed an additional review of studies which examined the effectiveness of screening mammography in women aged 40 to 49 (Ringash, 2001). The Task Force established that the evidence was not conclusive, and that women should be informed at age 40 of the benefits and harms of screening mammography, and assisted in their decision regarding at what age to begin screening (Ringash, 2001). In November 2011, the Canadian Task Force on Preventive Health Care conducted an update of the evidence reviewed by the U.S. Preventive Health Services Task Force in 2009, and released a full update to its 1994 screening guidelines. Currently, it is recommended that average risk women between the ages of 50 to 74 years be screened with mammography at an interval of 2 to 3 years (Canadian Task Force on Preventive Health Care et al., 2011). The 2011 report also recommended against screening women aged 40 to 49 years with mammography, as well as recommended against screening average-risk women of any age with breast MRI, CBE (alone or in conjunction with mammography) or BSE (Canadian Task Force on Preventive Health Care et al., 2011).

Canadian recommendations are largely in line with those of the U.S. Preventive Health Services Task Force, which currently recommends that average-risk women aged 50 to 74 years
be screened biennially with mammography, and recommends against screening average-risk women aged 40 to 49 years with mammography (US Preventive Services Task Force, 2009). The U.S. Task force also recommends against clinicians teaching women how to perform BSE, and found insufficient evidence to make recommendations regarding screening mammography in women aged 75 years or above or CBE in women aged 40 years and above (US Preventive Services Task Force, 2009).

Breast cancer screening recommendations for women with increased breast cancer risk due to family history are based on expert opinion, and typically dictate shorter screening intervals and screening beginning at an earlier age compared with the guidelines prescribed for women at average risk of breast cancer. Such strategies include annual mammographic screening beginning at age 40 years, or 10 years prior to the earliest age of onset observed in the family (whichever occurs earliest), or starting as young as age 25 years for BRCA mutation carriers (Eccles et al., 2000; Eisinger et al., 1998; Møller et al., 1999b; Warner et al., 1999a; Chart & Franssen, 1997). The American Cancer Society currently recommends annual breast MRI for identified BRCA1/2 mutation carriers, untested first-degree relatives of carriers and women identified to have a 20-25% lifetime risk of developing breast cancer (Saslow et al., 2007). The National Hereditary Cancer Task Force in Canada similarly recommends annual mammography and MRI for BRCA1/2 carriers aged 30 to 69 years (Horsman et al., 2007). BRCA1 mutation carriers may also be recommended to undergo transvaginal ultrasounds and evaluation of Cancer Antigen-125 (CA-125) serum levels every 6 to 12 months starting at age 25 to 35 years for ovarian cancer (Burke et al., 1997; Russo et al., 2009). A summary of North American guidelines and recommendations for screening for breast cancer is located in Table 2.1.
2.2.4 Breast Cancer Screening in Canada

In Canada, mammography is freely available to screen-eligible women through organized screening programs operated at the provincial level, and opportunistically (with referral by a physician) through mammography facilities which operate outside of the provincial screening programs (Canadian Partnership Against Cancer [CPAC], 2013). Canada’s first organized breast cancer screening program was launched in British Columbia in 1988, followed by programs in Ontario, Saskatchewan, Alberta and the Yukon Territory in 1990 (CPAC, 2013; Public Health Agency of Canada, 2011). Organized breast cancer screening programs now exist in all of the Canadian provinces and territories, with the exception of Nunavut, where only opportunistic screening is available (CPAC, 2013). Organized programs provide all women without a prior diagnosis of breast cancer, aged 50 to 69 years, with a biennial, bilateral, 2-view (cranio-caudal and medio-lateral oblique) screening mammogram, through a provincially managed universal health insurance plan (CPAC, 2013). Several programs continue to offer CBE performed by a trained nurse or technologist, but most provinces have removed CBE from the screening program based on scientific evidence which indicates performance of CBE does not confer a mortality benefit (CPAC, 2013). Canada’s organized breast screening programs also facilitate the navigation of women with abnormal or inconclusive screening results through the diagnostic phase, and issues recall notices to participants who have normal or non-malignant screening results when the next screening mammogram is due (Mai et al., 2009). In some cases, screening programs in a number of provinces and territories also screen women outside of this age group or at more frequent intervals, as requested by the health care provider or client (CPAC, 2013).

The Ontario Breast Screening Program (OBSP) was established in 1990 by the Ontario Ministry of Health, under the auspices of Cancer Care Ontario. The OBSP offers mammographic screening through self- or physician-referral to women at average risk for breast cancer aged 50
to 74 years (Chiarelli et al., 2006b; Cancer Care Ontario, 2013). Screening services are offered at 165 sites across the province, including 99 hospitals and 66 independent health facilities (IHF) affiliated with the OBSP (Cancer Care Ontario, 2013). There are also two mobile coaches, offering screening services to women in remote communities in Northwestern Ontario, and the Hamilton Niagara Haldimand Brant Local Health Integration Network (Cancer Care Ontario, 2013). Based on the results of the seminal study by Chiarelli et al. (2013), which found lower cancer detection rates for digital CR compared with screen-film and digital DR mammography, Cancer Care Ontario and Ontario’s Ministry of Health and Long-Term Care initiated the replacement of digital CR mammography technology with digital DR technology at all imaging sites across Ontario in 2013 (Cancer Care Ontario, 2013). The transition to digital DR technology was completed by early 2014 (Cancer Care Ontario, Internal Communication, 2014).

As of 1 July 2011, the OBSP was expanded to include annual combined breast MRI (or breast ultrasound where MRI is contraindicated) and mammographic screening for women at high risk of breast cancer. To date, Ontario is the first region worldwide to offer screening to high-risk women within the context of an organized screening program (Cancer Care Ontario, 2013). This expansion is supported by clinical practice guidelines which suggest women at high-risk of breast cancer would benefit from annual combined screening with mammography and breast MRI (Warner et al., 2012). Currently, 28 of the OBSP screening sites offer high-risk screening services to eligible women, and at least one OBSP high-risk screening centre is located in each of the regions across Ontario (Cancer Care Ontario, 2013). Screen-eligible women include those aged 30 to 69 years with no acute breast symptoms, considered to be at high risk of breast cancer due to: (i) a known deleterious mutation in \textit{BRCA1/2} or other gene predisposing to a markedly elevated breast cancer risk; (ii) untested first-degree relative of a gene mutation carrier; (iii) a family history consistent with hereditary breast cancer syndrome and estimated
personal lifetime risk of breast cancer ≥25%; (iv) history of therapeutic chest irradiation (before age 30 years and at least eight years previously) (Chiarelli et al., 2014). It was estimated that 34,000 women in Ontario (<1%) became eligible for screening based on these criteria, and that 17 cancers per year will be detected for every 1000 high-risk women screened through the high-risk program (Cancer Care Ontario, Internal Communication, 2011). Results from the first year of OBSP high risk screening program suggest annual MRI in combination with mammography may be an effective strategy for the early detection of breast cancer in women with highly elevated breast cancer risk, especially for *BRCA* mutation carriers; of the 35 cancers detected at initial screen, none were detected by mammography alone, 23 (65.7%) were detected by MRI alone, 12 (34.3%) were detected by both MRI and mammography, and 25 (71.0%) were detected in women with known *BRCA* mutations (Chiarelli et al., 2014). Positive predictive value was highest for detection based on both MRI and mammography (12.4%).

2.3 Breast Cancer Screening Use and Predictors of Use

2.3.1 Participation in breast cancer screening

*Self-reported breast cancer screening data*

In the 2008 Canadian Community Health Survey (CCHS), 72.5% of Canadian women aged 50 to 69 years self-reported undergoing a mammogram in the previous two years (Shields & Wilkins, 2009). While this represents a significant increase from the 40.5% of women who reported a mammogram in 1990, all of this increase occurred during 1990-2001, with self-reported rates from 2001-2008 remaining stable at approximately 72% (Shields & Wilkins, 2009). In Ontario, self-reported mammogram participation in the previous two years was 73.2% in 2008, down slightly from 73.6% in 2000-2001 (Shields & Wilkins, 2009). While these self-reported participation rates do not distinguish between screening and diagnostic examinations,
91% of CCHS respondents in 2008 reported that their mammogram was for screening purposes (Shields & Wilkins, 2009).

**Validity of self-reported breast cancer screening data**

Epidemiologic research relies heavily on self-reported mammography use data in determining rates of screening participation, due to the costs and difficulty of accessing medical records to collect these data. As such, understanding the accuracy of self-reported mammography use data is critical. Overall, the validity of self-reported mammography use data is supported. Evidence from several meta-analyses indicate that self-reported data performs well in determining whether or not a woman has undergone mammography, with rates of sensitivity exceeding 90% (Newell et al., 1999; Rauscher et al., 2008; Howard et al., 2009). However, self-reported data is much less accurate for determining the exact timing mammography use. Studies have consistently demonstrated that women often underestimate the time since their last mammogram (Paskett et al., 1996; Rauscher et al., 2008; Howard et al., 2009; Caplan et al., 2003a; Caplan et al., 2003b; McGovern et al., 1998; Gordon et al., 1993; Degnan et al., 1992; Zapka et al., 1996; Etzi et al., 1994; Fulton-Kehoe et al., 1992) This phenomenon, called ‘telescoping,’ occurs when individuals recall events as more recent than they actually were (Sudman & Bradburn, 1973). In the case of mammography, the effect of telescoping leads to an overestimation of mammogram use, inflating rates of screening adherence.

Evidence regarding the factors associated with mammography recall has been mixed, and many of these studies have focused on specific sub-populations of women based on ethnicity or income, limiting their generalizability. Some studies have demonstrated that age (Rivera et al., 2006; Brown & Adams, 1992; Bancej et al., 2004; Norman et al., 2003), ethnicity (Rauscher et al., 2008; Zapka et al., 1996; Rivera et al., 2006; Cronin et al., 2009; Hiatt et al., 1995; Lawrence et al., 1999), income (Bancej et al., 2004), education (Caplan et al., 2003a; Rivera et al., 2006),
marital status (Rivera et al., 2006), indication for mammogram (Rivera et al., 2006), recency of the mammogram (McGovern et al., 1998; Craig et al., 2009), and family history of breast cancer (Caplan et al., 2003a) are associated with accuracy of self-reported mammogram data. Others however, have provided no evidence that factors such as age (Caplan et al., 2003a; McGovern et al., 1998), income (Degnan et al., 1992; Zapka et al., 1996), ethnicity (Caplan et al., 2003a; McGovern et al., 1998), perceived risk (Caplan et al., 2003a), or number of years since last visit to a health professional (Caplan et al., 2003a) are significantly associated with recall.

While the quality of self-reported mammogram use data has been studied in depth, studies have focused on women with population-level risk of breast cancer. The two studies which validated self-reported mammogram data in women with familial risk only included women with very strong familial breast cancer histories (Pijpe et al., 2011; Larouche et al., 2012), who are likely to differ in their breast cancer screening behaviours and recall of these behaviours compared with women in the broader population of women with familial risk.

Administrative breast cancer screening data

Data from the Ontario Health Insurance Plan (OHIP) and the OBSP, demonstrates that participation in mammography screening in Ontario is lower than suggested by self-reported data from the CCHS. In 2010-2011, 60.8% of eligible women in Ontario were screened with mammography, remaining stable from 2008-2009 when 61.1% of eligible women in the province were screened with mammography (Cancer Care Ontario, 2013). These rates are slightly lower than the rates seen in 2007-2008, when an estimated 66.3% of eligible women of average-risk were screened, 64.0% in 2005-2006, and 61.5% in 2003-2004 and 2001-2002 (Cancer Care Ontario, 2010). The current rate of screening mammography participation in Ontario is currently below the national target of 70% (Cancer Care Ontario, 2013). The majority of screening mammograms performed in Ontario occur within the context of the OBSP; in 2010-2011, 71.1%
of screening mammograms were performed at an OBSP site (Cancer Care Ontario, 2013). This represents an increase from 2008-2009, when 65.7% of women were screened within the OBSP (Cancer Care Ontario, 2013).

2.3.2 Familial breast cancer risk and participation in breast cancer screening

A meta-analysis of 19 studies suggests there is a positive relationship between having a family history of breast cancer and mammogram use; women with familial risk were more likely to have screened with mammography than women without a family history of breast cancer (Pearson’s $r = 0.27, p < 0.001$) (McCaul et al., 1996). However, many of these studies measured the ever-use of screening mammography, as opposed to guideline-adherent screening use. Several subsequent studies of women with familial breast cancer risk, typically including $BRCA1/2$ mutation carriers or women attending genetic counselling, have suggested relatively high rates of adherence (67-90%) to mammography and CBE guidelines (Antill et al., 2006; Isaacs et al., 2002; Lerman et al., 2000; Meiser et al., 2000). One Australian population-based study of women of multiple-case breast cancer families demonstrated high adherence (74%) to mammography guidelines (Price et al., 2011). Two North-American population-based studies however, have demonstrated relatively lower levels of adherence (Madlensky et al., 2005; Campitelli et al., 2011). Results from one study indicated that only 40% of women had obtained a mammogram in the previous 11 months (Madlensky et al., 2005). The other, a cross-sectional study from the same Ontario cohort of female relatives of breast cancer cases who form the study population for this thesis, indicated that 36.1% of women at low familial risk and 55.5% of women at moderate to high familial risk had undergone mammography in the previous 12 months (Campitelli et al., 2011). An inverted u-shaped relationship has also been hypothesized, wherein women at the extreme ends of breast cancer risk due to family history may be screened less than women with moderate levels of breast cancer risk (Hailey, 1991). It is thought that this
relationship may be mediated by worry about cancer risk (Andersen et al., 2003; Kash et al., 1992).

2.3.3 Behavioural factors and breast cancer screening

A number of health behaviour theories have been used extensively in attempts to explain the cognitive processes which influence women to participate in breast cancer screening, including the Health Belief Model (Becker, 1974), Protection Motivation Theory (Rogers, 1975), and the Theory of Reasoned Action/Theory of Planned Behaviour (Fishbein & Ajzen, 1975; Ajzen, 1988).

The Health Belief Model

The Health Belief Model (HBM) was developed in the 1950’s by social psychologists at the U.S. Public Health Service, in an attempt to explain and predict the factors implicated in the widespread underutilization of disease preventives and screening tests for the early detection and diagnosis of disease, such as participation in screening programs for tuberculosis (Janz & Becker, 1984; Steckler et al., 2010). Since, the HBM has been used extensively to organize the theoretical predictors of early detection health behaviours, and specifically in the breast cancer screening literature to explain the conditions under which women will participate in breast cancer screening. Two assumptions underlie the HBM: (i) that an individual has a desire to avoid disease (or to become well) and; (ii) that an individual believes that undertaking a specific health behaviour will prevent or ameliorate that disease (Janz & Becker, 1984). Specifically, the HBM includes four dimensions believed to motivate health protective behaviours: (i) *perceived susceptibility*: perception of personal vulnerability or risk of developing a certain disease or condition; (ii) *perceived severity*: perception of the seriousness or consequences (clinical and social) of developing a disease or condition, or of leaving it untreated; (iii) *perceived benefits*:
beliefs regarding the effectiveness of the various health actions available in reducing or ameliorating the treat of developing a disease or condition; and (iv): perceived barriers: the potential negative aspects of a particular health behaviour or impediments perceived to the ability to undertake that particular behaviour (Rosenstock, 1974). According to the model, individuals engage in a subconscious cost-benefit analysis, and will undertake a particular preventive or early detection behaviour if the benefits of the behaviour outweigh the barriers (Rosenstock, 1974). A number of indirect factors were also thought to exert influence on the four dimensions, including: socio-demographic factors (age, race, ethnicity, socioeconomic status), psychological factors (personality) and structural factors (knowledge about disease) (Rosenstock, 1974).

Other Health Behaviour Theories

Following the development of the HBM, additional health behaviour theories were developed under a similar framework. Protection Motivation Theory is a theory of cognitive change that was developed by Rogers in 1975 to explain and predict how individuals cope with threats (Rogers, 1975). Generally, Protection Motivation Theory proposes that a fear appeal (fear-arousing communication regarding threat to an individual’s well-being and measures that can be taken to avoid it or reduce its impact) will initiate a corresponding cognitive process of protection motivation (an intervening variable that arouses, maintains and directs appropriate activity) that involves threat and coping appraisal (Rogers, 1975). Similar to the HMB, the process of threat appraisal includes appraisal of the following constructs: (i) perceived personal vulnerability to the threat; and (ii) perceived severity of the threat; but also includes (iii) magnitude of fear or anxiety that is evoked as a result of the threat (Rogers, 1975). The process of coping appraisal includes: (i) response efficacy: perceptions regarding whether the recommended coping response is effective in reducing the threat (similar to the HMB’s perceived benefits); (ii) self-efficacy: perceptions regarding ability to undertake the
recommended coping response; and (iii) response cost: perceptions regarding how costly (financially burdensome, time-consuming, inconvenient, painful, etc.) performing the recommended coping response will be (similar to the HBM’s perceived barriers) (Rogers, 1975).

The Theory of Reasoned Action was developed by Fishbein in 1975 in an attempt to explain health behaviours, assuming that individuals make rational choices based on available information (Fishbein & Ajzen, 1975). According to this theory, the most important determinant of undertaking a health behaviour is intention. Behavioural intention is further comprised of: (i) an individual’s belief toward the health behaviour and the outcomes of undertaking that behaviour; and (ii) the social normative influence of others who are considered significant in the individual’s life (Fishbein & Ajzen, 1975). The Theory of Planned Behaviour (Ajzen, 1991), is an extension of the Theory of Reasoned Action, adding the construct of perceived behavioural control. Perceived behavioural control refers to an individual’s belief regarding the ease or difficulty associated with performing a certain health behaviour (Ajzen, 1991).

Perceived risk and breast cancer screening

The relationship between objective measures of breast cancer risk, perceived breast cancer risk, and breast cancer screening participation has been studied extensively both in women with population-level breast cancer risk, and women with familial risk of breast and/or ovarian cancer. Briefly, it is believed that women who hold a more realistic perception of their risk of developing breast cancer will be motivated to undertake health protective behaviours appropriate to that level of risk, such as undergoing screening for breast cancer (Rosenstock, 1974; Levanthal et al., 1999). Results from two meta-analyses indicate that there is a small but significant association between perceived breast cancer risk and breast cancer screening (McCaul et al, 1996; Katapodi et al., 2004). These reviews have generally included studies of women from the general population, thus results are likely not generalizable to women at high-risk of breast
cancer. Additionally, many of these studies have examined the relationship between perceived risk and ever use of breast cancer screening, as opposed to screening according to prescribed guidelines. A number of studies have been conducted which focus on examining the relationship between perceived risk and breast cancer screening behaviours specifically in women with familial breast cancer risk; however, to our knowledge, no previous review of this evidence has been conducted. Synthesizing this evidence is critical to clearly understanding whether perceived breast cancer risk influences the use of breast cancer screening in women with familial breast cancer risk, to evaluate the quality of this evidence, and identify areas where future research may be needed. As such, we conducted a review of observational studies which investigated the relationship between perceived risk and adherence to breast cancer screening guidelines in women with a family history of breast and/or ovarian cancer. A meta-analytic approach was not taken due to the high levels of heterogeneity observed across studies (Higgins & Green, 2011; Bailar, 1997), in study design, study setting (time period, and country), inclusion criteria (age, and definition of family history), and measurement (measurement of perceived breast cancer risk, and definition of breast cancer screening adherence).
2.3.4 Manuscript 1: Perceived risk and adherence to breast cancer screening guidelines among women with a familial history of breast cancer: A review of the literature


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ABSTRACT

Objectives: A small positive association has been consistently demonstrated between perceived breast cancer risk and mammography use. Evidence specific to women with familial breast cancer risk has not been previously reviewed. Methods: A literature search was conducted. 186 studies were identified for abstract/full-text review, of which 10 articles were included. Manual searching identified 10 additional articles. Twenty articles examining the association between perceived breast cancer risk and adherence to mammography, clinical breast examination (CBE) or breast self-examination (BSE) guidelines among women with familial breast cancer risk were reviewed. Studies were classified according to screening modality, categorized by finding and ordered by year of publication. Studies assessing mammography were further classified according to the applied method of measuring perceived risk. Results: Our review found a weak positive association between higher perceived risk and adherence to mammography guidelines among women with familial breast cancer risk. Consistent associations between perceived risk and adherence to CBE and BSE guidelines were not observed. Conclusions: Our ability to understand the relationship between perceived breast cancer risk and adherence to breast screening guidelines is limited, because most previous research is cross-sectional. Future studies with prospective methodologies that use consistent measurement methods and are adequately powered are warranted.

Keywords: breast cancer; perceived risk; screening; mammography; family history; review
Introduction

Breast cancer is the leading incident cancer and cause of cancer-related mortality among women worldwide [1]. Having a family history of breast cancer has been established as one of the most important risk factors for breast cancer. Specifically, women with an affected first-degree relative have approximately twice the risk of developing breast cancer and risk is increased when more than one relative is affected or the relative is younger at age of diagnosis [2-4]. Two high-risk cancer-disposing genes, BRCA1 and BRCA2, have been identified, with carriers at an estimated 40-70% risk of developing breast cancer [5-8].

Mammography screening has been demonstrated to reduce breast cancer mortality among average risk women aged 50-74 years [9]. Similar benefits have not been established for clinical breast examination (CBE) and breast self-examination (BSE) [10-12]. Breast cancer screening guidelines for women at increased risk, based on expert opinion, typically include annual screening with mammography and CBE starting prior to age 50 [13-17]. The American Cancer Society recommends annual breast MRI for identified BRCA1/2 mutation carriers, untested first-degree relatives of carriers and women identified to have a 20-25% lifetime risk of developing breast cancer [18]. The National Hereditary Cancer Task Force in Canada also recommends annual mammography and breast MRI for BRCA1/2 mutation carriers aged 30-69 years [19]. BRCA1 mutation carriers are additionally recommended to undergo transvaginal ultrasounds and evaluation of Cancer Antigen-125 (CA-125) blood serum levels every 6-12 months from age 25-35 years for ovarian cancer [20,21].

While results from one meta-analysis suggest a positive relationship exists between familial breast cancer risk and mammogram use [22], many of these studies measured ever-use of screening as opposed to guideline adherent use. Recent results examining screening adherence among women with familial breast cancer risk have been mixed. One Australian population-
based study of women of multiple-case breast cancer families demonstrated high adherence (74%) to mammography guidelines [23]. Several recent North American population-based studies however, have demonstrated relatively lower rates of adherence, one indicating only 40% of women with familial risk had obtained a mammogram in the previous 11 months [24], and the other indicating only 36.1% of women at low familial risk and 55.5% at moderate to high familial risk had undergone mammography in the previous 12 months [25]. An inverted u-shaped relationship has also been suggested [26], wherein women at the extreme ends of risk may screen less, in a relationship influenced by worry [27,28].

Breast cancer screening requires behavioural action at the individual level. As such, understanding the factors which influence screening uptake is critical to increasing rates of adherence to screening guidelines. There is an extensive literature focusing on the relationship between perceived susceptibility to breast cancer and breast cancer screening behaviours. The construct of perceived risk is central to several health behaviour theories, including the Health Belief Model (HBM) [29], Protection Motivation Theory [30], and the Theory of Reasoned Action/Theory of Planned Behavior [31,32]. These theories, especially the HBM, have been used extensively in attempts to explain the cognitive processes which influence women to participate in breast screening. Briefly, it is believed that a realistic perceived risk would motivate individuals to undertake health-protective behaviours appropriate to the level of risk, facilitating the process of early detection and treatment [33,34].

There is a lack of consistency in the measurement of perceived risk due to a lack of consensus regarding the most valid approach. While there is no existing gold standard, the most commonly used scales include numeric probability scales, which ask respondents to rate their risk on a 0-100% probability continuum of developing breast cancer, verbal Likert-type scales,
which ask for similar responses using a verbal continuum from “extremely unlikely” to “extremely likely,” [35-41] or other types of numeric scales (e.g. “1 in x”) [42].

Results from two previous reviews indicate a small but significant positive association between perceived risk and mammography use ($r = 0.16$ and $g = 0.19$) [22,43]. These reviews have generally included studies of women with population-level risk of breast cancer and studies that examined the ever-use of screening. To our knowledge, no previous review has examined this relationship in women with familial breast cancer risk. This review is critical to better understanding whether perceived risk influences guideline-adherent breast screening use in women with familial breast cancer risk. Accordingly, the objectives of this review were to: (i) identify all observational studies that examined the association between perceived breast cancer risk and adherence to breast screening (mammography, CBE, BSE) recommendations among women with familial breast cancer history; (ii) examine these studies in regard to methodological criteria, including measurement of the construct of perceived risk and other study design features, including recruitment of the study population, sample size, and the analyses conducted.

Materials and Methods

Search Strategy

Searches of the following databases were performed: PubMed, PsycINFO (1960-2011), EMBASE (1980-2011) and The Cochrane Library. Queries were conducted of article titles, abstracts and keywords employing combinations of the following terms: breast cancer or breast neoplasm or mammary cancer and perceived risk or risk perception or attitudes and breast screening or early detection or health behavior or surveillance or mammography or breast self-examination or clinical breast examination and family history or family members or at-risk
No restrictions were placed on publication year or sample size, however studies were restricted to those with observational designs, published in English and female subjects.

**Selection Criteria**

The full selection process is shown in Figure 1. Initial queries identified a total of 313 articles from PubMed (n=93), PsycINFO (n=75), EMBASE (n=141) and The Cochrane Library (n=2). Duplicates were removed (n=127), leaving 186 studies. Titles and abstracts were screened. Full text review was conducted where the paper passed eligibility screening or the abstract did not provide sufficient information to determine eligibility. Articles were excluded if they: focused on cancer at a site other than the breast, did not assess the relationship between perceived risk and screening adherence, the study population did not have a family history of breast cancer, were reviews, dissertations or qualitative studies, had a non-observational design, were duplicate publications of the same data, could not be located, intention to undergo screening was assessed, only women with excessive BSE practices were included, perceived risk of BRCA1/2 mutation was assessed, scale of measurement of perceived risk was undefined, did not present findings indicating direction of the association, included women with a previous breast cancer diagnosis, or had limited generalizability.

Manual searches of bibliographic references of relevant articles identified by database search and two previously published meta-analyses were conducted, identifying 9 additional articles. One article authored by the authors’ research team was also included [44]. A total of 20 studies [23,28, 44-61] were included. Studies were classified according to screening modality, categorized by finding and ordered by publication year. Studies assessing adherence to mammography screening guidelines were further classified by perceived risk measurement scale. Studies were also examined and described on the basis of quality using eleven criteria specific to observational studies included in the checklist from the Downs and Black quality assessment tool.
Ratings included ‘poor’ (satisfied 5 or fewer criteria), ‘fair’ (satisfied 6-8 criteria) or ‘good’ (satisfied 9 or more criteria).

Results

Perceived Risk and Adherence to Mammography Guidelines

Table 1 summarizes 5 studies which analyzed the relationship between perceived risk of breast cancer measured on a numeric scale and adherence to mammography guidelines. Perceived risk was measured uniformly across all studies, using an absolute scale from 0 to 100. Zhang et al. [44] and Schwartz et al. [45] reported that higher ratings of perceived risk were associated with mammography adherence, with effect sizes ranging from Odds Ratio (OR) = 1.21 to 2.41. Three other studies reported no association, indicating ratings of perceived risk were approximately equal among adherent and non-adherent women [23,46,47]. Zhang et al. [44] employed a population-based recruitment strategy, while the remaining studies used clinic-based recruitment. Zhang et al. [44] also had a relatively large sample size (n = 1019) and performed multivariate analyses. Schwartz et al. [45], who reported a positive association which approached statistical significance, similarly recruited relatives of cases of breast cancer and performed multivariate analyses, however used clinic-based recruitment and had a small sample size (n = 200), which may have resulted in inadequate power to detect a significant effect. Zhang et al. [44] and Schwartz et al. [45] similarly defined adherence as undergoing mammography within the past 12 months, while the studies reporting null findings measured adherence over longer periods (2-3 years) [23,46].

Table 2 includes 12 studies which analyzed the relationship between perceived breast cancer risk measured on a verbal scale and mammography adherence. Findings were more consistent, with 6 studies reporting a positive association [44,48-52], four of which were
statistically significant [44,48-50]. Zhang et al. [44] and Lemon et al. [49], both used similar comparative measures of perceived risk, and reported adjusted estimates (OR =1.82-2.90). Both studies had relatively large sample sizes and defined adherence as undergoing mammography within the previous 12 months. Lemon et al. [49] employed a prospective design, while Zhang et al. [44] used cross-sectional data. Finney-Rutten & Iannotti [50] alternatively used an absolute measure of perceived risk and reported an effect size of a lower magnitude (OR =1.41; 95% CI: 1.05-1.89). Only Polednak et al. [53] reported a negative association. This study used a random sampling recruitment approach and reported unadjusted results. Five studies demonstrated no association between perceived risk and mammography adherence [54-58], generally defined as screening within the past 12 months. Recruitment methods for these studies were largely clinic-based, with the exception of Drossaert et al. [56] who recruited women through a population-based cancer screening program. With regard to design, two of the studies reporting null findings used prospective cohort designs, while the remainder were cross-sectional. These studies also had small to moderate sample sizes and only two reported multivariate results, leaving more than half vulnerable to confounding.

Perceived Risk and Adherence to CBE Guidelines

Six studies examined the relationship between perceived risk and adherence to CBE guidelines, and are summarized in Table 3. A majority reported null findings [23,51,54,59], with one study reporting a significant positive association [28] and another reporting a non-significant positive association [44]. Kash et al. [28] examined CBE adherence in a small sample of women who were self-selected into a breast screening group, employing a verbal measure of perceived risk and defining adherence as undergoing CBE within the past 6 months, but did not present adjusted results. Zhang et al. [44] who also reported a non-significant positive relationship, conversely employed a large population-based sample of female relatives of breast cancer cases,
used a numeric measure of perceived risk, defined adherence as undergoing CBE in the past 12 months and adjusted for a number of potential confounders. In regard to the studies reporting no association, there was wide variation in study populations, approaches for measuring perceived risk, definitions of guideline-adherence and analyses conducted. The two cohort studies by Price et al. [23] and Martin & Degner [54], measured screening adherence over 3-year periods, but differed on all other features. Price et al. [23] employed a population-based recruitment approach, had a large sample size (n=748), measured perceived risk numerically and presented adjusted results, indicating that perceived risk was approximately equal among under-screeners and adherent women (OR = 0.99). Martin & Degner [54], recruited a small sample of women (n=56) from a hereditary breast cancer clinic, used an absolute verbal measurement of perceived risk and reported bivariate results only. The two cross-sectional studies, conducted by Isaacs et al. [51] and Benedict et al. [59] similarly recruited relatively small samples of women who had undergone genetic testing or were daughters of cases of breast cancer, respectively.

**Perceived Risk and Adherence to BSE Guidelines**

Table 4 summarizes 8 studies which examined the relationship between perceived risk and adherence to BSE guidelines. Similar to the results observed with CBE, methodologies and findings were mixed. Brain et al. [60] and Zhang et al. [44] indicated that women with higher ratings of perceived risk practiced BSE more frequently than women with lower ratings of perceived risk. Both studies had substantial sample sizes, were cross-sectional and presented results that were adjusted for age, at minimum. Both studies also measured perceived risk using both absolute and comparative measures, however Brain et al. [60] used a verbal measure, while Zhang et al. [44], examined perceived risk with both verbal and numeric measures. Two studies, conducted by Kash et al. [28] and Lindberg & Wellisch [47], reported statistically significant negative relationships, wherein women with higher levels of perceived risk were less likely to
perform BSE. Both studies were cross-sectional and reported unadjusted results. Kash et al. [28] measured perceived risk verbally and had a relatively small sample (n=217) of women who were members of a breast screening program. Lindberg & Wellisch [47], however, had a larger sample of patients of a high-risk breast cancer clinic, who had all undergone genetic counseling, and measured perceived risk on an absolute numeric scale. Four studies reported no association between perceived risk and BSE performance [23,56,60,61], and demonstrated many methodological differences. Price et al. [23] who used a population-based recruitment strategy of female relatives of breast cancer cases, collected data prospectively, had a relatively large sample size (n=748), measured perceived risk using an absolute numeric scale and adjusted for a number of important socio-demographic and cognitive factors. Cohen [61] and Benedict et al. [59] both recruited small samples of only daughters of breast cancer cases and used a “1 in x” approach to measure perceived risk. Cohen [61] presented results adjusted for several cognitive factors, as well as age and education, while Benedict [59] reported bivariate results. Drossaert et al. [56], had a moderate sample size (n=379) of women invited for a mammogram by a screening program, used both an absolute and comparative verbal scale to measure perceived risk and similarly presented unadjusted results.

Discussion

Perceived breast cancer risk appears to be only weakly positively associated with adherence to screening mammography guidelines. This relationship does not hold for adherence to guidelines for CBE or BSE. While the association between perceived risk measured on a numeric scale and mammography was not consistently positive, when perceived risk was measured verbally, a more consistent positive association was found. With the exception of one study [49], no evidence of a curvilinear relationship was demonstrated. Lemon et al. [49], however, found that women who reported their chances of getting breast cancer as “higher” than
women without a family history were more likely to adhere to mammography guidelines compared with women who reported their chances as “the same/lower,” but women who reported their chances as “much higher,” were not more likely adherent. Only a few studies calculated objective breast cancer risk [46-48,52,54], generally finding that women significantly overestimated their risk [46,47,54].

Findings of this review were similar to the conclusions drawn from previously published meta-analyses examining perceived risk and breast screening use. Katapodi et al. [43] also indicated the association between perceived risk and BSE use has been inconsistently reported. Both McCaul et al. [22] and Katapodi et al. [43] demonstrated a small but significant positive association between higher levels of perceived risk and mammography use. However, many studies examined ever-use of screening as opposed to guideline-adherent screen use. Thus, women who reported single screening episodes were not distinguished from women who engaged in screening that conformed to prescribed guidelines. This is an important distinction as continual screening adherence is necessary for appreciably reducing risks. Additionally, a majority of the women included in the previous reviews had a population-level risk of breast cancer, rather than a family history of breast cancer. Women whose relatives have been diagnosed with breast cancer may hold exaggerated risk perceptions or disproportionately experience cognitions such as cancer-related distress, anxiety, depression, worry and fear regarding breast cancer. Previous research has indicated that as many as half to three-quarters of women with familial breast cancer history overestimate their personal risk of developing breast cancer [46,47,63,64]. This may result in a negative impact on coping abilities and in turn, reduce the likelihood of screening. Research has also demonstrated that women with higher levels of worry or anxiety are more likely vigilant or hypervigilant with regard to screening [55,
however several studies have indicated that intrusive levels of cancer anxiety, worry or distress may deter screening uptake in women with familial risk [28,45,47,58].

With regard to the methodological quality of the studies, 9 studies received a good quality rating [23,44-46,49,50,52,57,60], while the remaining 11 [28,47,48,51,53-56,58,59,61] were rated as fair. None of the included studies had a poor quality rating. Over half of the studies had samples of 300 subjects or less, giving them limited power to detect statistical significance given the observed effect sizes. Study populations varied, with only three studies employing population-based recruitment strategies [44,46,56]. Many samples consisted of women identified from high-risk clinical settings, limiting generalizability to women in the broader population with a familial breast cancer history. Many women recruited from clinical settings were reported to have undergone genetic testing, have strong familial histories of breast cancer and markedly high rates of adherence to screening mammography guidelines (80-95%) [47,51,54,55]. Study populations also varied by age. Previous research has suggested that rates of screening among women with familial risk may differ by age [25,66] and several studies included in this review suggest that age may modify the relationship between perceived risk and adherence to screening guidelines [49,53].

It is also critical to note the heterogeneity in measurement of perceived risk. Risk perception is a subjective construct, leading to difficulties in its conceptualization, measurement and translation. There are substantial differences in the types of measurement scales employed, including Likert-type verbal scales or numeric scales, and the measurement of absolute vs. relative or comparative risk. Differences have been demonstrated in the estimates of perceived risk produced by different types of scales. Numeric scales appear more likely to result in an overestimation of risk, while verbal scales are more likely to produce the opposite effect, particularly when women are asked about their comparative risk [43,67]. One previous study
demonstrated poor correlations between the numeric and verbal scales used to measure perceived cancer risk [68].

Several studies have demonstrated evidence that even highly-educated people have difficulty interpreting basic numeric probability statistics [69-71]. Numeracy (one’s aptitude for basic mathematical concepts) has been linked with consistency in using perceived risk measurement scales [72] as well as accuracy of risk estimates [70,73-74] and therefore offer improved levels of precision and interpretability to scientists compared to verbal scales. Nonetheless, research suggests that respondents favor verbal scales. For example, Diefenbach et al. [75] found that college students reported perceived risk scales with verbal anchors easier to use and more representative than numeric scales. Woloshin et al. [76] similarly found that the verbal scale demonstrated the highest usability and satisfaction scores, as well as test-retest reliability for assessing perceived breast cancer risk, while numeric scales (linear odds and “1 in \(x\)”) were reported to be harder to use, had lower satisfaction scores more missing responses and poorer test-retest reliability.

Scale performance can also be affected by factors including the ordering of items or perceived risk held by the respondent. Levy et al. [35] analyzed the psychometric properties of the numeric, verbal and comparative measures of perceived breast cancer risk, finding good convergent validity (\(r > 0.60\)). Scale performance however relied on the level of perceived risk actually held. This study [35] demonstrated that for identifying women with very high risk perceptions, the numeric and comparative measures had the highest sensitivity and specificity. For women with very low risk perception, the numeric measure demonstrated the lowest sensitivity while the comparative measure demonstrated the highest sensitivity and lowest specificity. Another study [77] indicated that perceptions of ovarian and colorectal cancer risk were lower when a question measuring comparative risk preceded an item measuring absolute
risk. Differences in the types of measurement of perceived risk may explain the inconsistent findings.

Lastly, it is critical to highlight the lack of prospective studies. Only a few studies employed prospective designs [23,48,49,55]. The simultaneous measurement of perceived risk and adherence to breast screening guidelines precludes insight into causality of the observed associations. It is possible that participation in breast cancer screening (or lack thereof), or the findings of previous screens may influence perceived breast cancer risk, making reverse causation a concern. This is a significant limitation and the need for future prospective studies has been deemed necessary to confirm previous findings [23,53,78-81].

The findings of this review must be considered in light of several limitations. It is based solely on published data in the English language. Publication bias may lead to an over-representation of positive and statistically significant results [82] and studies with positive results are more likely to be published in English language journals [83]. Additionally, a majority of studies that measure breast screening behaviours, including all of the studies described in this review, rely on the use of self-reported use of breast screening tests. While self-reported mammography data is useful in determining whether or not a woman has undergone screening, evidence suggests that women may underestimate the time since their last mammogram [84-86], which may lead to an overestimation of guideline-adherent use.

Perceived risk of breast cancer appears to have a weak to moderate positive relationship with mammography adherence among women with familial breast cancer risk, with the causal direction of the observed association not yet established. Previous work suggests that the weak association between perceived risk and breast screening is predictable [34], as the decision to undergo breast screening is dependent on the complex interaction of a number of cognitive and environmental factors [22,43]. The lack of a clear effect limits the ability to make
recommendations regarding strategies to facilitate increased adherence to breast screening guidelines among women with familial risk. Heterogeneity in design, measurement and screening guidelines likely account for much of the inconsistency observed. The most optimal method of accurately measuring perceived risk has yet to be determined and the lack of consistency in practice makes cross-study comparisons difficult. Future studies with prospective methodologies that use consistent measurement, are adequately powered and account for potential confounding, mediating and effect-modifying factors are warranted.

Appropriate use of mammography and other breast screening modalities is critical for early detection and diagnosis of women at increased risk of breast cancer and may impact overall prognosis. Further investigation of how high-risk women perceive their risk, the proximity of perceived risk to objective risk and how perceived risk may influence breast screening practices is needed. This will allow researchers and practitioners to understand where appropriate risk education and management efforts should be focused.

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Conflict of interest statement: The authors declare that there are no conflicts of interest.

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References


Figure 1. Flow diagram of study selection process

Unique articles identified by database search (n = 186)

Excluded following title/abstract screening (n = 148):
- Did not examine relationship of interest (n = 69)
- Did not conduct analyses separately for FH+ women (n = 37)
- Review, dissertation or qualitative study (n = 28)
- Non-observational design (n = 8)
- Cancer occurring at site other than the breast (n = 6)

Studies flagged potentially relevant and subjected to full-text review (n = 38)

- Excluded (n = 28):
  - Assessed intention to screen/interest in screening (n = 7)
  - Non-observational design (n = 6)
  - Did not measure screening use according to guidelines (n = 2)
  - Assessed women with excessive BSE practices only (n = 2)
  - Assessed perceived risk carrying BRCA mutation (n = 2)
  - No results presented (n = 1)
  - Perceived risk measurement scale not defined (n = 1)
  - Duplicate publication (n = 1)
  - Article could not be located (n = 1)
  - Did not conduct analyses separately for FH+ women (n = 1)
  - Included women with previous breast cancer diagnosis (n = 1)
  - Limited generalizability (n = 3)

Relevant articles identified by manual search (n = 10)

Included in review (n = 20)

* FH+ = family history of breast cancer; BSE = breast self-examination
### Table 1. Perceived Risk of Breast Cancer (Numeric Scale) and Adherence to Mammography Guidelines

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Sample (N) (Family History)</th>
<th>Design*</th>
<th>Perceived Risk (PR) Measure</th>
<th>Definition of Screening Adherence</th>
<th>Result</th>
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<tbody>
<tr>
<td><strong>Significant Positive Association</strong></td>
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<tr>
<td>Zhang et al., 2011, Canada [44]</td>
<td>Relatives aged 20-69 of BC cases (N = 1019) (1st-degree relative)</td>
<td>CR</td>
<td>Absolute lifetime risk – 0 to 100</td>
<td>≤ 12 months</td>
<td>Multivariate: Women with PR 50% (OR = 2.41, 1.29-4.49) or &gt;50% (OR = 1.94, 1.08-3.49) more likely to screen &gt; 12 months (OR= 2.09, 1.15-3.79), and ≤ 12 months (OR = 1.91, 1.15-3.16) vs. PR &lt;50%</td>
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<tr>
<td><strong>Non-Significant Positive Association</strong></td>
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<td>Schwartz et al., 1999, U.S. [45]</td>
<td>Relatives aged 40+ of BC cases (N = 200) (1st-degree relative)</td>
<td>CR</td>
<td>Absolute lifetime risk – 0 to 100%</td>
<td>≤ 12 months</td>
<td>Multivariate: Women with higher level of PR more likely to screen (OR = 1.21, 0.97-1.50, p &lt;0.10) vs. lower PR</td>
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<tr>
<td><strong>No Association</strong></td>
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<tr>
<td>Price et al., 2010, Aus./N.Z. [23]</td>
<td>Relatives of BC cases (N = 748) (multiple BC case families)</td>
<td>CO</td>
<td>Absolute lifetime risk – 0 to 100</td>
<td>0-3 screens in ≤ 3 years (based on age and breast cancer risk)</td>
<td>Multivariate: PR approx. equal among under-screeners (OR = 0.99, 0.98-1.00), over-screeners (OR = 1.00, 0.99-1.01) vs. adherent women</td>
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<tr>
<td>Bowen et al., 2003, U.S. [46]</td>
<td>Relatives aged 18-73 of BC cases (N = 357) (1 blood relative)</td>
<td>CR</td>
<td>Absolute risk – 0 to 100</td>
<td>≤ 24 months</td>
<td>Multivariate: PR approx. equal among women who screened (OR = 1.00, 0.99-1.20) vs. did not screen</td>
</tr>
<tr>
<td>Lindberg &amp; Wellisch, 2001, U.S. [47]</td>
<td>Patients aged 15-78 of a high-risk BC clinic (N =430) (self-reported family history)</td>
<td>CR</td>
<td>Absolute lifetime risk – 0 to 100%</td>
<td>Guideline-compliant - 1 (‘generally’) to 3 (‘rarely’)</td>
<td>Bivariate: No correlation between PR and screening compliance (r = 0.02, p &gt;0.01)</td>
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</tbody>
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* Design: CR = Cross-sectional; CO = Cohort; CC = Matched Case-Control
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<td>Zhang et al., 2011, Canada</td>
<td>Relatives aged 20-69 of BC cases (N = 1019) (1st-degree relative)</td>
<td>CR</td>
<td>Comparative lifetime risk (same-aged women) - 1 (‘much below avg.’) to 5 (‘much above avg.’)</td>
<td>≤ 12 months</td>
<td>Multivariate: Women with PR ‘above’/‘much above’ more likely to screen (OR = 1.82, 1.17-2.81) vs. PR ‘same’/‘below’/‘much below’</td>
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<tr>
<td>Somers et al., 2009, U.S.</td>
<td>Relatives aged 22-69 recruited through the community (N = 187) (1st-degree relative)</td>
<td>CO</td>
<td>Absolute and comparative risk (same-aged women); 4-item sum score</td>
<td>≥ 40: annual, &lt; 40: speak with health care professional</td>
<td>Bivariate: Perceived risk significantly correlated with adherence ($r = 0.27, p &lt;0.001$)</td>
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<tr>
<td>Lemon et al., 2006, U.S.</td>
<td>Relatives aged 18+ of BC cases (N = 577) (1st-degree relative)</td>
<td>CO</td>
<td>Comparative risk (women without family history) - 1 (‘much lower’) to 5 (‘much higher’)</td>
<td>Within 1 year of relative’s diagnosis</td>
<td>Multivariate: Among women 50-75, adherence higher among those with ‘higher’ PR (OR = 2.90, 1.29-6.50, $p = 0.01$) vs. ‘same’/lower PR. Adherence was not higher among women with PR ‘much higher’ (OR = 1.43, 0.60-3.43, $p = 0.42$) vs. ‘same/low’</td>
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<tr>
<td>Finney-Rutten &amp; Iannotti, 2003, U.S.</td>
<td>Women due for annual screen (N = 300) (≥ 1 relative with BC)</td>
<td>CR</td>
<td>Absolute risk - 1 (‘extremely unlikely’) to 7 (‘extremely likely’)</td>
<td>Within 2 months of reminder letter</td>
<td>Multivariate: Women with higher PR more likely to screen (OR = 1.41, 1.05-1.89) vs. lower PR</td>
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<tr>
<td><strong>Non-Significant Positive Association</strong></td>
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<td>Isaacs et al., 2002, U.S.</td>
<td>Genetic test patients aged 30+ (N = 216) (10% probability of being BRCA1/2+ or BRCA1/2+ relative)</td>
<td>CR</td>
<td>Comparative risk (same-age women) - 1 (‘much lower’) to 5 (‘much higher’)</td>
<td>≤ 12 months</td>
<td>Bivariate: Women with ‘higher’ PR more likely to screen (69%) vs. women with ‘same/less’ PR (56%) ($p &gt;0.10$)</td>
</tr>
<tr>
<td>Schildkraut et al., 1995, U.S.</td>
<td>Relatives aged 35+ of BC cases (N = 967) (1st-degree relative)</td>
<td>CR</td>
<td>Comparative risk (women without relative with BC) - 1 (‘less’) to 4 (‘much higher’)</td>
<td>35-39: ever, 40-49: past 1-2 years, 50+: past year</td>
<td>Multivariate: Women with PR ‘greater’ (OR = 1.26, 0.74-2.14, $p =0.37$) and ‘little greater’ (OR = 1.06, 0.65-1.73, $p =0.81$) more likely to adhere vs. women with PR ‘same.’ PR ‘less’ less likely to adhere (OR = 0.64, 0.31-1.34, $p = 0.25$)</td>
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<td>Polednak et al., 1991, U.S. [53]</td>
<td>Randomly sampled aged 50-75 (N = 141) (mother, grandmother, aunt, sister or daughter with a BC diagnosis)</td>
<td>CR</td>
<td>Absolute lifetime risk – 0 (‘not at all’) to 4 (‘very likely’)</td>
<td>≤ 12 months</td>
<td>Non-Significant Negative Association</td>
</tr>
<tr>
<td>Martin &amp; Degner, 2006, Canada [54]</td>
<td>Patients aged 23+ from hereditary BC clinic (N = 56) (BRCA1/2+ relative)</td>
<td>CO</td>
<td>Absolute lifetime and general risk - 1 (‘strongly agree’) to 5 (‘strongly disagree’); 3-items</td>
<td>50+: annual for past 3 years; &lt; 50: ≥ 1 in past 3 years</td>
<td>No Association</td>
</tr>
<tr>
<td>Diefenbach et al., 1999, U.S. [55]</td>
<td>Patients aged 18+ from family risk program (N = 213) (1st-degree relative)</td>
<td>CO</td>
<td>Absolute lifetime risk - 1 (‘not at all likely’) to 3 (‘very likely’)</td>
<td>≤ 12 months</td>
<td>No Association</td>
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<td>Drossaert et al., 1996, Netherlands [56]</td>
<td>Women aged 50-69 invited for a mammogram (N = 379) (1st-degree relative)</td>
<td>CR</td>
<td>Absolute and comparative risk (other women) - 1 (‘very small risk’) to 5 (‘very high risk’); 5-item sum score</td>
<td>Screen use following invitation</td>
<td>No Association</td>
</tr>
<tr>
<td>Audrain et al., 1995, U.S. [57]</td>
<td>Women identified by High Risk BC Consortium (N = 395) (1st degree relative)</td>
<td>CR</td>
<td>Comparative lifetime risk (women without close relative with BC) - 1 (‘lower’) to 4 (‘much higher’)</td>
<td>≤ 12 months, 1-2 yrs, &gt; 2 yrs or never</td>
<td>No Association</td>
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<tr>
<td>Lerman et al., 1993, U.S. [58]</td>
<td>Relatives aged 35-79 of BC cases (N = 140) (1st-degree relative)</td>
<td>CR</td>
<td>Absolute risk - 0 (‘no chance of developing BC’) to 10 (‘will get BC’); comparative risk (relative to avg. woman) - 1 (‘much more’) to 5 (‘much less’); 2 items</td>
<td>35-39: ever; 40-49: past 2 years; 50+: past year</td>
<td>No Association</td>
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<td>Kash et al., 1992, U.S. [28]</td>
<td>Women from Breast Protection Program (N = 217) (1st-degree relative)</td>
<td>CR</td>
<td>Question not provided – ‘low/no chance,’ ‘moderately likely,’ ‘very/extremely likely’</td>
<td>≤ 6-months</td>
<td>Bivariate: Trend towards positive correlation between PR and adherence ($d = 0.41, t = 0.06$)</td>
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<tr>
<td>Zhang et al., 2011, Canada [44]</td>
<td>Relatives aged 20-69 of cases of invasive BC (N = 1019) (1st-degree relative)</td>
<td>CR</td>
<td>Absolute lifetime risk – 0 to 100</td>
<td>≤ 12 months</td>
<td>Multivariate: Women with PR 50% or &gt;50% more likely to screen (OR= 1.79, 0.82-3.92 and OR = 1.15, 0.62-2.13) vs. PR &lt;50%</td>
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<td>Comparative lifetime risk (same-aged women) - 1 (‘much lower’) to 5 (‘much higher’)</td>
<td>≤ 12 months</td>
<td>Multivariate: Women with PR ‘above/much above average’ less likely to screen (OR = 0.80, 0.45-1.14) vs. PR ‘average/below average’</td>
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<tr>
<td>Price et al., 2010, Aus/NZ [23]</td>
<td>Female relatives of BC cases (N = 748) (multiple BC families)</td>
<td>CO</td>
<td>Absolute lifetime risk – 0 to 100</td>
<td>0-6 screens within 3 years (based on age and BC risk)</td>
<td>Multivariate: Under-screeners approx. equal to adherent women with regards to PR (OR = 0.99, 0.98-1.00, $p = ns$)</td>
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<tr>
<td>Martin &amp; Degner, 2006, Canada [54]</td>
<td>Patients aged 23+ from hereditary BC Clinic (N = 56) (BRCA1/2+ relative)</td>
<td>CO</td>
<td>Absolute lifetime and general risk - 1 (‘strongly agree’) to 5 (‘strongly disagree’); 3-items</td>
<td>≥ 3 screens within 3 years</td>
<td>Bivariate: No significant difference between women reporting moderate PR to high PR with regard to screening ($p = 0.138$)</td>
</tr>
<tr>
<td>Benedict et al., 1997, U.S. [59]</td>
<td>Daughters aged 18+ of mothers aged 40+ with BC (N = 54) (daughter of BC case)</td>
<td>CR</td>
<td>Absolute risk (1 in x) – ‘1 in 2’ to ‘no chance’</td>
<td>Frequency of screening</td>
<td>Bivariate: No correlation between PR and screening frequency ($r = -0.0514, p = 0.72$)</td>
</tr>
</tbody>
</table>

* Design: CR = Cross-sectional; CO = Cohort; CC = Matched Case-Control
### Table 4. Perceived Risk of Breast Cancer and Adherence to Breast Self-Examination (BSE) Guidelines

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Sample (N) (Family History)</th>
<th>Design*</th>
<th>Perceived Risk (PR) Measure</th>
<th>Definition of Screening Adherence</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Significant Positive Association</strong></td>
<td></td>
<td></td>
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<tr>
<td>Brain et al., 1999, U.K. [60]</td>
<td>Women identified by hospital surgeons (N = 833) (1st-degree relative)</td>
<td>CR</td>
<td>Absolute and comparative risk (average woman) – 1 to 5; 2 items</td>
<td>Infrequent: &lt; monthly; Appropriate: monthly/bi-weekly; Excessive: weekly/daily+)</td>
<td>Multivariate: Women with excessive BSE practices had significantly higher PR vs. women with appropriate or infrequent practices ($F=4.54, p \leq 0.01$). No significant difference in PR between appropriate and infrequent examiners.</td>
</tr>
<tr>
<td><strong>Non-Significant Positive Association</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Zhang et al., 2011, Canada [44]</td>
<td>Relatives aged 20-69 of cases of invasive BC (N = 1019) (1st-degree relative)</td>
<td>CR</td>
<td>Absolute lifetime risk – 0 to 100</td>
<td>Comparative lifetime risk (same-aged women) - 1 ‘much below average’ to 5 ‘much above average’</td>
<td>≤ once per yr, every 2-6 months, ≥ monthly</td>
</tr>
<tr>
<td><strong>Significant Negative Association</strong></td>
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<td></td>
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</tr>
<tr>
<td>Kash et al., 1992, U.S. [28]</td>
<td>Women from Breast Protection Program (N = 217) (1st-degree relative)</td>
<td>CR</td>
<td>Question not provided – ‘low/no chance,’ ‘moderately likely,’ ‘very/extremely likely’</td>
<td>≥ monthly</td>
<td>Bivariate: More women with high PR never performed BSE vs. women with moderate PR; women with moderate PR more frequently performed monthly BSE vs. women with high PR ($p &lt;0.05$)</td>
</tr>
<tr>
<td>Lindberg &amp; Wellisch, 2001, U.S. [47]</td>
<td>Patients aged 15-78 of a high-risk BC clinic (N =430) (self-reported family history)</td>
<td>CR</td>
<td>Absolute lifetime risk – 0 to 100%</td>
<td>Compliance (3 pt. scale from ‘generally’ to ‘rarely’)</td>
<td>Bivariate: High PR correlated with poorer compliance ($r = .16, p = 0.01$)</td>
</tr>
<tr>
<td>Author, Year, Country</td>
<td>Sample (N) (Family History)</td>
<td>Design*</td>
<td>Perceived Risk (PR) Measure</td>
<td>Definition of Screening Adherence</td>
<td>Result</td>
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<tr>
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<tr>
<td>Price et al., 2010, Aus/NZ [23]</td>
<td>Female relatives of BC cases (N = 748) (multiple-case families)</td>
<td>CO</td>
<td>Absolute lifetime risk – 0 to 100</td>
<td>≥ monthly</td>
<td>Multivariate: Over-screeners and adherent women were approx. equal with regard to PR (OR = 1.00, 0.99-1.01)</td>
</tr>
<tr>
<td>Cohen, 2002, Israel [61]</td>
<td>Cases: daughters of BC cases; Controls: daughters whose mothers never had BC (N = 127) (daughter of BC case)</td>
<td>CC</td>
<td>Absolute lifetime risk (1 in x) where x = 0 to 100</td>
<td>Frequency of screening</td>
<td>Multivariate: No association between PR and screening (coefficients and probability values not presented, defined as ns at p &lt;0.05)</td>
</tr>
<tr>
<td>Benedict et al., 1997, U.S. [59]</td>
<td>Daughters aged 18+ of mothers aged 40+ with BC (N = 54) (daughter of BC case)</td>
<td>CR</td>
<td>Absolute risk (1 in x) – ‘1 in 2’ to ‘no chance’</td>
<td>Screening frequency</td>
<td>Bivariate: No correlation between PR and screening frequency (r = 0.1319, p = 0.361)</td>
</tr>
<tr>
<td>Drossaert et al., 1996, Netherlands [56]</td>
<td>Women 50-69 invited for a mammogram (N = 379) (1st-degree relative)</td>
<td>CR</td>
<td>Absolute and comparative risk (other women) - 1 (‘very small risk’) to 5 (‘very high risk’); 5-item sum score</td>
<td>≥ monthly</td>
<td>Bivariate: Correlation coefficients and probability values not presented (defined as ‘very weak’)</td>
</tr>
</tbody>
</table>

* Design: CR = Cross-sectional; CO = Cohort; CC = Matched Case-Control
2.4 Summary of Evidence and Rationale for the Current Study

Effect of screening mammography and level of familial risk on breast outcomes in women with a family history of breast cancer

There is evidence that a significant reduction in breast cancer mortality can be achieved through mammography screening among average risk women aged 50 to 69 years. However, the impact of mammography screening on reducing mortality specifically in younger women, and women with a family history of breast and/or ovarian cancer remains unknown. Several studies have demonstrated that women with a family history of breast cancer may benefit from regular screening mammography, finding that women with a family history of breast cancer have higher cancer detection rates compared with women with a negative family history, and that screen-detected tumors are significantly smaller, free of nodal or distant metastases, and diagnosed earlier compared with symptomatic cancers in women with a family history. However, the effect of level of familial breast cancer risk on screening outcomes has not been evaluated. This evidence is required to develop definitive screening guidelines for women with a range of increased risks of developing breast cancer due to family history.

Effect of perceived breast cancer risk on breast cancer screening behaviours

The relationship between perceived risk of breast cancer and breast cancer screening in women with familial risk has been investigated in a number of observational epidemiologic studies, but never previously reviewed. Our review demonstrated a weak positive association between higher levels of perceived risk and adherence to screening mammography guidelines, but noted a number of important limitations, including a lack of consistency in the measurement of perceived risk, and limited generalizability due to inclusion of only women from high-risk clinical settings. Most importantly, the large majority of previous studies were cross-sectional,
limiting the ability to determine the temporal sequence between perceived risk and breast cancer screening. It is likely that women’s recent breast cancer screening histories also affect their risk perceptions. Thus, previous cross-sectional results which suggest higher levels of perceived risk motivate screening may be explained by temporal bias. While four prospective studies have been conducted (Price et al., 2010; Somers et al., 2009; Lemon et al., 2006; Diefenbach et al., 1999), their internal validity and generalizability are limited. Further prospective research is needed to clarify this relationship. A clearer understanding of how women with a family history perceive their risk, and how perceived risk affects breast cancer screening use will guide risk education and management efforts to increase screening participation in this population.

Accuracy of self-reported screening mammography data

Self-reported mammogram data is widely relied on in the context of epidemiologic research for evaluating the use of breast cancer screening, due to the costs and difficulties of accessing administrative data for these purposes. The validity of self-reported mammogram use has been studied extensively in women with population-level breast cancer risk. Overall, the validity of self-reported mammogram data has been demonstrated; however, these data are much less accurate in determining the precise timing of screening. Only two studies (Pijpe et al., 2011; Larouche et al., 2012) have validated self-reported mammogram dates in women with a family history of breast cancer, including only women with confirmed or suspected BRCA1/2 mutations. These women likely differ in their screening behaviours, and ability to recall their screening episodes compared to women in the broader population with familial risk. This study provides the first evidence of the accuracy of self-reported mammogram dates in women with varying levels of familial breast cancer risk.
Table 2.1 Summary of Guidelines and Recommendations for Screening for Breast Cancer in North America

<table>
<thead>
<tr>
<th>Organization or authors</th>
<th>Mammography</th>
<th>Clinical breast examination</th>
<th>Breast self-examination</th>
<th>Magnetic resonance imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canadian Task Force on Preventive Health Care, 2011</td>
<td>40-49 years: recommend against</td>
<td>Recommend against</td>
<td>Recommend against</td>
<td>Recommend against</td>
</tr>
<tr>
<td></td>
<td>50-74 years: every 2 to 3 years</td>
<td></td>
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<tr>
<td></td>
<td>≥75 years: recommend against</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>US Preventive Services Task Force, 2009</td>
<td>40-49 years: recommend against</td>
<td>Insufficient evidence</td>
<td>Recommend against</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td></td>
<td>50-74 years: biennial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥75 years: insufficient evidence</td>
<td></td>
<td></td>
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<tr>
<td><strong>Increased risk due to family history or genetics</strong></td>
<td></td>
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<tr>
<td>National Hereditary Cancer Task Force, Canada (Horsman et al., 2007)</td>
<td>&lt;30 years with known BRCA1/2 mutation: recommended against</td>
<td>Recommended as part of an individualized screening strategy</td>
<td>Recommend against</td>
<td>&lt;30 years with known BRCA1/2 mutation: recommend if imaging is clinically indicated</td>
</tr>
<tr>
<td></td>
<td>30-69 years with known BRCA1/2 mutation: annual</td>
<td>&lt;30 years: in combination with MRI</td>
<td></td>
<td>30-69 years with known BRCA1/2 mutation: annual</td>
</tr>
<tr>
<td></td>
<td>≥70 years with known BRCA1/2 mutation: no recommendation</td>
<td></td>
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<tr>
<td>Eisinger et al., 1998</td>
<td>≥30 years with ≥20% lifetime risk, or &lt;30 years (dependent on earliest age of diagnosis in family): annual</td>
<td>≥20 years with ≥20% lifetime risk: 2-3 times annually</td>
<td>Recommend against</td>
<td>Recommend against</td>
</tr>
<tr>
<td></td>
<td>Lifetime risk &lt;10%: recommend against</td>
<td>Lifetime risk &lt;10%: recommend against</td>
<td></td>
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<tr>
<td>Warner et al., 1999a</td>
<td>≥50 years at low risk: biennial</td>
<td>≥50 years at low risk: biennial</td>
<td>All ages at low/ moderate risk: encouraged</td>
<td>No recommendation</td>
</tr>
<tr>
<td></td>
<td>≥40 years at moderate risk: annual</td>
<td>≥40 years at moderate risk: annual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organization or authors</td>
<td>Mammography</td>
<td>Clinical breast examination</td>
<td>Breast self-examination</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>Saslow et al., 2007; American Cancer Society, 2013</td>
<td>≥40 years: annual</td>
<td>20-39 years: every 3 years</td>
<td>≥40 years: annual</td>
<td>No recommendation</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Known BRCA1/2 mutation, untested 1st-degree relatives of known carriers, ≥20-25% lifetime risk, Li-Fraumeni syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, or 1st-degree relative with one of these syndromes: annual</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>≤15% lifetime risk: recommend against</td>
</tr>
<tr>
<td>Moller et al., 1999b</td>
<td>≥30-59 years very high risk: annual</td>
<td>BRCA mutation carriers: twice annually</td>
<td>All ages: monthly</td>
<td>No recommendation</td>
</tr>
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<td></td>
<td>≥35-50 moderate/high risk: annual</td>
<td></td>
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<tr>
<td></td>
<td>&gt;50-60 years moderate/high risk: every 18 months</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>≥60 years moderate/high/very high risk: biennial</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>BRCA mutation carriers: twice annually</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chart &amp; Franssen, 1997</td>
<td>≥40 years with slightly increased risk: annual</td>
<td>≥40 years at slightly increased risk: annual</td>
<td>≥40 years at slightly increased risk: monthly</td>
<td>No recommendation</td>
</tr>
<tr>
<td></td>
<td>≥40 years or 10 years before the earliest age at which cancer was detected in the family with moderately increased risk: annual</td>
<td>≥40 years or 10 years before the earliest age at which cancer was detected in the family with moderately increased risk: annual</td>
<td>≥40 years or 10 years before the earliest age at which cancer was detected in the family with moderately increased risk: monthly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥40 years or 10 years before the earliest age at which cancer was detected in the family (whichever comes first) with highly increased risk: annual</td>
<td>≥40 years or 10 years before the earliest age at which cancer was detected in the family (whichever comes first) with highly increased risk: annual</td>
<td>≥40 years or 10 years before the earliest age at which cancer was detected in the family (whichever comes first) with highly increased risk: monthly</td>
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<tr>
<td></td>
<td>&lt;30 years: recommended against</td>
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Chapter 3
Study Methods

3.1 Summary of Study Design and Data Source

This thesis entailed a secondary analysis of data originally collected as part of the Family History Study (FHS). Data collection for the FHS was near completed when the PhD candidate became involved in this study. As such, all decisions regarding study design and variable measurement were made previously by the study investigators. The PhD candidate was independently responsible for conducting an extensive systematic review that led to the development of explicit study objectives and hypotheses relevant to this thesis project, testing specific hypotheses, conducting an extensive evaluation of methodological issues and data quality, and drafting the resulting manuscripts in full. A more detailed description of the candidate’s contribution is found in Chapter 6.

The FHS was a prospective cohort study undertaken by Dr. Anna Chiarelli (PI) et al., funded by the Canadian Cancer Society Research Institute, and Canadian Breast Cancer Research Alliance (Appendix A). The FHS was additionally supported by the United States National Cancer Institute, the Breast Cancer Family Registry and Cancer Care Ontario. The FHS followed a cohort of 1114 women from the Ontario site of the Breast Cancer Family Registry with a first-degree family history of breast and/or ovarian cancer over a two year period, interviewing them at annual intervals. The primary objectives of the FHS were to evaluate the effectiveness of breast cancer screening and to identify determinants of breast cancer screening behaviours, in women with varying levels of familial risk.
3.2 Study Population and Sample

3.2.1 Ontario site of the Breast Cancer Family Registry

The National Cancer Institute’s Breast Cancer Family Registry (BCFR) was established in 1995, and has six participating sites from the United States (New York, Philadelphia, Utah, and San Francisco), Canada (Ontario) and Australia (Sydney/Melbourne). Families are ascertained from cancer registries (population-based families) in San Francisco, Ontario and Sydney/Melbourne, or seen in high-risk clinical and community settings (clinic-based families) in New York, Philadelphia, Utah and in Sydney/Melbourne (John et al., 2004). In Ontario, recruitment from clinic-based families was limited to families of Ashkenazi Jewish ancestry (John et al., 2004). The BCFR includes lifestyle, medical history, and family history data, as well as biospecimens, collected from more than 55,000 women and men from 14,000 families with and without breast cancer for the purposes of studying the role of genetics in breast cancer. The BCFR and its Ontario site have been previously described in further detail (John et al., 2004; Sutherland et al., 2001; Knight et al., 2002). Briefly, with regard to the Ontario site of the BCFR, cases of pathologically-confirmed invasive breast cancer (probands), diagnosed between 1996 and 1998 were identified by Drs. Irene Andrulis (PI) and Julia Knight (co-PI) from the Ontario Cancer Registry (OCR). The OCR is a population-based tumor registry operated by Cancer Care Ontario since its inception in 1964. It consists of computerized vital information on all new cases of cancer (excluding non-melanoma skin cancers) within the province of Ontario which are identified by using probabilistic record linkage to reconcile information from: (i) pathology reports, (ii) electronic patient records from regional cancer treatment centres, (iii) hospital discharge and ambulatory care records from the Canadian Institute for Health Information, and (iv) death certificates from the Registrar General of Ontario. Completeness of case ascertainment for the OCR is estimated to be 98% (McLaughlin et al., 1991).
A detailed flowchart of recruitment for the Ontario site of the BCFR is located in Figure 3.1. Those eligible to participate in the Ontario site of the BCFR include all women diagnosed with breast cancer at age 20 to 54 years, a random sample (35%) of women diagnosed with breast cancer at age 55 to 69 years, and all men diagnosed with breast cancer at age 20 to 79 years (Sutherland et al., 2001). Surgeons named on the pathology report were contacted to obtain permission to mail their patients a cancer Family History Questionnaire (FHQ). The FHQ collects information about first-degree relatives of breast cancer cases with regard to their age, date of birth, status alive or dead, age and/or date of death, whether or not the relative has had cancer, cancer type, and age and/or date of diagnosis, along with details of any cancers in other relatives. Permission from physicians was granted for 91% of cases (n = 7668 of 8453).

Respondents meeting a defined set of criteria which deem them to be at moderate to high-risk of breast cancer (Table 3.1) and a random sample (25%) of those not meeting criteria (deemed low risk) were asked to participate in the Ontario site of the BCFR by completing a mailed risk factor questionnaire and providing a blood sample. Of those eligible probands (n = 2587), 1851 (71.5%) probands participated.

Probands were then asked for address information and permission to contact specific living relatives. These relatives include: proband’s first-degree relatives (children, siblings, parents), living relatives diagnosed with breast and/or ovarian cancer and their first-degree relatives, first-degree relatives of deceased relatives diagnosed with breast and/or ovarian cancer, relatives with an adult-onset cancer diagnosed prior to 50 years of age (excluding cervical, testicular, leukemia and lymphoma), and half-siblings on the “at-risk” side. An invitation letter to participate in the Ontario site of the BCFR was sent to all identified relatives (n = 8416), and the 5122 (60.9%) who agreed to be contacted were mailed a Personal History Questionnaire (PHQ) between 1998 and 2004.
3.2.2. Family History Study

The Family History Study (FHS) was conducted several years (range: 2 to 7 years) after the initial recruitment of relatives to the Ontario site of the BCFR. All female relatives of proband cases of invasive breast cancer who were enrolled in the Ontario site of the BCFR, who had completed a PHQ, were 20 to 69 years of age, still alive, residents of the province of Ontario at the outset of the study, and unaffected by breast cancer at the time of the proband’s diagnosis date were eligible to participate in the FHS. Of 3374 female relatives participating in the Ontario site of the BCFR, 1514 met all study criteria as defined above (44.9%), and were mailed a baseline Personal History and Screening Questionnaire (PHSQ) (Appendix B) for the FHS between November 2005 and March 2007.

A detailed flowchart of recruitment for the FHS is located in Figure 3.2. Of the 1514 women to whom a baseline PHSQ was sent, 162 (10.7%) were lost to follow-up and 37 (2.4%) were deemed ineligible (no longer residents of Ontario, or were deceased or otherwise ineligible to participate due to a health issue), leaving 1315 (86.9%) women who were contactable and eligible. Of the 1315 women contacted, 201 (15.3%) refused to complete a baseline PHSQ and 1114 (84.7%) completed it. Women had to be free of a breast cancer diagnosis to be eligible for follow-up through the FHS. Of the 1077 women who were eligible to complete the year 1 PHSQ, 11 (1.0%) were lost to follow-up and 4 were deemed ineligible (0.4%), leaving 1062 (98.6%) women contactable and eligible. Of the 1062 women contacted, 87 (8.2%) refused to complete the year 1 PHSQ and 975 (91.8%) completed it. Of the 969 women eligible to complete a year 2 PHSQ, 32 (3.3%) were lost to follow-up and 1 was ineligible (0.1%), leaving 936 (96.6%) contactable and eligible women. Of the 936 women contacted, 54 (5.8%) refused to complete the year 2 PHSQ and 882 (94.2%) completed it.
3.3 Data Collection

Data collection for the FHS took place from December 2005 to March 2011. Data were drawn from four sources, including (i) questionnaires; (ii) pathology/surgical reports; (iii) the Ontario Cancer Registry; and (iv) mammographic imaging reports. With regard to questionnaire data, this included the self-administered PHQ completed during recruitment to the Ontario site of the BCFR, as well as baseline, year 1 and year 2 PHSQ telephone-administered questionnaires completed as part of the FHS. The PHQ consisted of 16 pages with 73 questions, and collected information on socio-demographic characteristics (i.e. marital status, highest level of education, ethnicity), breast cancer risk factors (i.e. height/weight, reproductive history, previous exposure to radiation, history of smoking/alcohol use, use of HRT), surgical history, and some information on previous mammogram use.

The baseline PHSQ consisted of 22 pages with 73 questions, and collected updated information on socio-demographic characteristics, breast outcomes (diagnosis of breast cancer or benign breast disease, breast surgeries), breast cancer screening use (mammography, CBE, BSE, ultrasound or MRI) and use of other cancer screening tests (Pap test, trans-vaginal ultrasound, cancer antigen-125 blood test, fecal occult blood test) since completion of the PHQ, use of genetic testing or counselling since completion of the PHQ, behavioural characteristics (i.e. perceived risk of breast cancer, worry about breast cancer, knowledge of breast cancer screening guidelines), breast cancer risk factors (i.e. reproductive history, menopausal status, use of HRT), and other general health-related characteristics (i.e. self-reported general health, current depression, smoking/alcohol use since completion of the PHQ, physical activity during the previous two years). The year 1 and year 2 follow-up PHSQs consisted of 13 pages with 36 questions, and collected updated information on breast outcomes, use of breast cancer screening and genetic testing or counselling since completion of the previous PHSQ, behavioural
characteristics and general health-related characteristics. Approximately two weeks prior to being contacted by FHS personnel by telephone, an introductory letter and hard copy of the PHSQ was mailed to the subject, allowing respondents time to recall specific dates and events, check personal records prior to being interviewed, and refer to the questionnaire during the interview. This method was previously found to result in high response rates and more complete data than achieved by self-administered questionnaires (Chiarelli et al., 2000; Chiarelli et al., 1999). PHQ data were provided to FHS staff in an Excel spreadsheet using a unique identification number for each subject assigned by the Ontario site of the BCFR. PHSQ response data were transcribed on to hard copies of the questionnaire during the telephone interview, and entered into an Access dataset by trained study staff. All FHS participants were assigned a unique identification number, in addition to the unique identifier assigned by the Ontario site of the BCFR.

Pathology data were abstracted from pathology and surgical reports, where women self-reported a diagnosis of breast cancer or benign breast disease and provided written informed consent to release these reports to the FHS (Appendix C). Data on cancer stage were obtained from the OCR for cases of invasive breast cancer. Where women reported that they had a mammogram since the previous interview and provided written informed consent to release the imaging report to the FHS (Appendix D), mammography data were abstracted from imaging reports by trained research clerks. As part of a data quality assessment, the PhD candidate performed logic checks on all mammographic imaging data. As a result, the candidate re-abstracted and entered a small proportion (7.1% at baseline, 6.5% at year 1, 5.3% at year 2) of the imaging data that were found to contain errors.
3.4 Variable Definitions

3.4.1 Familial Breast Cancer Risk Classification

Classifications for familial breast and/or ovarian cancer risk were based on previously referenced groups for familial breast cancer risk (Eccles et al., 2000; Cortesi et al., 2006), with modifications based on key evidence (Collaborative Group on Hormonal Factors in Breast Cancer et al., 2001; Bevier et al., 2011; Vencken et al., 2013; National Institute for Health Care and Excellence [NICE], 2013; Egan et al., 1996; Toniolo et al., 1996) and expert opinion. Data were collected from the FHQ, which was completed by the relative’s proband during recruitment to the Ontario site of the BCFR, as well as with ongoing updates. The two main models used were developed by Eccles et al. (2000) and Cortesi et al. (2006), based on the Gail model (Gail et al., 1989), the Claus tables (Claus et al., 1991), and the BRCAPRO model (Parmigiani et al., 1998), to classify women as having low, moderate or high familial breast and/or ovarian cancer risk (Table 3.2).

Minimal modifications were made to the main models to ensure women were accurately classified, as there was a wide range of familial breast and/or ovarian cancer histories in our study cohort, which were not described by these models. Modifications were included for women with a first-degree family history of male breast cancer, as risks are increased above the 2- to 3-fold increased risk for women with 1 first-degree male relative, when a first-degree female relative is also diagnosed with breast cancer (Bevier et al., 2011). The women in our cohort with affected male relatives also had affected female relatives, thus these women were classified as high risk. We also classified women with 2 or more affected first-degree relatives as high risk, based on the key paper from the Collaborative Group on Hormonal Factors in Breast Cancer (2001), which found a relative risk for women with 2 affected first-degree
relatives of 2.93 (95% CI: 2.37-5.63), and 3.90 (95% CI: 2.03-7.49) for women with 3 or more
affected first-degree relatives, respectively. A few (n = 3) women in our cohort had a personal
history of ovarian cancer. These women were classified as high-risk because they also had
extensive first- and second-degree familial history of breast and/or ovarian cancer,
demonstrating increased likelihood of carrying a *BRCA1/2* gene mutation. *BRCA1/2* carriers
were recently demonstrated to have a 10-year risk of breast cancer of 11% following an ovarian
cancer diagnosis (Vencken et al., 2013). The United Kingdom’s NICE clinical guideline CG164
recommends that women with 10-year risks of breast cancer greater than 8% be classified as
high risk (NICE, 2013). Egan et al. (1996) found Ashkenazi Jewish women with a first-degree
family history of breast cancer have a relative risk of 3.78 (95% CI: 1.74-8.16), while Toniolo et
al. (1996) found a more modest relative risk of 1.69 (95% CI: 1.16-2.45). To ensure a
conservative estimate, we classified Ashkenazi women as moderate risk. A number of women in
our cohort also had a first-degree female relative with breast cancer, and additionally, 2 or more
second-degree relatives with breast cancer. Based on expert opinion, these women were
classified as moderate risk.

A number of statistical breast cancer risk estimation models have been developed over
the past two decades. A detailed summary of these models is located in Table 3.3. The Gail
model (Gail et al., 1989) was originally developed in 1989 to ascertain eligibility for the Breast
Cancer Prevention Trial, and subsequently modified in 1999 to take into account other factors,
including ethnicity (Costantino et al., 1999). The Gail model has been validated in a number of
databases (Amir et al., 2010). A recent systematic review found that the Gail model was well-
calibrated, but had limited discriminatory accuracy when evaluated using receiver operating
characteristic (ROC) curves (the area under the curve [AUC] ranged from 0.58 to 0.62)
(Cummings et al., 2009). The Gail model was additionally extended by Chen et al. (2006), to
incorporate breast density. While the extended Gail model had improved discriminatory accuracy over the original Gail model, it has been criticized for using a continuous measure of density (% mammographic density), which is not routinely available in the clinical setting. The Claus model (Claus et al., 1991) is also commonly used. While the Claus model incorporates more detailed information about family history compared with the Gail model (second-degree relatives, and age of relative’s breast cancer diagnosis), it does not include hormonal or other breast cancer risk factors. The concordance between risk estimates produced by the Gail and Claus models has been shown to be low (Amir et al., 2010). Jonker et al. (2003) developed an extended Claus model which includes family history of bilateral breast cancer and ovarian cancer, but similarly does not include other breast cancer risk factors. The BRCAPRO model (Parmigiani et al., 1998) uses a software program to estimate the risk of carrying a BRCA mutation, as well as determine lifetime risk of breast cancer using a Bayesian statistical algorithm (Amir et al., 2010). BRCAPRO incorporates unaffected and affected relatives, and can handle complex familial cancer histories; however, like the Claus model, it does not incorporate other breast cancer risk factors (Amir et al., 2010). The International Breast Intervention Study (IBIS) or Tyrer-Cuzick model (Tyrer et al., 2004), attempted to address some of the limitations of previous models by incorporating detailed first- and second-degree cancer family history, as well as hormonal and other breast cancer risk factors, including history of benign breast disease. Similar to the Claus models and BRCAPRO, the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) incorporates detailed cancer family history, but does not include other breast cancer risk factors. BOADICEA is recommended in the NICE clinical guideline CG164 (NICE, 2013), and has been incorporated into the guidelines of several countries for the management of familial breast cancer (Lee et al., 2014), including the OBSP high risk screening program along with IBIS.
Amir et al. (2003) conducted a prospective study to evaluate the Gail, BRCAPRO (Claus) and IBIS models, finding that IBIS (AUC = 0.762) was the most accurate model for predicting breast cancer risk, compared with the Gail (AUC = 0.735) and BRCAPRO (Claus) (AUC = 0.716) models. It was also noted that Gail and BRCAPRO (Claus) underestimated breast cancer risk (Amir et al., 2003). A subsequent retrospective study evaluated the Gail, Gail 2 (Jonker et al., 2003), Claus, IBIS and BOADICEA models, and demonstrated that the Gail, Gail 2, and Claus models underestimated breast cancer risk, and concluded that the IBIS and BOADICEA models have the highest accuracy for predicting breast cancer risk (Jacobi et al., 2009).

3.4.2 Breast Cancer Screening Measures

Self-reported data were collected on the use of several breast cancer screening modalities in both the self-administered PHQ and the telephone-administered PHSQs. In the PHQ, women were asked if they had ever had a mammogram, to provide the date of their last mammogram, and how many mammograms over their lifetime they had undergone. Women were asked during the baseline, year 1 and year 2 PHSQ interview if they had undergone mammography, CBE, BSE, breast ultrasound and breast MRI since completion of their previous interview. For mammography and CBE, women were asked to specify the month and year, or their age at their last examination. For mammography, CBE, breast ultrasound and MRI, women were asked to indicate the main reason for having their examination. Response options included: ‘part of a regular check-up or routine screening’, ‘part of the Ontario Breast Screening Program’, ‘family history of breast cancer’, or ‘breast problem or symptom’. Women could also provide other relevant reasons using an open-ended option. In the year 1 and 2 PHSQs, an additional response option was, ‘being part of this study’. The first three response options (‘part of a regular check-up or routine screening’, ‘part of the OBSP’ and ‘family history of breast cancer’) were coded as
screening, and the response ‘breast problem or symptom’ was coded as diagnostic. Finally, women who reported having a mammogram were also asked to indicate anything that had encouraged them to obtain a mammogram. Response options included: ‘family physician,’ ‘familial cancer genetic clinic,’ ‘family member,’ ‘friend,’ ‘family member with breast cancer,’ ‘someone with breast cancer,’ ‘media’ or ‘community presentation’.

Mammogram data were also abstracted from imaging reports among women who reported undergoing mammography, consented to release the imaging report, and where the relevant imaging report was obtained from the imaging facility. Specifically, the mammogram date (day, month and year), the imaging clinic, indication for the mammogram (screening or diagnostic/follow-up), as well as the mammographic finding, as given by the Breast Imaging - Reporting and Data System (BI-RADS) assessment (Balleyguier et al., 2007), were abstracted by trained research clerks.

3.4.3 Pathologic Measures

The self-reported date and location of any diagnosis of breast disease (breast cancer or benign breast disease) were obtained from the PHSQ, and written informed consent was obtained granting access to pathology and surgical records. Copies of relevant reports were requested from the OCR and medical record departments of hospitals and/or clinics. Reports were obtained and reviewed for all diagnoses of breast cancer or benign breast disease by the pathology consultant (Dr. Mitra Nabavi). Histology, tumor characteristics, as well as severity of benign breast disease were abstracted from pathology and surgical records.

Invasive breast cancer includes the diagnosis of primary invasive breast cancer of any histologic type. For invasive breast cancers, a number of tumor characteristics were abstracted. Tumor size was recorded in millimeters, and was defined as the largest diameter (tumor size is
typically measured in three dimensions) of the primary invasive carcinoma, as measured before any tissue is removed. Multifocal tumors were sized using the largest diameter of the largest centre. Tumor size was categorized as ≤15 millimeters and >15 millimeters. Among women who had axillary assessment with either sentinel lymph node biopsy or axillary node dissection, lymph node status was defined as positive if the cancer had invaded any of the sentinel or other lymph nodes, or negative if there were no positive lymph nodes. The TNM staging classification from the 6th Edition of the AJCC Cancer Staging Manual (Greene et al., 2002) was used for the pathologic staging of breast cancers (Greene et al., 2002). The TNM classification takes into account tumor size (T), nodal involvement (N), and the presence of distant metastasis (M), and is located in Table 3.4. In the majority of cases, stage was obtained directly from the OCR. However, in several cases where stage was unavailable from the OCR, but pathology/surgical reports contained sufficient data on tumor size, lymph node involvement and distant metastasis, invasive cancers were staged by the pathology consultant. TNM stage was defined as follows: I, IIa, IIb, IIIa, IIIb, IIIc, or IV, and further grouped as stage I and stage II-IV to increase power for sub-group analyses. The AJCC TNM stage groupings are located in Table 3.5.

Histopathologic grading of invasive carcinomas was performed using the Nottingham grading system (Elson & Ellis, 1991). The Nottingham grading system takes into account individual scores for tubule formation, nuclear pleomorphism and mitotic rate. Grades were categorized as I, II or III. Tumors were classified as grade I if the combined score was 3-5 (well-differentiated), grade II if the combined score was 6-7 (moderately-differentiated) or grade III if the combined score was 8-9 (poorly-differentiated). Additional detail regarding scoring for tubule formation, nuclear pleomorphism, and mitotic rate can be found in Section 2.1.2. Mitotic rate was determined by assessing the number of mitoses per 10 high powered fields, which were standardized to the field diameter of the high power objective and classified as low (score 1),
intermediate (score 2) or high (score 3). The absence or presence of lymphovascular invasion within the endothelial-lined channels of the breast was also recorded. Estrogen receptor (ER) and progesterone receptor (PR) status was defined as positive if immunohistochemical (IHC) assays showed >1% tumor cell positivity, or otherwise defined as negative (Hammond et al., 2010).

Ductal carcinoma in situ (DCIS) included intraductal carcinoma and Paget’s disease of the nipple with no invasive component. Breast cancer diagnoses that had components of both DCIS and invasive breast cancer were classified as invasive cancers. Pathologic characteristics of cases of DCIS were abstracted, including: nuclear grade, necrosis, architectural type, extent, and the presence of calcifications or microinvasion. However, as there were few cases of DCIS with no invasive component in our study population (n = 6), pathologic characteristics were not examined for this subgroup. Cases of BBD were categorized by severity according to their relative risk for subsequent breast cancer, as detailed in Chapter 2, Sections 2.1.1 and 2.1.5: fibrocystic changes or proliferative breast disease without atypia was classified as mild (RR for subsequent breast cancer = 1.5 to 2.0), proliferative breast disease with atypical hyperplasia was classified as moderate (RR = 3.5 to 6.0), and LCIS was classified as severe (RR = 10.0). As few cases of BBD were moderate or severe (n = 12), these categories were combined for analyses which examined severity of BBD.

3.4.4 Perceived Breast Cancer Risk Measures

Given the lack of consensus regarding the optimal method to measure perceived risk, and the differences in risk estimates produced by varying questions, two questions previously developed by Lipkus et al. (2000), were used to measure perceived risk in the FHS. The first question measured perceived risk on an absolute numeric scale, and asked women: “on a scale
from 0 to 100, where 0 = certain not to happen, and 100 = certain to happen, how likely are you
to get breast cancer in your lifetime?” Based on the distribution of numeric perceived risk in the
sample (Figure 3.3), and strong preference for reporting a perceived risk of exactly 50%,
categorical measures were also derived. Analyses including both the continuous numeric and 3-
level categorized variables were conducted for Objective 2; however, only the 3-level
categorized variable is shown in Manuscript 2 due to low statistical power when using the 5-
level categorized measure.

The second question measured perceived risk on a comparative Likert-type verbal scale,
by asking subjects: “compared to other women your age, how likely are you to get breast cancer
in your lifetime?” Response anchors included: ‘much below average’, ‘below average’, ‘same as
average risk’, ‘above average’, ‘much above average’, or ‘don’t know’. As extremely few
women perceived their risk as much below average (n = 8, <1%) and few women perceived
their risk as below average (n = 42, 4.7%), these categories were combined with women who
reported their risk was same as average (n = 265, 30.0%). Similarly, few women reported their
risk was much above average (n = 81, 9.2%), so this category was combined with the above
average category (n = 488, 55.2%) for analyses.

Internal consistency between the absolute numeric scale and comparative verbal scale
measures of perceived risk was estimated using Cronbach’s alpha ($\alpha$). The low level of
correlation observed ($\alpha = 0.67$) was not unexpected, given the differences that exist between
different models for measuring perceived risk that are discussed in detail in Manuscript 1. A
previous study similarly found correlation between numeric and comparative measures of
perceived breast cancer risk to be $r = 0.60$ (Gurmankin Levy et al., 2006). The study also found
the numeric and comparative measures had similarly high rates of sensitivity (0.91 for numeric,
0.86 for comparative) and specificity (0.99 for numeric, 0.96 for comparative) for identifying
women with very high risk perceptions (perceived risk of ≥50%) (Gurmankin Levy et al., 2006). In Manuscript 3, 76% of women in our study reported a perceived risk of 50% or more. Perceived risk was measured in the PHSQ questionnaires using the absolute numeric scale, followed by the comparative verbal scale, and separated by five questions regarding breast cancer worry, confidence in several breast cancer screening modalities to detect cancer, knowledge regarding screening intervals and knowledge regarding appropriate age to start and stop screening mammography. Previous research has demonstrated that risk perceptions may be lower when a question measuring comparative risk precedes an item measuring absolute risk (Taylor et al., 2002), thus, the risk perceptions observed in the FHS may be slightly elevated.

3.4.5 Potential Confounders

Confounders for each analysis were chosen *a priori*, based on evidence from previous literature or theoretical grounds for inclusion. Confounders were not excluded based on a lack of statistical significance during univariate testing, as this method can exclude variables known to be important (Szklo & Nieto, 2007; Mickey & Greenland, 1989). Age (at interview or diagnosis of breast cancer or BBD) was included in all adjusted models. For Manuscript 3, variables that changed the effect estimates by a minimum of 5% in one or more of the full models were retained in the final adjusted models. This conservative cut-off was chosen to reduce residual confounding. As missing confounder data were minimal (<2.5% for all confounders), the relative gain in precision afforded by using a higher change in parameter cut-off value (i.e. 10% or 15%) was negligible.

Age at interview was calculated as the difference in years between the woman’s date of birth and completion date of the relevant PHSQ interview (for women without a breast diagnosis). Age at diagnosis was calculated as the difference in years between the woman’s date
of birth and date of diagnosis of breast cancer or BBD. The method employed to estimate age takes into account leap years and does not use month or year mid-points, instead relying on real calendar dates which account for the fluctuations in lengths of months and years in the modern Gregorian calendar. Stratified analyses for Objective 1 used age categories of <50 years and ≥50 years. Descriptive analyses for Objective 2 used age categories of 25-29, 30-39, 40-49, and ≥50. Descriptive analyses for Objective 3 used age categories of <40 years, 40-49 years, and ≥50 years. All other analyses, and model adjustments used the continuous measure of age.

Age at menarche (age at first menstrual period) was self-reported by women in the PHQ completed during recruitment to the Ontario site of the BCFR. Parity was determined based on combined responses to the PHQ and baseline PHSQ interviews. Women who reported giving birth once or more were classified as parous, and otherwise classified as nulliparous. Menopausal status was determined with combined responses to the PHQ and baseline PHSQ. Women who reported that their menstrual periods had stopped for at least 1 year were classified as menopausal, or otherwise classified as peri-menopausal/pre-menopausal. HRT use was determined using combined responses from the PHQ and baseline PHSQ, and restricted to post-menopausal women only. Post-menopausal women were classified as ever HRT users if they reported ever or currently using HRT, or otherwise classified as non-users. History of BBD was determined based on combined responses to the PHQ and baseline PHSQ. Women were asked: “has a doctor ever told you that you had benign breast disease (non-cancerous lump or cyst or breast lump) that was not breast cancer?” Women who reported they had ever been told they had BBD were classified as having a positive history, or otherwise classified as negative.

Education was based on self-reported highest level of education achieved as reported at the baseline PHSQ. Response options included: less than high school, some or all of high school, vocational or technical school, some college or university, and Bachelor’s degree or
higher. These categories were further collapsed into a 3-category measure (≤ high school, some college or university/vocational or technical school, ≥ Bachelor’s degree) in the analyses for Objectives 2 and 3. Annual frequency of health care visits was estimated by asking women: “how many times on average, did you go to the doctor’s office, clinic, health centre, or other place that you usually go to when you were sick or needed advice about your health?” Response options included: less than once per year, once per year, 2-3 times per year, 4-5 times per year, 6 or more times per year. For the purposes of descriptive analyses, these groups were further collapsed as follows: ≤ 1 time per year, 2-3 times per year, ≥4 times per year.

Use of genetic counselling was determined based on responses from the baseline PHSQ and year 1 PHSQ. Women were asked: “have you ever had an appointment at a specialist clinic to discuss your family history of cancer and the possibility of genetic testing?” Use of genetic testing was similarly determined based on responses from the baseline PHSQ and year 1 PHSQ. Women were asked: “have you ever had a genetic test for the breast cancer genes BRCA1 or BCRA2?” To both questions, response options included: yes, no, or I don’t know.

3.5 Statistical Analysis

An overview of the statistical analyses used throughout the thesis is provided in this section; however, each of the manuscripts contained within the thesis provide additional detail regarding statistical methodology specific to each study objective. All statistical analyses were conducted using SAS, version 9.2. Statistical significance was defined as $P$-value less than 0.05, and all statistical tests were two-sided.

3.5.1 Descriptive Analyses

The distribution of variables was examined, and the presence of missing data, impossible and extreme values for all variables was evaluated for each objective. For categorical measures,
frequencies and percentages were examined. For continuous measures, measures of central
tendency and distributional properties were examined (mean, standard deviation, median,
interquartile range).

3.5.2 Univariate Tests of Association and Logistic Regression Analyses

Objective 1

Differences in breast cancer risk factors and screening mammogram history between
exposed (women with high familial risk) and unexposed (women with low to moderate familial
risk) subjects were evaluated using chi-square tests (for binary measures) and t-tests (for
continuous measures). These differences were also evaluated using general linear (for
continuous measures) and logistic (for binary measures) regression, adjusted for age at
interview. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95%
confidence intervals (CI) to test associations between level of familial breast cancer risk
(low/moderate risk vs. high risk), and diagnosis of breast cancer (invasive and/or DCIS) and
BBD in all women adjusting for age. Similar analyses were also conducted stratifying on age at
diagnosis or interview (<50 years, ≥50 years), and screening mammography status (screening
mammogram prior to diagnosis, non-screening mammogram prior to diagnosis). In age-
stratified models, continuous age was also adjusted for to reduce residual confounding. As this
did not result in any change to the effect estimates (<1% change in all age-stratified models),
continuous age was not included in the final models. ORs and 95% CIs were also estimated
from multivariable logistic regression models to test associations between level of familial
breast cancer risk (low/moderate risk vs. high risk) and screening mammography status, and
prognostic characteristics of invasive breast cancer and BBD, adjusting for age at diagnosis. It
was not necessary to adjust for breast MRI or ultrasound screening use, as very few women
without a breast outcome, and no women with a breast outcome, were screened with either modality during the study period.

Objective 2

Differences in baseline characteristics (familial risk, age at interview, education, frequency of health care visits, menopausal status, history of BBD, history of genetic counselling, and baseline mammogram and CBE status) by exposure status (perceived breast cancer risk) were evaluated using overall chi-square tests. For age at interview, the \( p \)-value was estimated from a Fisher’s exact test, as one cell count for women aged 25 to 29 years was less than five. Multivariable logistic regression was used to estimate ORs and 95% CIs to test for associations between both the numeric and comparative measures of perceived breast cancer risk at baseline and use of screening mammography and CBE within the 15 months following baseline, and ever use of genetic testing. As results from the numeric and comparative models were similar, and given the slightly higher sensitivity and specificity of the numeric model in women with high perceived risk noted by Gurmankin Levy et al. (2002), only the models using numeric estimates of perceived risk are presented in Manuscript 3. The relationship between numeric perceived risk as a continuous predictor and screening use was also modeled.

Several methods of testing for non-linearity of the associations between numeric perceived risk and screening use were employed. Firstly, a quadratic term for numeric perceived risk was fit for each model. Second, likelihood ratio tests were used to compare models using continuous numeric perceived risk (0% to 100%) to models using a categorized version of numeric perceived risk (<50%, = 50%, >50%). None of the quadratic terms were statistically significant, and likelihood ratio tests could not exclude a linear relationship, at \( p < 0.05 \). However, because women displayed a very strong preference for reporting a perceived risk of exactly 50%, and \( p \)-values for likelihood ratio tests approached statistical significance for
women at moderate/high familial risk ($p = 0.08$ for mammography, $p = 0.08$ for CBE), the
categorized perceived risk measure was used for final models.

Familial risk was identified as a potential effect modifier, *a priori*. Statistical interaction
between perceived breast cancer risk and familial breast cancer risk was evaluated by entering
interaction terms into multivariable models. While interaction terms were not statistically
significant at $p < 0.05$, heterogeneity in the stratified OR estimates was suggested, as strata-
specific estimates of the association between perceived risk and screening use were of different
directions. As such, analyses were conducted including overall models of the full cohort, as well
as models stratified by level of familial risk (low familial risk, and moderate/high familial risk).
Final models were adjusted for age at year 1 interview, education, annual frequency of health
care visits, menopausal status, history of BBD, baseline screening behaviour and history of
genetic counselling. All models were also adjusted for breast cancer worry; however, as this did
not result in any change to the effect estimates, it was left out of final models. Sensitivity
analyses were conducted which excluded women under 30 years of age, and under 40 years of
age, respectively, as some of these women may not yet be recommended to undergo screening
for breast cancer (depending on the earliest age of diagnosis observed in the family). As this did
not alter the main results, final models included the full cohort to conserve study power.

**Objective 3**

For Objective 3, distributions of socio-demographic characteristics, health and cancer
screening behaviours were summarized for women at each PHSQ interview. Self-reported
screening mammogram dates were compared to dates abstracted from imaging reports (“gold
standard”) to estimate rates of agreement. Date agreement among self-reported and abstracted
dates was examined for those who self-reported a full date (exact agreement on month and
year), or a partial date (agreement on year only, or agreement on age at examination). To
examine the direction of inaccurate recall, date disagreement was further classified as overestimation or underestimation of the time since last mammogram. To examine the magnitude of inaccurate recall, the difference in months between self-reported and abstracted imaging dates was compared among women who overestimated and underestimated their imaging date. T-tests were used to determine whether the difference in months between those who overestimated and underestimated their imaging date was significantly different from zero.

Polytomous logistic regression was used to estimate ORs and 95% CIs to test for associations between inaccurate recall and a number of factors, including: familial breast cancer risk, age at interview, education, marital status, annual frequency of visiting a health professional, CBE use, BRCA1/2 genetic test use, perceived breast cancer risk, number of months since last mammogram, and the mammographic finding. Final models were adjusted for age at interview, and number of days since last mammogram. Women who overestimated their imaging date, and who underestimated their imaging date were compared to women who accurately reported their imaging date. As these categories of mammography recall have no natural ordering, a generalized logit model was fit.

3.5.3 Clustering

The Ontario site of the BCFR is composed of many breast cancer families. As such, many subjects in the FHS population are biologically related. Overall, there are 1114 women from 677 families who participated in the FHS; there are 396 families with 1 member, 166 families with 2 members, 68 families with 3 members, 20 families with 4 members, 10 families with 5 members, 5 families with 6 members, 2 families with 7 members, and 1 family with 8 members (mean: 1.26 relatives per familial cluster). Characteristics measured on participants within clusters are often correlated (Heeringa et al., 2010). Women in the FHS who are related
share a similar familial breast cancer risk, and may share other similar characteristics such as breast cancer screening behaviours, perceived risk of breast cancer, breast cancer risk factors, and socio-demographic factors such as education.

The amount of statistical information contained within a clustered study sample is less than that contained within an independently selected random sample of the same size (Heeringa et al., 2010). The variance estimation formulae for a simple random sample do not apply to more complex sample designs, as these formulae are based on an assumption of independence of observations. It is important then, to account for these potential similarities within clusters by using methodology that correctly estimates variance for the estimates produced by a clustered sample, to ensure standard errors are not erroneously small. All analyses presented in the thesis employed Taylor series linearized methods for robust variance estimation (RVE) to adjust p-values for familial clustering (Binder, 1983; Morel, 1989). The Taylor series method (linearization) is the most commonly used method to estimate the covariance matrix of the regression coefficients for complex survey data (SAS Institute, 2010). Specifically, the Morel adjustment method (Morel, 1989) for RVE was employed to adjust the variance estimator for the model parameters. The Morel method considers the design effect, and reduces bias reflected in Type I error rates when sample size is small (SAS Institute, 2010).

Hierarchical or multilevel modeling was also considered as an analytic strategy for cluster adjustment. Multilevel models are commonly used to analyze data which are hierarchically structured (Bell et al., 2010; Hox, 1998). While there is no consensus regarding the required sample size for this type of analysis, one of the commonly cited ‘rules of thumb’ calls for a minimum of 30 units of observation at each level of the analysis (Bell et al., 2010; Maas & Hox, 2004). Several simulation studies have been conducted to examine the effect of various design conditions on variance estimates, fixed effect estimates, standard errors, and
model convergence. While these studies showed little or no bias in fixed effect estimates (Maas & Hox, 2004; Maas & Hox et al, 2005; Clarke & Wheaton, 2007), variance estimates were biased where the number of level-two units were small (Maas & Hox, 2005; Clarke & Wheaton, 2007). Clarke & Wheaton (2007) also examined the effect of the proportion of singleton groups in two-level models, and found that bias in intercept and slope variance estimates was present when singleton groups were included. A large proportion (58.5%) of the 677 familial clusters in the FHS consisted of singleton groups (families with only one member). Therefore, multilevel modeling was not selected, as it was not the best-suited technique for the structure of these data.

Generalized estimating equations (GEE) was also considered as a potential statistical strategy for cluster adjustment. GEE is an extension of the quasi-likelihood approach, and is often used to analyze repeated measures and correlated data (Hanley et al., 2003). Similar to RVE, GEE accounts for non-independence of data by correcting the variance-covariance matrix (Zorn, 2006). Fitting a GEE model requires that the link function, distribution of the dependent variable, and correlation structure be specified (Ballinger, 2004). One important advantage of GEEs over the RVE method is the ability to use information regarding the structure of intracluster correlation to produce more efficient standard errors (Zorn, 2006; Odueyungbo et al., 2008). However, GEE models are sensitive to outlier values (Diggle et al., 2002), have inflated rates of type I errors when sample size is small (though this bias decreases when the number of clusters increases) (Teerenstra et al., 2010; Ziegler et al., 1998), and can produce inefficient estimates if the true structure of the correlation matrix is incorrectly specified (Odueyungbo et al., 2008). During the period when all statistical analyses were conducted, only ordinal multinominal models were supported in SAS for GEE (SAS Institute, 2010). As a generalized logit model to handle the nominal response variable in Objective 3 could not be fit, it was recommended by SAS software developers that the RVE technique be employed (SAS Institute, 2010).
Technical Support, Personal Communication, 2009). To ensure consistency in the technique for variance estimation used in the thesis project, the RVE approach was used for all analyses.

3.5.4 Data Quality Analyses

Several additional analyses were undertaken for the purposes of evaluating data quality. As previously described, the 1514 female relatives identified as eligible for recruitment to the FHS completed a questionnaire (PHQ) during their recruitment to the Ontario site of the BCFR, with 1114 (73.6%) of these women consenting to participate in the FHS. Among the 400 (26.4%) non-participating women, 37 (9.2%) were ineligible, 162 (40.5%) were unreachable, and 201 (50.3%) refused to participate. PHQ data were available for all of these women, thus an evaluation of selection bias due to non-participation was possible. Women who participated in the FHS (n = 1114) were compared to women who were unreachable (n = 162), and refused to participate (n = 201) on a number of socio-demographic measures, level of familial risk, breast cancer risk factors, and mammogram history. The full analysis is located in Appendix E, and the anticipated impact on results of the thesis are discussed in Chapter 5.

Women who completed a PHSQ at year 1 or year 2, and reported that they had undergone a mammogram or CBE since the previous PHSQ were asked to indicate the main reasons for undergoing these examinations. Women who reported a mammogram were also asked to specify any factors which encouraged them to have a mammogram. One of the response options provided was, “participating in this study.” Thus, an evaluation of a crude measure of Hawthorne effect (Roethlisberger & Dickson, 1939), the phenomenon wherein research participants change their behaviour as a result of having knowledge that they are being studied, was undertaken. The frequency of reporting that study participation was either the main
reason for undergoing mammography, or encouraged mammography use, was examined. Results of this analysis are discussed in Chapter 5.

3.6 Ethical Approval

Ethical approval for the Family History Study was initially obtained from the Research Ethics Boards of the University Health Network, and Mount Sinai Hospital in 2005 by Dr. Anna Chiarelli (PI), and was renewed on an annual basis until data collection was completed in 2011. Additional ethical approval for this thesis project was obtained from the University of Toronto Research Ethics Board by the candidate in December 2011, and renewed for one year in 2012 until December 2013, when all analyses were completed (Appendix F). This thesis project involved secondary data analysis only, and study participants were not contacted to provide any additional information. Unique identification numbers were assigned to ensure anonymity of subjects at all times. To ensure data confidentiality, all hard copies of data were kept in locked filing cabinets which could only be accessed by approved study staff, and located on a restricted-access floor at Cancer Care Ontario. All soft copies of data were stored in encrypted files on a secured network, which could also only be accessed by approved study staff. As such, the research risk of this thesis project was classified by the University of Toronto as low, and expedited review was granted.
Table 3.1 Moderate/high-risk criteria for the Ontario site of the Breast Cancer Family Registry (BCFR)

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Proband + ≥ 1 first-degree relative(s) with breast and/or ovarian cancer</td>
</tr>
<tr>
<td>Proband + &gt; 2 second-degree relatives with breast and/or ovarian cancer</td>
</tr>
<tr>
<td>Proband diagnosed with breast cancer ≤ 35 years of age</td>
</tr>
<tr>
<td>Proband + 1 second-degree relative or ≥ 3 third-degree relatives diagnosed with breast cancer ≤ 35 years of age or diagnosed with ovarian cancer ≤ 60 years of age</td>
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<tr>
<td>Male proband</td>
</tr>
<tr>
<td>Proband with 1 second-degree relative or ≥ 1 third-degree relative(s) with male breast cancer</td>
</tr>
<tr>
<td>Proband with breast and ovarian or multiple breast cancers</td>
</tr>
<tr>
<td>Proband + second-degree relative or ≥ 1 third-degree relative with breast and ovarian cancer</td>
</tr>
<tr>
<td>Proband + second-degree relative or ≥ 1 third-degree relative with multiple breast cancers</td>
</tr>
<tr>
<td>≥3 first-degree relatives (of each other) with cancer of the breast, ovarian, colon, prostate, pancreas or sarcoma, 1 diagnosed ≤ 50 years of age</td>
</tr>
<tr>
<td>Of Ashkenazi Jewish descent (at least 1 grandparent)</td>
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Table 3.2 Classification scheme of familial breast and/or ovarian cancer risk

<table>
<thead>
<tr>
<th>Familial Risk Group</th>
<th>Family History of Breast and/or Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>≥ 2 first-degree relatives diagnosed with breast and/or ovarian cancer at any age</td>
</tr>
<tr>
<td></td>
<td>≥ 1 first-degree relative(s) diagnosed with both breast and ovarian cancer at any age</td>
</tr>
<tr>
<td></td>
<td>≥ 1 first-degree relative(s) diagnosed with bilateral breast cancer at any age</td>
</tr>
<tr>
<td></td>
<td>≥ 1 first-degree male relative(s) diagnosed with breast cancer at any age</td>
</tr>
<tr>
<td></td>
<td>Personal history of ovarian cancer</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Self-reported Ashkenazi Jewish background</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative diagnosed with breast cancer before age of 40</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative diagnosed with ovarian cancer at any age</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative diagnosed with breast cancer after the age of 40 and ≥ 2</td>
</tr>
<tr>
<td></td>
<td>second-degree relatives diagnosed with breast cancer at any age</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative with breast cancer diagnosed after the age of 40 and ≥ 1</td>
</tr>
<tr>
<td></td>
<td>second-degree male relatives diagnosed with breast cancer at any age</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>1 first-degree relative diagnosed with breast cancer after the age of 40</td>
</tr>
</tbody>
</table>
Table 3.3 Summary of breast cancer risk assessment models (modified from Amir et al., 2010)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Gail</th>
<th>Gail 2</th>
<th>Claus</th>
<th>Claus 2</th>
<th>BRCAPRO</th>
<th>BOADICEA</th>
<th>IBIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Personal factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Body mass index</td>
<td>No</td>
<td>Yes(^a)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ashkenazi Jewish ancestry</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Hormonal &amp; reproductive factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at menarche</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Age at first live birth</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Age at menopause</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hormone replacement therapy use</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Breast feeding history</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Plasma estrogen level</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Personal history of breast disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast biopsies</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Atypical ductal hyperplasia</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lobular carcinoma in situ (LCIS)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Breast density</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Family history of cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1(^{st})-degree relatives - breast cancer</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2(^{nd})-degree relatives - breast cancer</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3(^{rd})-degree relatives - breast cancer</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Relative’s age - breast cancer</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bilateral breast cancer in a relative</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ovarian cancer in a relative</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

\(^a\): Gail 2 model (Chen et al., 2006) includes body weight, not body mass index.

* BOADICEA = Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; IBIS = International Breast Cancer Intervention Study.
Table 3.4 TNM classification for breast cancer from the AJCC Cancer Staging Manual, Sixth Edition (Greene et al., 2002, with permission from Springer)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor (T)</td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in-situ</td>
</tr>
<tr>
<td>Tis (DCIS)</td>
<td>Ductal carcinoma in-situ</td>
</tr>
<tr>
<td>Tis (LCIS)</td>
<td>Lobular carcinoma in-situ</td>
</tr>
<tr>
<td>Tis (Paget)</td>
<td>Paget disease of the nipple with no tumor (Paget disease associated with a tumor is classified according to the size of the tumor)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤2 cm in greatest dimension</td>
</tr>
<tr>
<td>T1mic</td>
<td>Microinvasion ≤0.1cm in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor &gt;0.1cm but ≤0.5cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt;0.5cm but ≤1cm in greatest dimension</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor &gt;1cm but ≤2cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;2cm but ≤5cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;5cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with direct extension to chest wall/skin, only as described below</td>
</tr>
<tr>
<td>T4a</td>
<td>Extension to chest wall, not including pectoralis muscle</td>
</tr>
<tr>
<td>T4b</td>
<td>Edema (including peau d’orange) or ulceration of the skin of breast, or satellite skin nodules confined to the same breast</td>
</tr>
<tr>
<td>T4c</td>
<td>Both T4a and T4b</td>
</tr>
<tr>
<td>T4d</td>
<td>Inflammatory carcinoma</td>
</tr>
<tr>
<td>Regional lymph nodes (N)</td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed (e.g. previously removed)</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastases to movable ipsilateral axillary lymph node(s)</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in ipsilateral axillary lymph node(s) fixed to one another (matted) or to other structures</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in ipsilateral infraclavicular lymph node(s), or in clinically apparent* ipsilateral internal mammary lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in ipsilateral infraclavicular lymph node(s) and axillary lymph node(s)</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in ipsilateral internal mammary and axillary lymph node(s)</td>
</tr>
<tr>
<td>N3c</td>
<td>Metastasis in ipsilateral supraclavicular lymph node(s)</td>
</tr>
<tr>
<td>Classification</td>
<td>Definition</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Regional lymph nodes (pN)†</td>
<td>Regional lymph nodes cannot be assessed (e.g. previously removed or not removed for pathologic study)</td>
</tr>
<tr>
<td>pNX</td>
<td>Regional lymph nodes cannot be assessed (e.g. previously removed or not removed for pathologic study)</td>
</tr>
<tr>
<td>pN0</td>
<td>No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)‡</td>
</tr>
<tr>
<td>pN0(i-)</td>
<td>No regional lymph node metastasis histologically, negative IHC§</td>
</tr>
<tr>
<td>pN0(i+)</td>
<td>No regional lymph node metastasis histologically, positive IHC§, no IHC§ cluster &gt;0.2mm</td>
</tr>
<tr>
<td>pN0(mol-)</td>
<td>No regional lymph node metastasis histologically, negative molecular findings (RT-PCR¶)</td>
</tr>
<tr>
<td>pN0(mol+)</td>
<td>No regional lymph node metastasis histologically, positive molecular findings (RT-PCR¶)</td>
</tr>
<tr>
<td>pN1</td>
<td>Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent*</td>
</tr>
<tr>
<td>pN1mi</td>
<td>Micrometastasis (&gt;0.2mm, none &gt;2.0mm)</td>
</tr>
<tr>
<td>pN1a</td>
<td>Metastasis in 1 to 3 axillary lymph nodes</td>
</tr>
<tr>
<td>pN1b</td>
<td>Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent*</td>
</tr>
<tr>
<td>pN1c</td>
<td>Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent*(if associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)</td>
</tr>
<tr>
<td>pN2</td>
<td>Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis</td>
</tr>
<tr>
<td>pN2a</td>
<td>Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit &gt;2.0mm)</td>
</tr>
<tr>
<td>pN2b</td>
<td>Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph-node metastasis.</td>
</tr>
<tr>
<td>pN3</td>
<td>Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes</td>
</tr>
<tr>
<td>pN3a</td>
<td>Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit &gt;2.0mm), or metastasis to the infraclavicular lymph nodes</td>
</tr>
<tr>
<td>pN3b</td>
<td>Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel node dissection but not clinically apparent*</td>
</tr>
<tr>
<td>pN3c</td>
<td>Metastasis in ipsilateral supraclavicular lymph nodes</td>
</tr>
<tr>
<td>Distant metastases (M)</td>
<td></td>
</tr>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

* Clinically apparently is defined as detected by imaging studies (excluding lymphoscintigraphy) or clinical examination.
† Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for “sentinel node,” such as pN0(i+)(sn).
‡ Isolated tumor cells are defined as single tumor cells or small cell clusters ≤0.2mm, usually detected only by immunohistochemical or molecular methods but which may be verified on hematoxylin and eosin stains. Isolated tumor cells do not usually show evidence of metastatic activity (e.g. proliferation or stromal reaction).
§ IHC = immunohistochemical.
¶ RT-PCT = reverse transcriptase/polymerase chain reaction.
Table 3.5 Stage grouping for breast cancer from the AJCC Cancer Staging Manual, Sixth Edition (Greene et al., 2002, with permission from Springer)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary Tumor (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1*</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T0</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1*</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T0</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1*</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

*T1 includes T1mic.

Figure 3.1 Recruitment flowchart for the Ontario site of the Breast Cancer Family Registry

Excluded

- 3063 (38%) did not respond or agree to participate
- 1497 (30%) male relatives
- 815 (24%) live outside Ontario
- 634 (24%) did not complete a Personal History Questionnaire
- 172 (9%) had a breast cancer diagnosis prior to proband diagnosis

Included

- 2580 proband cases of invasive breast cancer eligible to participate in OFBCR
- 8021 male and female relatives of proband cases sent letter of invitation
- 4958 (62%) relatives agreed to participate
- 3461 (70%) female relatives
- 2646 (76%) live in Ontario
- 2012 (76%) completed a Personal History Questionnaire
- 1840 (91%) did not have breast cancer diagnosis prior to proband diagnosis
Figure 3.2 Sample flow diagram for the Family History Study

Baseline

Women eligible for the FHS
n = 1514

Lost to follow-up (n = 162, 10.7%)
Ineligible (n = 37, 2.4%)

Contacted
n = 1315, 86.9%

Refused (n = 201, 15.3%)

Completed baseline interview
n = 1114, 84.7%
Breast cancer, n = 37
BBD, n = 84
Breast cancer free
n = 1077

Eligible for follow-up
n = 1077

Lost to follow-up (n = 11, 1.0%)
Ineligible (n = 4, 0.4%)

Year 1

Contacted
n = 1062, 98.6%

Refused (n = 87, 8.2%)

Completed Year 1 interview
n = 975, 91.8%
Breast cancer, n = 6
BBD, n = 9
Breast cancer free
n = 969

Eligible for follow-up
n = 969

Lost to follow-up (n = 32, 3.3%)
Ineligible (n = 1, 0.1%)

Contacted
n = 936, 96.6%

Refused (n = 54, 5.8%)

Completed Year 1 interview
n = 882, 94.2%
Breast cancer, n = 7
BBD, n = 8
Breast cancer free
n = 875
Figure 3.3. Distribution of Numeric Perceived Breast Cancer Risk at Baseline (n = 899)
Chapter 4
Results

4.1 Overview of Results

The results of this thesis are presented in manuscript format, comprising 4 independent papers. While the research papers have multiple authors, the candidate was responsible for developing the research objectives, conducting literature reviews, performing statistical data analysis, and drafting each manuscript in full. Additional detail regarding the candidate’s role in the project can be found in Chapter 6.

The first manuscript is contained within Chapter 2, and describes the results of a systematic review of observational studies examining the relationship between perceived breast cancer risk and adherence to breast cancer screening guidelines for mammography, CBE, and BSE in women with a family history of breast and/or ovarian cancer (Objective 2). The second manuscript evaluated the effect of level of familial breast cancer risk and mammography screening on diagnoses and prognostic features of breast cancer and benign breast disease in women with familial breast cancer risk (Objective 1). The third manuscript was written in direct response to the findings of the systematic review paper, and prospectively examined the relationship between perceived breast cancer risk and use of screening mammography, CBE, and genetic testing, as well as assessed the presence of effect modification by level of familial risk (Objective 2). The fourth manuscript details the results of a data quality assessment, which evaluated the validity of self-reported screening mammography dates in women with varying levels of familial risk in our study population (Objective 4).
4.2 Manuscript 2: Impact of familial risk and mammography screening on prognostic indicators of breast disease among women from the Ontario site of the Breast Cancer Family Registry

Walker MJ, Mirea L, Cooper K, Nabavi M, Glendon G, Andrulis IL, Knight JA, O’Malley FP, Chiarelli AM.

Published in Familial Cancer. 2014; 13(2): 163-172.

ABSTRACT

Although several studies have found screen-detected cancers in women with familial breast cancer risk have favorable prognostic features compared with symptomatic cancers, the impact of level of familial risk is unknown. A cohort of 899 first-degree female relatives of cases of breast cancer from the Ontario site of the Breast Cancer Family Registry was followed for 2 years. Logistic regression analyses compared diagnoses of breast cancer or benign breast disease (BBD) between women at high (n = 258, 28.7%) versus low/moderate (n = 641, 71.3%) familial risk. Similar analyses compared prognostic features of invasive cancers and BBD by level of familial risk and mammography screening status. Among 899 women, 44 (4.9%) were diagnosed with invasive breast cancer and/or ductal carcinoma in situ, and 56 (6.2%) with BBD. Women with high familial risk were significantly more likely to be diagnosed with breast cancer [odds ratio (OR) = 2.84, 95% confidence interval (CI) 1.50-5.38] than low/moderate risk women, particularly if diagnosed at age ≥50 (OR = 2.99, 95% CI 1.37-6.56) or screened with mammography (OR = 3.33, 95% CI 1.54-7.18). High risk women were more likely to be diagnosed with BBD (OR = 1.94, 95% CI 1.03-3.66). Level of familial risk was not associated with prognostic features. Cancers among unscreened women were larger (OR = 9.72, 95% CI 1.01-93.61) and diagnosed at stage II or above (OR = 7.80, 95% CI 1.18-51.50) compared with...
screen-detected cancers. Screening mammography may be effective for women with a first-degree family history of breast cancer, irrespective of level of familial risk.

**Keywords:** Breast cancer; benign breast disease; mammography screening; prognosis; family history

**Introduction**

Having a family history of breast cancer has been established as one of the most important risk factors for the development of breast cancer. Women with one affected first-degree relative are about twice as likely to develop breast cancer compared with women who have no affected relatives, and risks are higher when more than one first-degree relative is affected or the relative is younger at diagnosis [1–3]. A woman with a first-degree relative diagnosed with ovarian cancer is approximately twice as likely to develop breast cancer [4].

There is evidence that a significant reduction in breast cancer mortality can be achieved through mammography screening [5]. The Canadian Task Force on Preventive Health Care recommends screening for breast cancer with mammography every 2–3 years for average risk women aged 50–74 [6]. In Ontario, mammography is available to women aged 50–74 through the Ontario Breast Screening Program (OBSP), and opportunistically through facilities outside of the screening program [7]. In 2011, the OBSP was expanded to include annual combined MRI and mammographic screening for women aged 30–69 considered to be at very high risk (i.e. BRCA1/2 mutation carriers or family history suggestive of hereditary breast cancer) (Cancer Care Ontario, Internal Communication, 2011).

Although breast cancer screening guidelines for women with a family history recommend screening before age 50 and at more frequent intervals [8–14], the impact of screening on reducing mortality in these women is unknown. There is evidence that cancer
detection rates are greater in women with a family history compared to women without a family history [15, 16]. Some studies have also shown that screen-detected tumors among women with a family history of breast cancer are smaller [17], less likely to demonstrate nodal or distant metastases [17–20], and diagnosed at an earlier stage [20] when compared with symptomatic cancers.

Benign breast disease (BBD) represents changes in normal breast tissue that can indicate an increased risk of invasive breast cancer or may behave as a non-obligate precursor lesion [21]. Specific histologic abnormalities based on pathologic examination have a range of relative risks for subsequent invasive breast cancer. For example, mild hyperplasia without atypia has no increased risk, while risk is increased four- to five-fold when atypical hyperplasia is present [22]. Women with a family history have been found to have an increased risk of high-risk types of BBD (such as atypical hyperplasia) and women with both a family history and atypical hyperplasia have a greater risk of breast cancer [23, 24].

A few studies examining screening outcomes have shown that women with a family history may benefit from regular breast screening, reporting higher cancer detection rates and favorable prognostic features of screen detected cancers. However, few studies have examined screening outcomes by varying levels of familial risk [25]. This evidence is required for the development of definitive screening guidelines for women with a range of increased risks of breast cancer due to familial history. The purpose of this study was to compare diagnoses of breast disease and prognostic indicators by varying levels of familial risk and mammography screening status in a population-cohort of Ontario women aged 26–73 years, who had at least one first-degree relative diagnosed with breast or ovarian cancer.
Methods

Study population

This study identified a cohort of female relatives of incident cases of invasive breast cancer from the Ontario site of the Breast Cancer Family Registry (BCFR) funded by the United States National Cancer Institute (NCI). The details of the BCFR and the Ontario site of the BCFR have been previously described [26, 27]. Briefly, cases of invasive breast cancer (probands), pathologically confirmed, and diagnosed between 1996 and 1998 were identified from the Ontario Cancer Registry (OCR). Physicians were contacted to obtain permission to mail their patients a cancer Family History Questionnaire (FHQ). Respondents meeting a defined set of genetic risk criteria, and a random sample (25%) of those not meeting criteria were asked to participate in the Ontario site of the BCFR. Of those eligible at this stage (n = 2,587), 1,851 (72%) probands participated. Probands were asked for permission to contact specific living relatives (all first-degree relatives, any other relatives affected with breast, ovarian or certain other cancers and their first-degree relatives). An invitation letter to participate in the Ontario site of the BCFR was sent to relatives (n = 8,416), and those who agreed to be contacted (n = 5,122) were mailed an Epidemiology Questionnaire (EQ) between 1998 and 2004.

Our study was conducted several years after initial recruitment of relatives to the BCFR. In this study, we identified all first-degree female relatives enrolled in the Ontario site of the BCFR who had completed the EQ, were alive and unaffected by breast cancer at the time of the proband’s diagnosis, and residents of Ontario. These 1,289 eligible women were aged 20–69 years as of January 1st, 2006 and sent a baseline Personal History and Screening Questionnaire (PHSQ) between 2005 and 2007. Of these women, 201 did not complete the baseline PHSQ, 87 did not complete a year 1 PHSQ, 54 did not complete a year 2 PHSQ, 43 were lost to follow-up.
and 5 were deceased or ineligible due to health issues. The final cohort consisted of 899 women. This study was approved by the Research Ethics Boards of Mount Sinai Hospital and the University Health Network, and written informed consent was obtained from all participants.

Data collection

The women in this study were initially contacted by mailed questionnaire during recruitment to the BCFR. Since several years had elapsed, PHSQs were telephone-administered to update changes in health behaviors and key demographic characteristics. In addition, detailed information on breast screening examinations and diagnosis of any breast outcomes (breast cancer or BBD) was collected. Further details of the questionnaire instruments have been previously described [27–29].

Age at interview, age at menarche, parity, menopausal status, use of hormone replacement therapy, mammogram use since completion of the EQ, and number of months since last mammogram were determined using responses to the baseline PHSQ. Total number of lifetime mammograms was determined using combined responses from the EQ and baseline PHSQ. PHSQs asked women to give the date (month and year) of their last mammogram, or age at the time of last examination. Additionally, women were asked whether their mammogram was for screening (part of a regular check-up or family history of breast cancer) or nonscreening (breast problem or symptom). Classification of family history of breast and/or ovarian cancer was based on information collected from the FHQ completed by the relative’s proband using previously referenced groups for familial breast cancer risk [9, 30], with modifications based on key evidence [1, 3, 31–34] and expert opinion due to the range of familial breast and/or ovarian cancer histories in the study cohort. Table 1 shows criteria for classifying women as having low, moderate or high familial risk of breast and/or ovarian cancer.
Tumor characteristics

The self-reported date and location of any breast diagnosis were obtained from the PHSQ, and written informed consent was obtained granting access to pathology and surgical records. Copies of relevant reports were requested from the OCR or medical record departments of hospitals and/or clinics. Reports were obtained and reviewed for all diagnoses of breast cancer or BBD by the pathology consultant (MN). Invasive breast cancer includes the diagnosis of primary invasive breast cancer of any histologic type. Ductal carcinoma in situ (DCIS) includes intraductal carcinoma and Paget’s disease of the nipple with no invasive component.

Tumor size was defined as the largest diameter of the primary invasive carcinoma. Among women who had axillary assessment with either sentinel lymph node biopsy or axillary node dissection, lymph node status was defined as positive if the cancer had invaded the sentinel or other nodes. The 6th Edition of the TNM staging classification scheme [35] was used for the staging of breast cancers. Histopathologic grading of invasive carcinomas was performed using the Nottingham grading system [36], which takes into account architectural differentiation, nuclear pleomorphism and mitotic rate. Tumors were considered well-differentiated if the overall score was 3–5 (grade I), moderately-differentiated if the score was 6–7 (grade II) or poorly-differentiated if the score was 8–9 (grade III). Mitotic index was determined by assessing the number of mitoses per 10 high powered fields, which were standardized to the field diameter of the high power objective and classified as low (score 1), intermediate (score 2) or high (score 3). The absence or presence of lymphovascular invasion within the endothelial-lined channels of the breast was also recorded. Estrogen receptor (ER) and progesterone receptor (PR) status was defined as positive if immunohistochemical assays showed >1% tumor cell positivity [37].

Cases of BBD were categorized according to their relative risk for subsequent breast cancer, into the following severity groups: mild (fibrocystic changes or proliferative disease
without atypia), moderate (proliferative disease with atypical hyperplasia) or severe (lobular carcinoma in situ).

Statistical analysis

The distributions of breast cancer risk factors and screening mammography practices were compared by level of familial risk and screening status using general linear (for continuous measures) and logistic regression (for binary measures), adjusting for age at interview. Odds ratios (OR) and 95% confidence intervals (CI) were estimated from logistic regression to test associations between level of familial risk and diagnosis of breast cancer (invasive and/or DCIS) and BBD in all women adjusting for age, as well as stratified by age at interview or diagnosis and screening mammography status. Similar analyses examined associations between familial risk and screening mammography status, and prognostic characteristics of invasive breast cancers and BBD, adjusting for age at diagnosis. All analyses compared women at high familial risk to women at low/moderate risk. It was not necessary to adjust for breast MRI and ultrasound screening use, as very few women without a breast outcome and no women with a breast outcome were screened with these modalities during the study period. As many study participants were related, robust variance estimation techniques were applied to adjust P values and CIs for familial clustering [38, 39]. Analyses were conducted using SAS, Version 9.2 (SAS Institute Inc., 2004), and significance was evaluated using two-sided P values at the 5% testing level.

Results

Participants included 899 women from 599 families, of which 399 (66.6%) had one family member, 124 (20.7%) had two family members, and 76 (12.7%) had three to seven family members. Using our familial risk definitions, 429 (47.7%) women were low risk, 212
(23.6%) were moderate risk and 258 (28.7%) were high risk. Of 899 women, 799 (88.9%) remained free of a breast outcome. There were 46 self-reported cases of breast cancer, 44 (95.6%) of which were pathologically-confirmed. Of cancers with pathological confirmation, 38 (86.4%) had an invasive component, while 6 were DCIS-only (13.6%). There were 75 self-reported cases of BBD, 56 (74.7%) of which were pathologically-confirmed.

Women at high familial risk were significantly older at interview ($P < 0.0001$), more often post-menopausal ($P = 0.04$), and had a higher number of total lifetime mammograms ($P = 0.003$) than women at low/moderate risk (Table 2). Screened women were also significantly older at interview ($P < 0.0001$).

Women at high familial risk were significantly more likely to be diagnosed with breast cancer (OR = 2.84; 95% CI 1.50-5.38) or BBD (OR = 1.94; 95% CI 1.03-3.66) compared with women at low/moderate risk (Table 3). This association was significant for invasive breast cancer (OR = 2.95; 95% CI 1.51-5.78), but not for DCIS. Women at high familial risk were significantly more likely to be diagnosed with breast cancer at age 50 or above (OR = 2.99; 95% CI 1.36-6.59), while diagnosis of BBD was borderline significant among women at high familial risk below age 50 (OR = 2.26; 95% CI 0.98-5.20). Among women screened with mammography, those at high familial risk were more likely to be diagnosed with breast cancer (OR = 3.33; 95% CI 1.54-7.18) than women at low/moderate risk.

Prognostic features did not differ significantly by level of familial risk (Table 4). Invasive cancers in unscreened women were significantly more likely to be larger than 15 mm (OR = 9.72; 95% CI 1.01-93.61), and diagnosed at stage II–IV versus I (OR = 7.80; 95% CI 1.18-51.50) compared with screened women. Unscreened women also had proportionally more tumors with metastases to the lymph nodes, higher histological grade, higher mitotic index, lymphovascular invasion, and ER- and PR-negativity compared to screened women, however
these differences were not significant after adjusting for age.

**Discussion**

Overall, our study found that women with high familial risk were significantly more likely to be diagnosed with invasive breast cancer and BBD than women at low/moderate risk. While prognostic features of invasive breast cancers and BBD did not differ by level of familial breast cancer risk, women screened with mammography had more favorable prognostic profiles. Tumors in unscreened women were significantly larger and diagnosed at a later stage compared with screen-detected tumors.

Women at high familial risk were approximately three times more likely to be diagnosed with breast cancer in our study. Findings are in line with two meta-analyses, demonstrating that women with a first-degree family history have twice the risk of developing breast cancer, while risk increases three- to four-fold when the number of affected first-degree relatives increases [1, 2]. Women at high familial risk were approximately twice as likely to be diagnosed with BBD compared with low/moderate risk women. This association was more pronounced in women below age 50, though not statistically significant. To our knowledge, this study is the first to examine diagnoses of BBD by gradients of familial risk. However, previous studies have found women with a first-degree family history are two to three times more likely to be diagnosed with BBD than women without a family history [24, 40–45] and several studies, which stratified by age, noted this association was more important in younger or premenopausal women [24, 40–43].

Only one previous study has examined prognostic features of screen-detected breast cancers by gradients of familial risk, similarly finding women at moderate/high risk had proportionally fewer tumors larger than 20 mm, however statistical significance was not reported [25]. Many studies that examined differences in prognostic features between women
with a first- or second-degree family history of breast cancer and women without a family history have noted no significant differences [46–53]. However, a few studies have reported that tumors in women with familial risk are smaller [54, 55], and more often node-negative [56, 57] and ER+ [55] than tumors in women without a family history. These results may explain why some studies have observed a survival benefit in women with familial risk compared with family history negative women [54, 56, 57]. However, familial breast cancers, particularly in BRCA1 mutation carriers, are more likely to be of a higher grade and ER- than are sporadic cancers [58, 59]. Severity of BBD did not differ by familial risk in our study. While it has been demonstrated that women with familial risk are more likely to develop high-risk types of BBD compared with women without a family history [23, 24, 44], no differences in the degree of atypia have been reported [40, 45].

Our study found that tumors among unscreened women were significantly more likely to be larger in size (≥ 15 vs. <15 mm) and of a higher stage (stage II–IV vs. I) compared with tumors in screened women. These findings are in line with other studies that have reported screen detected cancers among women with familial risk tend to be smaller [17], less often metastasized to the lymph nodes or distantly metastasized [17–20] and diagnosed at an early stage [20] compared with symptomatic cancers. Studies in women with population-level breast cancer risk have similarly reported that screen-detected cancers are significantly smaller [60–64], node negative [60–62, 64], and of a lower stage [60, 61] and grade [61–64] at diagnosis than symptomatic cancers.

Findings should be interpreted in light of several limitations. First, the number of invasive cancers was small, reducing statistical power to detect small differences in prognostic features by level of familial risk and screening status. Second, cases of breast cancer and BBD were identified by self-report, and women may have been misclassified as being free of a breast
outcome if the outcome was unreported. High rates of sensitivity (90%) for self-reported breast cancers have been demonstrated [65–68], and one study found higher sensitivity for women with a family history of breast cancer compared with women without a family history, and higher sensitivity for self-reported invasive breast cancers compared with DCIS [69]. Similarly, data on family history of breast cancer was self-reported by probands and may be subject to misclassification. However, studies have shown patient-reported family cancer histories for first-degree relatives are highly accurate for breast cancer risk assessments [70]. Third, although self-reported data is accurate for determining whether a woman has had a mammogram, it is less accurate for determining the precise timing of screening [71,72]. To estimate recall error, we validated self-reported mammogram dates against imaging reports, finding over 95% of women accurately reported their mammogram use in the previous 12 months [73]. Fourth, the majority of data on human epidermal growth factor receptor-2 (HER-2) status was missing and we were unable to examine distributions of HER-2 expression or tumor subtypes. Phipps et al. [74] observed increased risk of triple-negative breast tumors in women with stronger familial histories, which is associated with poorer survival [75, 76]. Fifth, breast cancers were not limited to those detected after the index screen (incident cancers), thus results could be subject to length bias [77]. As the majority (88.8%) of screened women in our study had undergone two or more mammograms, the effect of length bias was likely minimal. Finally, women who were younger in age, less educated, single, pre-menopausal, users of hormone replacement therapy, and smokers, were significantly less likely to participate in the study. As such, self-referral bias cannot be excluded.

A notable strength of this study is its novel examination of prognostic features of breast outcomes in a population of women with differing levels of familial risk, with at least a first degree familial history. Participants were identified from a large population-based cohort of
relatives of cases of breast cancer, with a range of familial breast/ovarian cancer histories. The population-based recruitment also limits self-referral bias. Additionally, the province of Ontario has a comprehensive network of cancer treatment centers, where the majority of breast cancers are treated and medical charts contained extensive pathology data that were consistently complete.

Breast cancers in women screened with mammography were significantly smaller and diagnosed at an early stage compared with unscreened women, suggesting that screening mammography may be effective for women with a first-degree familial history, irrespective of level of familial risk. Level of familial risk was not significantly associated with prognostic features of invasive breast cancers or severity of BBD. Thus, women at high familial risk would not be predicted to demonstrate poorer survival compared to women at lower familial risk. It is also important to note that women younger in age have lower mammographic sensitivity compared with women aged 50 years or above [78, 79]. Few studies have examined the effectiveness of mammography screening specifically in younger women with a family history of breast cancer; however, one recent study reported interim findings which demonstrated favorable prognostic characteristics, and a predicted survival benefit of 20% for women younger than 50 years of age with a moderate or high family history of breast cancer, attributable to annual screening with mammography [80]. Future studies with longer follow-up which examine breast cancer mortality among larger samples of women with a range of familial breast/ovarian cancer histories and age groups must be conducted to determine whether screening mammography is effective for all women with a family history of breast cancer. This future work will inform optimal breast cancer screening guidelines for women with varying levels of familial risk.
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Conflict of interest: The authors declare that they have no conflict of interest.
References


80. FH01 collaborative teams (2010) Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single arm, FH01 study. Lancet Oncol 11:1127-1134
Table 1. Classification of familial risk of breast and/or ovarian cancer

<table>
<thead>
<tr>
<th>Familial risk group</th>
<th>Family history of breast and/or ovarian cancer</th>
</tr>
</thead>
</table>
| High                | ≥ 2 first-degree relatives diagnosed with breast and/or ovarian cancer at any age  
|                     | ≥ 1 first-degree relative(s) diagnosed with both breast and ovarian cancer at any age  
|                     | ≥ 1 first-degree relative(s) diagnosed with bilateral breast cancer at any age  
|                     | ≥ 1 first-degree male relative(s) diagnosed with breast cancer at any age  
|                     | Personal history of ovarian cancer |
| Moderate            | Self-reported Ashkenazi Jewish background  
|                     | 1 first-degree relative diagnosed with breast cancer before age of 40  
|                     | 1 first-degree relative diagnosed with ovarian cancer at any age  
|                     | 1 first-degree relative diagnosed with breast cancer after the age of 40 and ≥ 2 second-degree relatives diagnosed with breast cancer at any age  
|                     | 1 first-degree relative with breast cancer diagnosed after the age of 40 and ≥ 1 second-degree male relative(s) diagnosed with breast cancer at any age |
| Low                 | 1 first-degree relative diagnosed with breast cancer after the age of 40 |
Table 2. Breast cancer risk factors and mammography practices at baseline by level of familial breast cancer risk and screening status

<table>
<thead>
<tr>
<th>Risk factors and mammography practices</th>
<th>Level of familial risk</th>
<th>Screening status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low/moderate n = 641</td>
<td>High n = 258</td>
</tr>
<tr>
<td>Age at interview (years), mean (SD)</td>
<td>48.5 (11.3)</td>
<td>53.7 (9.9)</td>
</tr>
<tr>
<td>Age at menarche (years), mean (SD)</td>
<td>12.6 (1.4)</td>
<td>12.7 (1.4)</td>
</tr>
<tr>
<td>Parous, n (%)</td>
<td>533 (83.3)</td>
<td>223 (86.4)</td>
</tr>
<tr>
<td>Post-menopausal, n (%)</td>
<td>286 (44.7)</td>
<td>158 (61.2)</td>
</tr>
<tr>
<td>Ever used hormone replacement therapy*, n (%)</td>
<td>128 (45.4)</td>
<td>70 (45.4)</td>
</tr>
<tr>
<td>Had a mammogram since the EQ, n (%)</td>
<td>506 (79.1)</td>
<td>234 (91.4)</td>
</tr>
<tr>
<td>Months since last mammogram, mean (SD)</td>
<td>14.5 (15.5)</td>
<td>12.3 (15.3)</td>
</tr>
<tr>
<td>Number of lifetime mammograms, mean (SD)</td>
<td>3.3 (2.9)</td>
<td>4.6 (3.1)</td>
</tr>
</tbody>
</table>

a P-values from general linear regression, adjusted for age at interview.
b P-values from logistic regression, adjusted for age at interview.
c Post-menopausal women only.
Table 3. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for associations between level of familial breast cancer risk and diagnosis of breast cancer or benign breast disease

<table>
<thead>
<tr>
<th>Level of familial risk</th>
<th>Breasts or breast outcomes</th>
<th>High vs. low/moderate risk OR (95% CI)a</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All breast cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>579 (96.3)</td>
<td>210 (90.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>22 (3.7)</td>
<td>22 (9.5)</td>
<td>2.84 (1.50-5.38)</td>
</tr>
<tr>
<td>Ductal carcinoma in situb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>579 (99.5)</td>
<td>210 (98.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>3 (0.5)</td>
<td>3 (1.4)</td>
<td>2.31 (0.37-14.49)</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>579 (96.8)</td>
<td>210 (91.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>19 (3.2)</td>
<td>19 (8.3)</td>
<td>2.95 (1.51-5.78)</td>
</tr>
<tr>
<td>Aged &lt; 50 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>288 (96.3)</td>
<td>51 (92.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (3.7)</td>
<td>4 (7.3)</td>
<td>2.26 (0.68-7.45)</td>
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<tr>
<td>Aged ≥ 50 years</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>291 (96.4)</td>
<td>159 (89.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (3.6)</td>
<td>18 (10.2)</td>
<td>2.99 (1.37-6.56)</td>
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<tr>
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<td></td>
</tr>
<tr>
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<td>440 (97.1)</td>
<td>181 (90.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>13 (2.9)</td>
<td>18 (9.1)</td>
<td>3.33 (1.54-7.18)</td>
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<td>Unscrened</td>
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<tr>
<td>No</td>
<td>45 (83.3)</td>
<td>10 (71.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (16.7)</td>
<td>4 (28.6)</td>
<td>2.70 (0.52-13.92)</td>
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<td>Benign breast disease (BBD)</td>
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<td>579 (94.1)</td>
<td>210 (91.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>36 (5.9)</td>
<td>20 (8.7)</td>
<td>1.94 (1.03-3.66)</td>
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<td>Aged &lt; 50 years</td>
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<tr>
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<td>288 (92.0)</td>
<td>51 (83.6)</td>
<td>1.00</td>
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<td>Yes</td>
<td>25 (8.0)</td>
<td>10 (16.4)</td>
<td>2.26 (0.98-5.20)</td>
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<tr>
<td>Aged ≥ 50 years</td>
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<tr>
<td>No</td>
<td>291 (96.4)</td>
<td>159 (94.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (3.6)</td>
<td>10 (5.9)</td>
<td>1.66 (0.69-3.99)</td>
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<tr>
<td>Screened</td>
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</tr>
<tr>
<td>Yes</td>
<td>440 (95.2)</td>
<td>181 (93.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>22 (4.8)</td>
<td>12 (6.2)</td>
<td>1.66 (0.76-3.64)</td>
</tr>
<tr>
<td>Unscrened</td>
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<tr>
<td>Yes</td>
<td>45 (78.9)</td>
<td>10 (62.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>12 (21.1)</td>
<td>6 (37.5)</td>
<td>3.23 (0.74-14.08)</td>
</tr>
</tbody>
</table>

a Adjusted for age at interview (women without a diagnosed breast outcome) or age at diagnosis (excluding age-stratified models) and familial clustering.

b Ductal carcinoma in situ only; breast cancer diagnoses including components of both ductal carcinoma in situ and invasive breast cancer are classified as invasive cancers.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Familial risk</th>
<th>Screening status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low/moderate</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Invasive breast cancer cases</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 15</td>
<td>6 (31.6)</td>
<td>9 (47.4)</td>
</tr>
<tr>
<td>&gt; 15</td>
<td>13 (68.4)</td>
<td>10 (52.6)</td>
</tr>
<tr>
<td>Nodal involvement&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>10 (62.5)</td>
<td>8 (61.5)</td>
</tr>
<tr>
<td>Positive</td>
<td>6 (37.5)</td>
<td>5 (38.5)</td>
</tr>
<tr>
<td>Stage at diagnosis&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6 (33.3)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>II-IV</td>
<td>12 (66.7)</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>Histologic grade</td>
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<td></td>
</tr>
<tr>
<td>I</td>
<td>5 (26.3)</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>II</td>
<td>4 (21.1)</td>
<td>10 (52.6)</td>
</tr>
<tr>
<td>III</td>
<td>10 (52.6)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Mitotic score&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Low</td>
<td>8 (42.1)</td>
<td>11 (68.7)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>5 (26.3)</td>
<td>2 (12.5)</td>
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<td>High</td>
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<td>3 (18.8)</td>
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<tr>
<td>Lymphovascular invasion&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Absent</td>
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<td>13 (76.5)</td>
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<tr>
<td>Present</td>
<td>6 (33.3)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Estrogen receptor&lt;sup&gt;†&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Positive</td>
<td>12 (80.0)</td>
<td>13 (81.2)</td>
</tr>
<tr>
<td>Negative</td>
<td>3 (20.0)</td>
<td>3 (18.8)</td>
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<tr>
<td>Progesterone receptor&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Positive</td>
<td>11 (73.3)</td>
<td>11 (68.7)</td>
</tr>
<tr>
<td>Negative</td>
<td>4 (26.7)</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td></td>
<td>Low/moderate n = 615</td>
<td>High n = 230</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Benign breast disease</td>
<td>36 (58.3)</td>
<td>20 (83.3)</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
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<tr>
<td>Mild</td>
<td>27 (75.0)</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>9 (25.0)</td>
<td>3 (15.0)</td>
</tr>
</tbody>
</table>

a: P-values from logistic regression, adjusted for age at diagnosis and familial clustering.
b: Frequencies do not add to stated totals due to undetermined status; percentages based on non-missing values.

* P = 0.049.

** P = 0.033.
4.3 Manuscript 3: Does perceived risk predict breast cancer screening use? Findings from a prospective cohort study of female relatives from the Ontario site of the Breast Cancer Family Registry

Walker MJ, Mirea L, Glendon G, Ritvo P, Andrulis IL, Knight JA, Chiarelli AM.

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ABSTRACT

While the relationship between perceived risk and breast cancer screening use has been studied extensively, most studies are cross-sectional. We prospectively examined this relationship among 913 women, aged 25-72 with varying levels of familial breast cancer risk from the Ontario site of the Breast Cancer Family Registry. Associations between perceived lifetime breast cancer risk and subsequent use of mammography, clinical breast examination (CBE) and genetic testing were assessed using logistic regression. Overall, perceived risk did not predict subsequent use of mammography, CBE or genetic testing. Among women at moderate/high familial risk, those reporting a perceived risk greater than 50% were significantly less likely to have a CBE (odds ratio (OR) = 0.52, 95% confidence interval (CI): 0.30–0.91, p = 0.04), and non-significantly less likely to have a mammogram (OR = 0.70, 95% CI: 0.40–1.20, p = 0.70) or genetic test (OR = 0.61, 95% CI: 0.34–1.10, p = 0.09) compared to women reporting a perceived risk of 50%. In contrast, among women at low familial risk, those reporting a perceived risk greater than 50% were non-significantly more likely to have a mammogram (OR = 1.13, 95% CI: 0.59–2.16, p = 0.78), CBE (OR = 1.11, 95% CI: 0.63–1.95, p = 0.74) or genetic test (OR = 1.29, 95% CI: 0.50–3.33, p = 0.35) compared to women reporting a perceived risk of 50%. Perceived risk did not significantly predict screening use overall, however this relationship may be moderated by level of familial risk. Results may inform risk
education and management strategies for women with varying levels of familial breast cancer risk.

**Keywords:** breast cancer; perceived risk; breast cancer screening; familial risk

**Introduction**

Family history is one of the most important risk factors for the development of breast cancer. Women with one affected first-degree relative are about twice as likely to develop breast cancer compared with women who have no affected relatives, and risks are higher when more than one first-degree relative is affected or the relative is younger at diagnosis [1-3].

A reduction in breast cancer mortality attributable to mammography screening among women aged 50–74 has been demonstrated [4]. In Ontario, mammography is freely available to average-risk women aged 50–74 every 2–3 years through the Ontario Breast Screening Program (OBSP), or with physician referral through imaging facilities outside of the OBSP [5]. The impact of mammography on reducing mortality in women with a family history of breast cancer is unknown; however, some studies have shown that screen-detected tumors in women with a family history are smaller [6,7], less likely to demonstrate nodal or distant metastases [6,8,9], and diagnosed at an earlier stage [7,9] compared to symptomatic cancers. Breast screening guidelines for women with a family history of breast cancer are based on expert opinion, and typically include screening mammography, clinical breast examination (CBE) and/or MRI on an annual basis starting at age 40 or 10 years prior to the earliest age of diagnosis in the family, or as young as age 25 for BRCA mutation carriers [10-16]. Certain women with a strong family history of breast or ovarian cancer are also eligible for referral to a specialist genetic clinic where genetic testing may be performed [17]. In 2011, the OBSP was expanded to include annual combined MRI and mammography for women aged 30–69 considered to be at very high
risk of breast cancer (i.e. BRCA1/2 mutation carriers or family history suggestive of hereditary breast cancer) [18].

While there is a positive association between family history of breast cancer and mammogram use [19], rates of adherence to screening guidelines in women with familial risk remain suboptimal. One Australian population-based study of women with familial risk demonstrated high adherence (74%) to mammography guidelines, but lower adherence (55%) to CBE guidelines [20]. Several North American population-based studies have demonstrated lower rates of adherence; in one study, 40% of women with familial risk screened with mammography in the previous 11 months [21], while another study reported 36% of women at low familial risk and 55% at moderate/high risk screened with mammography in the previous year [22]. An inverted U-shaped relationship has also been suggested [23], wherein women at the extreme ends of risk may screen less, in a relationship mediated by worry [24,25].

The relationship between perceived risk of breast cancer and breast cancer screening behaviors has been widely studied. The construct of perceived risk is central to health behavior theories, including the Health Belief Model (HBM) [26], and Protection Motivation Theory [27]. Briefly, it is suggested that a realistic perception of risk motivates individuals to engage in health behaviors appropriate to the level of risk [28,29]. Two meta-analyses found a small, significant association between perceived risk and mammogram use in women with population-level breast cancer risk [19,30]. This was confirmed for women with familial risk in our recent review [31].

We previously conducted a cross-sectional study examining the relationship between perceived risk and breast cancer screening behaviors in this study population, finding a significant positive relationship between higher levels of perceived risk and annual use of screening mammography [32]. Few prospective studies among women with familial risk have
been conducted [20,33-35], and are necessary to confirm previous cross-sectional findings. The few prospective studies may not generalize to the broader population of women with familial risk. As in many previous studies, Diefenbach et al. [35] recruited women with strong family histories from a clinical setting, and Lemon et al. [34] examined screening in the year following relative's breast cancer diagnosis when screening behaviors may be modified. The objective of the present study was to prospectively assess the influence of perceived risk of breast cancer on subsequent breast cancer screening practices and genetic test use in women with varying levels of familial breast cancer risk.

**Materials and Methods**

Study population

This study utilized data from a cohort of female relatives of incident cases of invasive breast cancer identified from the Ontario site of the Breast Cancer Family Registry (BCFR), funded by the United States National Cancer Institute. Details of the BCFR and the Ontario site of the BCFR have been previously described [36,37]. Briefly, cases of pathologically-confirmed invasive breast cancer (probands), diagnosed between 1996 and 1998 were identified from the Ontario Cancer Registry. Physicians were contacted to obtain permission to mail their patients a cancer Family History Questionnaire (FHQ). Respondents meeting a defined set of high-risk criteria [37] and a random sample (25%) of those not meeting these criteria were asked to participate in the Ontario site of the BCFR. Of the 2587 eligible probands, 1851 (71.5%) participated. Probands were then asked for permission to contact specific living relatives (all first-degree relatives, any other relatives affected with breast, ovarian or certain other cancers and their first-degree relatives). An invitation letter to participate in the Ontario site of the BCFR was sent to all relatives (n = 8416), and the 5122 who agreed to be contacted were mailed an Epidemiology Questionnaire (EQ) between 1998 and 2004.
This prospective cohort study was conducted several years after the initial recruitment of relatives to the Ontario site of the BCFR. All female relatives enrolled in the Ontario site who completed an EQ, were 20–69 years of age and unaffected by breast cancer at the time of the proband's diagnosis were eligible to participate. From the 3374 participating female relatives, 1514 met these study criteria. A baseline Personal History and Screening Questionnaire (PHSQ) was sent between November 2005 and March 2007 to the 1514 eligible women, of which 1308 (86.4%) could be contacted and 1114 (85.2%) were interviewed. A follow-up questionnaire was sent to 1077 eligible women approximately one year following the baseline PHSQ, of which 1062 could be contacted and 975 (91.8%) were interviewed. We further excluded 6 women diagnosed with breast cancer, 26 women without a first-degree family history of breast/ovarian cancer, 5 women who had undergone bilateral mastectomy, 10 women who were pregnant or breastfeeding, and 15 women missing data on their perceived breast cancer risk. The final cohort consisted of 913 women. This study was approved by the Mount Sinai Hospital, the University Health Network and the University of Toronto Research Ethics Boards, and written informed consent was obtained from all women.

Data collection

Information was obtained from three questionnaires. The first (EQ) was self-administered during recruitment of female relatives to the Ontario site of the BCFR and collected detailed information on demographics and key behavioral risk factors for breast/ovarian cancer. As several years had elapsed since recruitment to the registry, subsequent questionnaires (baseline and year 1 PHSQ) with similar content were telephone-administered to update changes in demographic and health behavior characteristics, and collect detailed information on cancer screening. Eligible participants were sent a copy of the PHSQ approximately two weeks prior to contact by telephone. This allowed time for participants to
recall specific dates and events, and allowed reference to the questionnaire during the interview. Further details of the questionnaire instruments have been previously described [22,32,36].

Data measures

Perceived risk was assessed in the baseline *PHSQ* with two questions adapted from Lipkus et al. [38]. The first asked, “On a scale from 0 to 100%, where 0 = certain not to happen and 100 = certain to happen, how likely are you to get breast cancer in your lifetime?” The second asked, “Compared with other women your age, how likely are you to get breast cancer in your lifetime?” Responses ranged from “much below average” to “much above average.” The outcomes of interest were use of screening mammography and CBE within 15 months, as well as genetic testing. Extending the screening interval for mammography and CBE beyond the standard 12 months allows flexibility for factors such as wait-times at imaging facilities [39,40]. Self-reported dates and reasons for screening examinations were obtained from the year 1 *PHSQ*. Women were asked to provide the date (month and year) or their age at last examination. Women were also asked to indicate if the main reason for the last exam was for screening (regular check-up or family history of breast cancer) or non-screening (breast symptom or participation in a research study). Women were asked at year 1 whether they ever had a genetic test for mutation of the breast and ovarian cancer susceptibility genes BRCA1/BRCA2.

Classifications of familial breast cancer risk were based on data collected by the cancer *FHQ* completed by the proband, using previously referenced groups for familial breast cancer risk [12,41], with modifications based on key evidence [1,2,17,42-44], and expert opinion. Table 1 shows the criteria for classifying women as low, moderate or high risk. Age at interview was calculated as the difference in years between date of birth and date of year 1 interview. Education, frequency of visiting a healthcare professional, and use of screening mammography or CBE within the 15 months prior to baseline, were determined using responses from the
baseline *PHSQ*. Menopausal status, history of benign breast disease, and use of genetic testing and counseling was derived from responses to questions from the *EQ*, baseline and year 1 *PHSQ* interviews.

Statistical analysis

Distributions of socio-demographic characteristics and health behaviors were compared among levels of perceived breast cancer risk using overall Chi-square tests or Fisher's exact tests where cell counts were <5. Logistic regression was used to estimate adjusted odds ratios for associations between perceived risk (numeric and comparative) at baseline and use of screening mammography, CBE and BRCA1/2 genetic testing at year 1. As results from the numeric and comparative models were similar, only the models using numeric estimates of perceived risk are shown. The relationship between numeric perceived risk as a continuous predictor and screening use was also modeled. As results did not differ substantially from the main results, and women demonstrated a strong preference for reporting perceived risk of exactly 50%, the categorized perceived risk measure was used for final models. To test for non-linearity of the associations between perceived risk and screening use, likelihood ratio tests were conducted to compare the models using continuous perceived risk (0–100%) with the models using categorized perceived risk (<50%, 50%, >50%). As familial risk was identified as a potential effect modifier of the association between perceived risk and screening use, analyses were stratified by level of familial risk (low familial risk, and moderate/high familial risk). Final multivariate models were adjusted for age at interview, education, annual frequency of health care visits, menopausal status, and history of benign breast disease. Models for screening mammography and CBE were also adjusted for the corresponding baseline screening behavior and history of genetic counseling. All models were also adjusted for breast cancer worry; however, as this did not result in any change to the estimates, it was left out of final models. As women are clustered
within families, techniques for robust variance estimation were applied to estimate \( p \)-values and confidence intervals (CI) in all regression models [45,46]. Analyses were conducted using SAS, Version 9.2 (SAS Institute Inc., 2004) and the significance of all statistical tests was evaluated using two-sided \( p \)-values at the 5% testing level.

**Results**

Participants included 913 women from 597 families, of which 394 (66.0%) had 1 family member, 127 (21.3%) had 2 family members and 76 (12.7%) had 3–8 family members. On the numeric scale, 211 (23.7%) women perceived their risk as <50%, 231 (25.9%) perceived their risk as exactly 50% and 449 (50.4%) perceived their risk as >50%. Those reporting the highest risk estimates were significantly younger (\( p < 0.0001 \)), more educated (\( p = 0.03 \)), pre-menopausal (\( p = 0.006 \)), visited health care professionals more frequently (\( p = 0.05 \)), and more often underwent genetic counseling (\( p = 0.01 \)) (Table 2).

At follow-up, 503 (55.8%) women reported having a mammogram, 621 (68.8%) women reported having a CBE, and 132 (14.7%) women reported having a genetic test. Women at low familial risk were non-significantly more likely to screen with mammography if they reported their risk as <50% vs. 50% (odds ratio (OR) = 1.48, 95% CI: 0.69–3.16, \( p = 0.30 \)) or >50% vs. 50% (OR = 1.13, 95% CI: 0.59–2.16, \( p = 0.78 \)) (Table 3). In contrast, women at moderate/high familial risk were less likely to undergo mammography if their reported risk was <50% vs. 50% (OR = 0.58, 95% CI: 0.30–1.12, \( p = 0.20 \)) or >50% vs. 50% (OR = 0.70, 95% CI: 0.40–1.20, \( p = 0.70 \)). Although likelihood ratio tests could not exclude a linear relationship, our results are consistent with a U-shaped relationship with higher mammography use for women at low familial risk with perceived risk of <50% or >50%, and an inverted U-shaped relationship with lower mammography use for women at moderate/high familial risk with perceived risk of <50% or >50%.
Women at low familial risk were similarly likely to screen with CBE if they reported their risk as <50% vs. 50% (OR = 1.04; 95% CI: 0.53–2.03, \( p = 0.96 \)), and non-significantly more likely to screen with CBE if they reported their risk as >50% vs. 50% (OR = 1.11; 95% CI: 0.63–1.95, \( p = 0.74 \)). A similar pattern of reduced OR estimates was observed in women at moderate/high familial risk for CBE and genetic testing comparing women reporting their risk as >50% vs. 50%. Women at moderate/high familial risk were non-significantly less likely to screen with CBE if they reported their risk as <50% vs. 50% (OR = 0.76; 95% CI: 0.38–1.51, \( p = 0.86 \)), and significantly less likely to screen with CBE if they reported their risk as >50 vs. 50% (OR = 0.52, 95% CI: 0.30–0.91, \( p = 0.04 \)) compared to women who perceived their risk as exactly 50%.

**Discussion**

In our prospective study, baseline perceived risk of breast cancer did not predict subsequent use of mammography, CBE or genetic testing in the overall cohort. We found some evidence to suggest this relationship may be modified by familial breast cancer risk. Among women at low risk, women who perceived their risk as less than 50% or greater than 50% were non-significantly more likely to report screening with mammography and CBE compared with women who perceived their risk as 50% (U-shaped relationship). A curvilinear (inverted U-shaped) relationship between perceived risk and screening use was observed among women at moderate/high familial risk; women were non-significantly less likely to have a screening mammogram, or genetic test, and significantly less likely to have a CBE if they perceived their risk to be less than 50% or greater than 50% compared with women who perceived their risk as 50%.

Studies examining the relationship between perceived risk and adherence to mammography guidelines in women with familial breast cancer risk have reported mixed
results. Several cross-sectional studies examining annual or biennial screening mammogram use found a positive relationship between higher levels of perceived risk and adherence [47-51]. An earlier cross-sectional analysis in the same cohort described in the present study found that women with higher levels of perceived risk were significantly more likely to report an annual mammogram [32]. Alternatively, other cross-sectional studies did not observe an association [52-56]. One prospective study reported a significant positive correlation between perceived risk and adherence [33], while another prospective study found women with ‘higher’ perceived risk (but not ‘much higher’) were significantly more likely to have a mammogram than women with lower perceived risk in the year following their relative's diagnosis [34]. Consistent with our overall results, two prospective studies found perceived risk did not predict mammogram use [20,35].

Most previous studies, mainly cross-sectional [32,49,52,57] and one prospective study [20], have not observed a significant association between perceived risk and CBE adherence in women with familial breast cancer risk. Few studies have examined the influence of perceived risk on genetic testing, instead focusing on intention to undergo testing. In our study, perceived risk was not associated with undergoing genetic testing. In Ontario, genetic testing requires referral by a physician based on a strong familial cancer history, and thus it is not expected that perceived risk would influence use of genetic testing.

It is likely that different study designs and screening guidelines account for much of the inconsistency in findings across studies. The simultaneous measurement of perceived risk and screening use in cross-sectional research makes the direction of this relationship impossible to establish. It is probable that women's recent breast cancer screening histories influence their perceived risk. This reverse influence likely explains why many cross-sectional studies (including the earlier cross-sectional analysis of this cohort) have observed associations, while
perceived risk did not predict subsequent screening in our study overall, as well as a few other prospective studies [20,35]. Factors such as physician recommendation or other individual-level characteristics such as breast cancer worry likely have a more direct impact on screening behaviors.

There is also a lack of consensus regarding the most valid approach to measuring risk perception, leading to differences in the measurement scales employed across studies, and the risk estimates produced [30,58,59]. A recent study which asked study participants to explain their reported numeric mortality risk estimates demonstrated that 50% was significantly more likely than other probabilities to be reflective of one being unaware of their risk, particularly among those with lower education and numeracy [60]. It should be noted that approximately 26% of women in our study reported a perceived risk of 50%, and these women tended to have lower levels of education and no history of genetic counseling.

Due to the wide range of familial breast cancer histories in our cohort, we were able to examine the influence of perceived risk on screening use within strata of familial risk. To our knowledge, this is the first study to examine this relationship among subgroups of objective breast cancer risk. Women with strong family histories may hold exaggerated risk perceptions and disproportionately experience worry about developing cancer, which could influence screening behaviors. It has been demonstrated that highly elevated levels of cancer anxiety or worry may deter breast cancer screening in women with familial risk [25,47,53,56], and there is some evidence that the relationship is curvilinear [24,61-63], where moderately elevated levels of worry are most predictive of screening. It is plausible that highly elevated levels of perceived risk may negatively impact coping abilities and promote avoidance of screening in a similar way to breast cancer worry, deterring the regular use of breast cancer screening, as our findings in women with moderate/high familial risk suggest.
The main strength of this study is the prospective design, which limits reverse causality. This study was conducted within a population-based cohort of relatives of cases of breast cancer, thus generalizability is extended to the larger population of women with familial risk. As the mortality benefits of breast screening are afforded through regular use, we investigated screening within 15 months, while previous studies have often examined ever-screening. To avoid underestimating screening use, our analyses excluded women who were pregnant, breastfeeding or had undergone mastectomy and thus have modified breast screening practices.

Limitations include possible misclassification resulting from use of self-reported data to measure screening use. While self-reported mammogram data is valid for determining if a woman has had a mammogram, it is less accurate for determining timing of screening [64,65]. To estimate the magnitude of recall error, we validated self-reported mammogram dates against medical records. We found that self-reported mammogram use within the previous 12 months was accurate for over 95% of women across all study years [66]. Additionally, we had low statistical power to detect small differences in screening behaviors by level of perceived and familial risk in stratified analyses. Finally, we note that our finding regarding the influence of perceived risk on screening behaviors may be different in populations with different breast cancer screening recommendations or healthcare systems.

Breast cancer screening requires behavioral action at the individual level. Understanding the factors which influence screening is needed to develop strategies to increase rates of regular use. In this cohort of women with familial breast cancer risk, perceived risk did not predict subsequent use of screening mammography, CBE or genetic testing overall. Among women at high familial risk, an inverted U-shaped curvilinear relationship was suggested. Women at high familial risk were less likely to screen with any modality if they perceived their risk as less than or greater than 50% compared with women who perceived their risk as exactly 50%. Low, and
highly elevated risk perceptions may deter appropriate screening use in women with high familial risk. Further investigation of the concordance between objective and subjective measures of risk, and the influence of perceived risk on breast screening in women with varying levels of familial risk is needed. This will allow researchers and clinicians to understand where appropriate risk management efforts should be focused in women with familial breast cancer risk.

**Sources of funding**

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**Conflict of interest statement**

None declared.

**Acknowledgements**

The authors thank the study staff and participants of the Ontario site of the Breast Cancer Family Registry.
References


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<thead>
<tr>
<th>Familial risk group</th>
<th>Family history of breast and/or ovarian cancer</th>
</tr>
</thead>
<tbody>
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<td><strong>High</strong></td>
<td>≥ 2 first-degree relatives diagnosed with breast and/or ovarian cancer at any age</td>
</tr>
<tr>
<td></td>
<td>≥ 1 first-degree relative(s) diagnosed with both breast and ovarian cancer at any age</td>
</tr>
<tr>
<td></td>
<td>≥ 1 first-degree relative(s) diagnosed with bilateral breast cancer at any age</td>
</tr>
<tr>
<td></td>
<td>≥ 1 first-degree male relative(s) diagnosed with breast cancer at any age</td>
</tr>
<tr>
<td></td>
<td>Personal history of ovarian cancer</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Self-reported Ashkenazi Jewish background</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative diagnosed with breast cancer before age of 40</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative diagnosed with ovarian cancer at any age</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative diagnosed with breast cancer after the age of 40 and ≥ 2 second-degree relatives diagnosed with breast cancer at any age</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative with breast cancer diagnosed after the age of 40 and ≥ 1 second-degree male relative(s) diagnosed with breast cancer at any age</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>1 first-degree relative diagnosed with breast cancer after the age of 40</td>
</tr>
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</table>
Table 2. Distribution of baseline characteristics by level of perceived lifetime risk of developing breast cancer for female relatives from the Ontario site of the Breast Cancer Family Registry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Perceived risk of breast cancer [n (%a)]</th>
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<tr>
<td></td>
<td>&lt;50%</td>
</tr>
<tr>
<td>Familial breast cancer risk</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>106 (50.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>49 (23.2)</td>
</tr>
<tr>
<td>High</td>
<td>56 (26.6)</td>
</tr>
<tr>
<td>Age at interview</td>
<td>&lt;0.0001</td>
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<tr>
<td>25-29</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>30-39</td>
<td>26 (12.3)</td>
</tr>
<tr>
<td>40-49</td>
<td>49 (23.2)</td>
</tr>
<tr>
<td>≥ 50</td>
<td>133 (63.1)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>≤ High school diploma</td>
<td>63 (29.9)</td>
</tr>
<tr>
<td>Some college/university/vocational/technical school</td>
<td>76 (36.0)</td>
</tr>
<tr>
<td>≥ Bachelor’s degree</td>
<td>73 (34.1)</td>
</tr>
<tr>
<td>Frequency of health care visits</td>
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<tr>
<td>≤ 1 time per year</td>
<td>82 (40.6)</td>
</tr>
<tr>
<td>2-3 times per year</td>
<td>82 (40.6)</td>
</tr>
<tr>
<td>≥ 4 times per year</td>
<td>38 (18.8)</td>
</tr>
<tr>
<td>Menopausal status</td>
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<tr>
<td>Pre-/peri-menopausal</td>
<td>103 (48.8)</td>
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<tr>
<td>Post-menopausal</td>
<td>108 (51.2)</td>
</tr>
<tr>
<td>History of benign breast disease</td>
<td></td>
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<tr>
<td>No</td>
<td>134 (64.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>73 (35.3)</td>
</tr>
<tr>
<td>Underwent genetic counselling</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>146 (69.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>65 (30.8)</td>
</tr>
<tr>
<td>Baseline mammogram</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>71 (34.1)</td>
</tr>
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<td>Yes</td>
<td>137 (65.9)</td>
</tr>
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<td>Baseline clinical breast examination</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>39 (19.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>166 (80.0)</td>
</tr>
</tbody>
</table>

a: Percentages based on non-missing values.
<table>
<thead>
<tr>
<th>Screening Behaviour</th>
<th>Numeric-scale perceived risk [n (%)]</th>
<th>&lt;50% vs. =50%</th>
<th>&gt;50% vs. =50%</th>
<th>LR test&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adjusted OR</td>
<td>Adjusted OR</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>(95% CI)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mammogram within 15 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women at low familial risk</td>
<td>No</td>
<td>46 (43.4)</td>
<td>62 (55.9)</td>
<td>119 (57.2)</td>
</tr>
<tr>
<td>Women at moderate/high familial risk</td>
<td>No</td>
<td>38 (36.2)</td>
<td>38 (32.8)</td>
<td>90 (38.5)</td>
</tr>
<tr>
<td>Women at low familial risk</td>
<td>Yes</td>
<td>67 (63.8)</td>
<td>78 (67.2)</td>
<td>144 (61.5)</td>
</tr>
<tr>
<td>Women at moderate/high familial risk</td>
<td>No</td>
<td>25 (24.0)</td>
<td>32 (27.4)</td>
<td>83 (35.5)</td>
</tr>
<tr>
<td>Women at low familial risk</td>
<td>Yes</td>
<td>79 (76.0)</td>
<td>85 (72.6)</td>
<td>151 (64.5)</td>
</tr>
<tr>
<td>Ever underwent genetic testing</td>
<td>No</td>
<td>97 (93.3)</td>
<td>104 (92.9)</td>
<td>192 (91.4)</td>
</tr>
<tr>
<td>Women at moderate/high familial risk</td>
<td>Yes</td>
<td>7 (6.7)</td>
<td>8 (7.1)</td>
<td>18 (8.6)</td>
</tr>
<tr>
<td>Women at low familial risk</td>
<td>No</td>
<td>81 (78.6)</td>
<td>84 (73.7)</td>
<td>192 (81.7)</td>
</tr>
<tr>
<td>Women at moderate/high familial risk</td>
<td>Yes</td>
<td>22 (23.4)</td>
<td>30 (26.3)</td>
<td>43 (18.3)</td>
</tr>
</tbody>
</table>

a: Models for mammogram and CBE adherence adjusted for age at interview, education, frequency of health care visits, menopausal status, history of benign breast disease, corresponding baseline screening behavior, history of genetic counselling, and confidence intervals corrected for familial clustering.

b: Model for BRCA1/2 genetic testing adjusted for age at interview, education, frequency of health care visits, menopausal status, history of benign breast disease, and confidence intervals corrected for familial clustering.

c: Likelihood ratio tests compared models with perceived risk defined as a continuous variable (0-100%) to models with perceived risk defined as a categorical variable (<50%, =50%, >50%).
4.4 Manuscript 4: Accuracy of self-reported screening mammography use: examining recall among female relatives from the Ontario site of the Breast Cancer Family Registry.

Walker MJ, Chiarelli AM, Mirea L, Glendon G, Ritvo P, Andrulis IL, Knight JA.

Published in ISRN Oncology, 2013. doi: 10.1155/2013/810573.

**ABSTRACT**

Evidence of the accuracy of self-reported mammography use among women with familial breast cancer risk is limited. This study examined the accuracy of self-reported screening mammography dates in a cohort of 1,114 female relatives of breast cancer cases, aged 26 to 73 from the Ontario site of the Breast Cancer Family Registry. Self-reported dates were compared to dates abstracted from imaging reports. Associations between inaccurate recall and subject characteristics were assessed using multinomial regression. Almost all women (95.2% at baseline, 98.5% at year 1, 99.8% at year 2) accurately reported their mammogram use within the previous 12 months. Women at low familial risk (OR = 1.77, 95% CI: 1.00–3.13), who reported 1 or fewer annual visits to a health professional (OR = 1.97, 95% CI: 1.15, 3.39), exhibited a lower perceived breast cancer risk (OR = 1.90, 95% CI: 1.15, 3.15), and reported a mammogram date more than 12 months previous (OR = 5.22, 95% CI: 3.10, 8.80), were significantly more likely to inaccurately recall their mammogram date. Women with varying levels of familial risk are accurate reporters of their mammogram use. These results present the first evidence of self-reported mammography recall accuracy among women with varying levels of familial risk.
1. Introduction

Having a family history of breast cancer has been established as one of the most important risk factors for the development of breast cancer [1–3]. A reduction in breast cancer mortality attributable to mammography among women aged 50 to 74 has been demonstrated [4–6]. In Canada, average-risk women aged 50 to 74 are recommended to undergo screening mammography every 2 to 3 years [7]. In Ontario, mammography is available to women aged 50 to 74 through the Ontario Breast Screening Program (OBSP), and with physician referral through imaging facilities outside of the screening program [8]. Screening guidelines for high-risk women, based on expert opinion, typically include annual mammography and/or MRI starting at age 40 or 10 years prior to the earliest age of onset observed in the family, or as young as age 25 for BRCA mutation carriers [9–15]. In 2011, the OBSP was expanded to include annual combined MRI and mammography screening for women aged 30 to 69 considered to be at very high risk of breast cancer (i.e., BRCA1/2 mutation carriers or family history suggestive of hereditary breast cancer) (Cancer Care Ontario, Internal Communication, 2011).

Self-reported data is often used in epidemiologic research evaluating the use of cancer screening. The validity of self-reported mammography use has been studied extensively in women with population-level breast cancer risk [16–18]. Overall, the validity of self-reported data has been demonstrated [17,18]; however, it is less accurate in determining the precise timing of screening. Women often underestimate the amount of time since their last mammogram [17–23]. This phenomenon, known as “telescoping,” occurs when events are reported as being more recent than when they actually occurred [24].
Few studies have validated self-reported mammogram data among women with familial risk [25, 26]. These two studies have only included women with very strong familial breast cancer histories, who likely differ in their breast cancer screening behaviors or recall of these behaviors compared to women in the broader population with familial risk. To the authors’ knowledge, the accuracy of screening mammography recall among women with varying levels of familial history has not previously been examined. The objectives of the present study were to examine the accuracy of self-reported screening mammogram dates among women with varying levels of familial breast cancer risk, determine the direction of inaccurate recall, and examine factors associated with inaccurate recall.

2. Materials and Methods

2.1. Study Population

This study utilized data from a cohort of female relatives of incident cases of invasive breast cancer identified from the Ontario site of the Breast Cancer Family Registry (BCFR) funded by the United States National Cancer Institute. Details of the BCFR and the Ontario site have been previously described [27, 28]. Briefly, cases of pathologically-confirmed invasive breast cancer (probands), diagnosed between 1996 and 1998, were identified from the Ontario Cancer Registry. Physicians were contacted to obtain permission to mail their patients a cancer Family History Questionnaire (FHQ). Respondents meeting a defined set of genetic risk criteria and a random sample (25%) of those not meeting criteria were asked to participate in the Ontario site of the BCFR. Of the 2,587 eligible women, 1,851 (71.5%) probands participated. Probands were then asked for permission to contact specific living relatives (first-degree, those affected with breast, ovarian or certain other cancers, and their first-degree relatives). An invitation letter to participate in the Ontario site of the BCFR was sent to all relatives (n = 8,
416), and the 5,122 who agreed to be contacted were mailed an *Epidemiology Questionnaire (EQ)* from 1998 to 2004.

This prospective cohort study was conducted several years after initial recruitment of relatives to the Ontario site of the BCFR. Baseline, year 1, and year 2 *Personal History and Screening Questionnaires (PHSQ)* were administered to update changes in demographic characteristics, cancer screening behaviors and breast outcomes. All female relatives enrolled in the Ontario site of the BCFR, who completed an *EQ* and were 20 to 69 years of age and unaffected by breast cancer at the time of the proband's diagnosis, were eligible to participate. From the 3,374 participating female relatives, 1,514 met all study criteria. A baseline *PHSQ* was sent between 2005 and 2007 to the 1,514 eligible women. Of these women, 1,114 (73.6%) completed the baseline *PHSQ*. A year 1 *PHSQ* was sent to 1,077 eligible women approximately one year following the baseline *PHSQ* and 975 (90.5%) completed it. A year 2 *PHSQ* was sent to 969 eligible women and 882 (91.0%) completed it.

2.2. Validation Sample

Women who completed baseline (n = 1114), year 1 (n = 975), and year 2 (n = 882) *PHSQs* and reported having a mammogram since their previous interview (n = 885 at baseline, n = 557 at year 1, n = 544 at year 2) were eligible. Women were excluded if they had a personal breast cancer diagnosis, they did not have a first-degree family history of breast or ovarian cancer, they did not provide consent to release the imaging report, the imaging report was not available from the imaging centre, or the indication for the mammogram was for nonscreening purposes. Final sample sizes included 699 women at baseline, 469 at year 1 and 456 at year 2. This study was approved by the Research Ethics Boards of Mount Sinai Hospital, the University Health Network, and University of Toronto.
2.3. Data Collection

Information was obtained from four questionnaires. The first (EQ) was self-administered during recruitment of female relatives to the Ontario site of the BCFR and collected detailed information on demographics and key behavioral risk factors for breast and ovarian cancer. As several years had elapsed since completion of the EQ, three subsequent questionnaires (baseline, year 1, and year 2 PHSQ) of similar contents were telephone-administered to update changes in key demographic and health behavior characteristics and collect detailed information on breast cancer screening. Eligible participants were sent an introductory letter with a copy of the PHSQ approximately two weeks prior to being contacted by telephone. This allowed participants to recall dates and events and allowed reference to the questionnaire during the interview. This method was found to result in higher response rates and more complete data than achieved by self-administered questionnaires [29]. The questionnaire instruments have been previously described [28, 30, 31].

2.4. Data Measures

Self-reported dates and reasons for mammograms were obtained from PHSQ interviews. The baseline PHSQ asked women if they had a mammogram since EQ completion. The year 1 and 2 PHSQs asked women if they had a mammogram since completing the last PHSQ. Women were asked to provide the date (month and year) or their age at last mammogram. Women were also asked to indicate if the main reason for the last exam was for screening (part of a regular checkup, the OBSP, or have a family history of breast cancer), or nonscreening (breast problem/symptom, follow-up of a previous breast problem, or participation in a research study). For women who provided consent, imaging reports were obtained from the imaging facility and
abstracted for: (i) imaging date (day, month, and year); (ii) indication (screening or diagnostic); and (iii) breast imaging-reporting and data system (BI-RADS) classification [32].

Classifications of familial breast cancer risk were based on data collected by the cancer FHQ completed by the proband, using a modified definition of previously referenced groups for familial breast cancer risk [10, 33]. Table 1 shows the criteria for classifying women as low, moderate, or high familial risk. Age at interview was calculated as the difference in years between date of birth and date of the interview. Descriptive analyses used categories of less than 40 years, 40 to 49 years, 50 years and above, while all models were adjusted for age as a continuous variable. Marital status (married/common law, single), education (high-school or less, some college, university, vocational or technical school, Bachelor's degree, or higher), and frequency of visiting a healthcare professional in the past 2 years (once per year or less, 2 to 3 times per year, 4 or more times per year) were determined using responses from the baseline PHSQ. Use of clinical breast examination (CBE) and BRCA1/2 genetic testing was updated at each PHSQ and based on self-reported use since the previous interview. Perceived risk of developing breast cancer (much below or below average, same as average, above or much above average) was updated at each PHSQ and determined using a question adopted from Lipkus et al. [34]. Women were asked, “compared with other women your age, how likely are you to get breast cancer in your lifetime?” Time since last mammogram was calculated as the difference in days between the date on the imaging report and interview date. Descriptive analyses used categories of within 12 months and more than 12 months ago, while models were adjusted using days since last mammogram.
2.5. Statistical Analysis

Distributions of sample characteristics at each *PHSQ* were summarized. Self-reported screening mammogram dates and abstracted imaging dates ("gold standard") were compared to assess rates of agreement. Inaccurate recall was classified as overestimation or underestimation of the time since last mammogram. The difference in months between self-reported and abstracted mammogram dates was compared among women who inaccurately reported mammogram dates. Multinomial logistic regression was used to estimate adjusted associations between inaccurate recall and a number of sociodemographic, health behavior and cancer screening characteristics. All models included familial breast cancer risk, age at interview, and number of days since last mammogram (except for models including time since last mammogram in categories). As women are clustered within families, robust variance estimation was used to estimate all confidence intervals (CI) [35, 36]. All analyses were conducted using SAS, Version 9.2 (SAS Institute Inc., 2004) and the significance of statistical tests was evaluated using two-sided *P* values at a 5% testing level.

3. Results

At baseline, 42.6% of women were classified as low familial risk, while 26.2% and 31.2% were moderate and high risk, respectively (Table 2). The majority of women were 50 years of age or older (63.0%), while 31.3% were aged 40 to 49 and 5.7% were under the age of 40. Almost all women (97.7%) reported a CBE but had not undergone genetic testing (82.9%) since completion of the *EQ*. Most women (61.5%) perceived their lifetime breast cancer risk to be higher than average. Since completion of the *EQ*, 34.3% reported a mammogram within the previous 6 months, 33.1% reported a mammogram 7 to 12 months prior, and 32.6% reported
that their last mammogram was more than 12 months prior. Distributions of sociodemographic and health behavior characteristics were similar at years 1 and 2.

Most women were able to report the month and year (73.8% at baseline, 88.7% at year 1, and 93.0% at year 2) of their last mammogram, while 24.2% at baseline, 11.1% at year 1 and 6.6% at year 2 were only to report the year or their age (Table 3). Among women who reported the month and year, the majority were accurate, though rates of accuracy were higher at year 1 (78.9%) and year 2 (80.4%) than at baseline (61.8%), as the recall period at baseline (time between completing the EQ and PHSQ) was longer (5 to 7 years). Among women who inaccurately recalled the date of their last mammogram, proportions of women who underestimated and overestimated this time interval were approximately equal at baseline and year 1, but more women overestimated at year 2. Women who underestimated this interval did so by a longer amount of time at baseline and year 2, compared with women who overestimated (5.48 months versus 3.54 months at baseline, 2.35 months versus 1.56 months at year 2). This difference was statistically significant at baseline (P = 0.036).

At baseline, women with low familial risk were more likely to overestimate the time since last mammography compared to high-risk women (OR = 1.77; 95% CI: 1.00, 3.13). Women who reported an average of 1 or fewer visits to a health professional per year were almost twice as likely to overestimate the time since last mammogram (OR = 1.97; 95% CI: 1.15, 3.39) compared to women with 2 to 3 visits per year, as were women who perceived their breast cancer risk to be below or the same as average (OR = 1.90; 95% CI: 1.15, 3.15) (Table 5). Women who had mammograms more than 12 months prior were more than five times as likely to underestimate the time since last mammogram (OR = 5.22; 95% CI: 3.10, 8.80). At year 1 and year 2, only time since last mammogram remained statistically significant following adjustment (results not shown).
4. **Discussion**

Our study presents some of the first evidence of the accuracy of self-reported screening mammography use among women with varying levels of familial risk. We found that self-reported screening mammogram use within a 12-month period is highly accurate (over 95%). Additionally, 62% of women at baseline, 79% at year 1, and 80% at year 2 accurately reported the exact timing (month and year) of their last screening mammogram. While we did not find systematic evidence of telescoping, we found that the difference in months between self-reported and abstracted dates was significantly larger in women who telescoped the date at baseline. Fewer visits to a health professional per year, lower perceived breast cancer risk, and having a mammogram more than 12 months prior were significantly associated with inaccurate recall, while the association between inaccurate recall and level of familial risk approached significance.

The high rates of recall accuracy we observed differ from previous studies, most of which focused on women in the general population. For example, two studies [21, 37] reported that approximately 70% of women who reported undergoing mammography in the past year had actually done so. Lower levels (48%) of recall accuracy for mammogram use in the previous year among low-income minority populations have also been reported [38, 39]. Our finding was not unanticipated, as women with heightened risk are likely to be more conscious of their screening behaviors than women in the general population. Accordingly, Larouche et al. [26], who examined recall among a population of women with high familial breast cancer risk, found corresponding administrative records for 85% of women who reported a mammogram in the 12 months following genetic testing.
Telescoping has been one of the most consistent findings of previous studies [17–23]. Pijpe et al. [25], who examined the validity of self-reported lifetime mammogram histories among BRCA1/2 mutation carriers, found that women underestimated the time since last mammogram. While telescoping was minimal in our study, we did find that women who underestimated the time since their last screening mammogram did so by a significantly longer period of time compared with women who overestimated this interval.

Studies which have previously examined predictors of mammogram recall have reported inconsistent results, likely due to differences in study populations and definitions of accurate recall. When examining predictors of recall, most previous studies have not further classified inaccurate recall as overestimation or underestimation of the time since last mammogram. Pijpe et al. [25], who did, examined recall among BRCA1/2 mutation carriers and similarly found that a longer recall period was associated with greater likelihood of underestimating time since last mammogram. While our results at years 1 and 2 are similar to those observed by Pijpe et al. [25], we also found that the odds of overestimating the time since last mammogram were approximately twofold higher for women who reported fewer visits to a health professional and had a lower perceived breast cancer risk at baseline. Two studies similarly found that women with higher perceived risk more accurately report their mammogram use; however, these relationships were not statistically significant [20, 26]. We found that women with a lower familial risk were more likely to overestimate the time since last mammogram. While no studies have previously evaluated mammogram recall by gradients of risk, two studies have demonstrated that women with a first-degree familial breast cancer history are more likely to accurately recall their mammogram use compared to women without a family history [20, 40].

Our study is unique in that it is one of the first to examine the accuracy of self-reported mammography data among a population of women with a range of family histories of breast
cancer. The population-based recruitment, large sample size, longer follow-up period, and
exclusion of diagnostic mammograms are also notable strengths. This study has several
limitations. Due to the challenge of verifying reports from multiple service providers, this study
was not designed to assess recall among women who reported nonuse of mammography.
Previous evidence suggests women are unlikely to falsely report the nonuse of mammography
[20, 22, 23]. In a small number of cases where women reported a mammogram, imaging centres
could not provide a report. As it was not possible to distinguish reports missing because the
woman did not have a mammogram, from reports missing because the respondent incorrectly
recalled the screening facility, these participants were excluded (n = 3 at baseline, n = 22 at year
1, n = 16 at year 2). As women were mailed a copy of the questionnaire approximately two
weeks before being contacted by study staff, they could have checked their personal records or
otherwise verified the date of their last mammogram prior to completing the questionnaire. This
may have inflated rates of recall accuracy. Finally, it should be noted that the accuracy of recall
may differ in populations with different breast cancer screening recommendations and systems
of healthcare.

Self-reported mammography use data is widely relied upon in epidemiologic research for
measuring adherence to breast cancer screening guidelines. Overall, our study found women
with familial breast cancer risk to be extremely accurate reporters of their mammogram use
within 12 months and reasonably reliable reporters of the exact timing of their mammogram
attendance. Recall was poorer among women with low familial breast cancer risk and lower
perceived breast cancer risk, and when asked to recall screening episodes more than one year
prior. Where possible, strategies demonstrated to improve the accuracy of self-reported data
should be employed by researchers [16]. Women who cannot recall the timing of their
mammograms continue to present a challenge to clinicians with regard to medical management,
researchers, and to breast cancer surveillance efforts. Caution must be exercised when relying exclusively on self-reported data for the purposes of medical decision making and reporting of surveillance statistics.

**Conflicts of interest:** The authors declare that there are no conflicts of interest.

**Acknowledgements:** This work was supported by the Canadian Breast Cancer Foundation, Ontario Region. This work was also supported by the Canadian Breast Cancer Research Alliance (Grant 016270) and Grant UM1 CA164920 from the National Cancer Institute. The content of this paper does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the BCFR. The authors also thank the study staff and participants of the Ontario site of the Breast Cancer Family Registry.
References


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<thead>
<tr>
<th>Familial risk group</th>
<th>Family history of breast and/or ovarian cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>≥ 2 first-degree relatives diagnosed with breast and/or ovarian cancer at any age</td>
</tr>
<tr>
<td></td>
<td>≥ 1 first-degree relative(s) diagnosed with both breast and ovarian cancer at any age</td>
</tr>
<tr>
<td></td>
<td>≥ 1 first-degree relative(s) diagnosed with bilateral breast cancer at any age</td>
</tr>
<tr>
<td></td>
<td>≥ 1 first-degree male relative(s) diagnosed with breast cancer at any age</td>
</tr>
<tr>
<td></td>
<td>Personal history of ovarian cancer</td>
</tr>
<tr>
<td>Moderate</td>
<td>Self-reported Ashkenazi Jewish background</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative diagnosed with breast cancer before age of 40</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative diagnosed with ovarian cancer at any age</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative diagnosed with breast cancer after the age of 40 <em>and</em> ≥ 2 second-degree relatives diagnosed with breast cancer at any age</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative with breast cancer diagnosed after the age of 40 <em>and</em> ≥ 1 second-degree male relative(s) diagnosed with breast cancer at any age</td>
</tr>
<tr>
<td>Low</td>
<td>1 first-degree relative diagnosed with breast cancer after the age of 40</td>
</tr>
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</table>
Table 2. Distribution of socio-demographic, health behaviour and cancer screening characteristics for female relatives of the Ontario site of the Breast Cancer Family Registry

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>Baseline n = 699</th>
<th>Year 1 n = 469</th>
<th>Year 2 n = 456</th>
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<tr>
<td>Familial breast cancer risk</td>
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<td></td>
</tr>
<tr>
<td>Low</td>
<td>298 (42.6)</td>
<td>190 (40.5)</td>
<td>193 (42.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>183 (26.2)</td>
<td>127 (27.1)</td>
<td>123 (27.0)</td>
</tr>
<tr>
<td>High</td>
<td>218 (31.2)</td>
<td>152 (32.4)</td>
<td>140 (30.7)</td>
</tr>
<tr>
<td>Age at interview</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>40 (5.7)</td>
<td>26 (5.6)</td>
<td>24 (5.3)</td>
</tr>
<tr>
<td>40-49</td>
<td>219 (31.3)</td>
<td>116 (24.7)</td>
<td>100 (21.9)</td>
</tr>
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<td>≥ 50</td>
<td>440 (63.0)</td>
<td>327 (69.7)</td>
<td>332 (72.8)</td>
</tr>
<tr>
<td>Education</td>
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<tr>
<td>≤ High school</td>
<td>235 (33.7)</td>
<td>161 (34.3)</td>
<td>149 (32.7)</td>
</tr>
<tr>
<td>Some college/university/vocational/technical school</td>
<td>273 (39.1)</td>
<td>186 (39.7)</td>
<td>182 (39.9)</td>
</tr>
<tr>
<td>≥ Bachelor’s degree</td>
<td>190 (27.2)</td>
<td>122 (26.0)</td>
<td>125 (27.4)</td>
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<td>Marital status</td>
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<td>Married/common law</td>
<td>572 (82.0)</td>
<td>393 (83.8)</td>
<td>383 (84.0)</td>
</tr>
<tr>
<td>Single</td>
<td>126 (18.2)</td>
<td>76 (16.2)</td>
<td>73 (16.0)</td>
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<tr>
<td>Visits to health professional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1 time per year</td>
<td>224 (32.6)</td>
<td>145 (31.2)</td>
<td>137 (30.5)</td>
</tr>
<tr>
<td>2-3 times per year</td>
<td>291 (42.3)</td>
<td>218 (47.0)</td>
<td>214 (47.7)</td>
</tr>
<tr>
<td>≥ 4 times per year</td>
<td>173 (25.1)</td>
<td>101 (21.8)</td>
<td>98 (21.8)</td>
</tr>
<tr>
<td>Clinical breast examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>683 (97.7)</td>
<td>414 (88.5)</td>
<td>395 (87.8)</td>
</tr>
<tr>
<td>No</td>
<td>16 (2.3)</td>
<td>54 (11.5)</td>
<td>55 (12.2)</td>
</tr>
<tr>
<td>BRCA1/2 genetic test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>112 (17.1)</td>
<td>4 (0.9)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>No</td>
<td>542 (82.9)</td>
<td>457 (99.1)</td>
<td>454 (99.8)</td>
</tr>
<tr>
<td>Perceived risk of breast cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below/same as average</td>
<td>255 (38.5)</td>
<td>155 (34.7)</td>
<td>184 (41.3)</td>
</tr>
<tr>
<td>Higher than average</td>
<td>407 (61.5)</td>
<td>292 (65.3)</td>
<td>261 (58.7)</td>
</tr>
<tr>
<td>Months since last</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6</td>
<td>240 (34.3)</td>
<td>247 (52.7)</td>
<td>246 (54.0)</td>
</tr>
<tr>
<td>7-12</td>
<td>231 (33.1)</td>
<td>198 (42.2)</td>
<td>204 (44.7)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>228 (32.6)</td>
<td>24 (5.1)</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>Mammographic finding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/benign</td>
<td>582 (83.3)</td>
<td>383 (81.7)</td>
<td>366 (80.3)</td>
</tr>
<tr>
<td>Abnormal/incomplete</td>
<td>117 (16.7)</td>
<td>86 (18.3)</td>
<td>90 (19.7)</td>
</tr>
</tbody>
</table>

Subgroups may not add to stated totals due to missing values; valid percentages reported.
Table 3. Accuracy of screening mammography date recall among female relatives from the Ontario site of the Breast Cancer Family Registry

<table>
<thead>
<tr>
<th>Screening mammography date recall</th>
<th>Interview</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Year 1</td>
<td>Year 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 699</td>
<td>n = 469</td>
<td>n = 456</td>
<td></td>
</tr>
<tr>
<td>TOTAL RECALL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reported month and year, n (%)</td>
<td>516 (73.8)</td>
<td>416 (88.7)</td>
<td>424 (93.0)</td>
<td></td>
</tr>
<tr>
<td>Accurately recalled imaging date</td>
<td>319 (61.8)</td>
<td>328 (78.9)</td>
<td>341 (80.4)</td>
<td></td>
</tr>
<tr>
<td>Overestimated imaging date</td>
<td>95 (18.4)</td>
<td>43 (10.3)</td>
<td>52 (12.3)</td>
<td></td>
</tr>
<tr>
<td>Underestimated imaging date</td>
<td>102 (19.8)</td>
<td>45 (10.8)</td>
<td>31 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Months difference (reported vs. imaging), mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overestimated imaging date</td>
<td>3.54 (5.4)</td>
<td>2.07 (2.1)</td>
<td>1.56 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Underestimated imaging date</td>
<td>5.48 (7.3)*</td>
<td>2.04 (1.9)</td>
<td>2.35 (2.5)</td>
<td></td>
</tr>
<tr>
<td>PARTIAL RECALL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reported year only, n (%)</td>
<td>136 (19.5)</td>
<td>28 (6.0)</td>
<td>25 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Accurately recalled imaging year</td>
<td>81 (59.6)</td>
<td>22 (78.6)</td>
<td>24 (96.0)</td>
<td></td>
</tr>
<tr>
<td>Overestimated imaging year</td>
<td>24 (17.6)</td>
<td>2 (7.1)</td>
<td>1 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Underestimated imaging year</td>
<td>31 (22.8)</td>
<td>4 (14.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Self-reported age only, n (%)</td>
<td>33 (4.7)</td>
<td>24 (5.1)</td>
<td>5 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Accurately reported imaging age</td>
<td>20 (60.6)</td>
<td>20 (83.3)</td>
<td>2 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Overestimated imaging age</td>
<td>5 (15.2)</td>
<td>0 (0.0)</td>
<td>1 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Telescopied imaging age</td>
<td>8 (24.2)</td>
<td>4 (16.7)</td>
<td>2 (40.0)</td>
<td></td>
</tr>
<tr>
<td>NO RECALL</td>
<td>14 (2.0)</td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>

* p = 0.036 for women who underestimated vs. overestimated the imaging mammogram date.
Table 4. Accuracy of self-reported adherence to screening mammography guidelines among female relatives from the Ontario site of the Breast Cancer Family Registry

<table>
<thead>
<tr>
<th></th>
<th>Interview</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline n = 516*</td>
</tr>
<tr>
<td>Self-reported mammogram within 12 months, n (%)</td>
<td>417 (80.8)</td>
</tr>
<tr>
<td>Imaging date within 12 months</td>
<td>397 (95.2)</td>
</tr>
<tr>
<td>Imaging date &gt;12 months ago</td>
<td>20 (4.8)</td>
</tr>
<tr>
<td>Self-reported mammogram &gt;12 months ago, n (%)</td>
<td>99 (19.2)</td>
</tr>
<tr>
<td>Imaging date &gt;12 months ago</td>
<td>87 (87.9)</td>
</tr>
<tr>
<td>Imaging date within 12 months</td>
<td>12 (12.1)</td>
</tr>
</tbody>
</table>

* Women who self-reported the month and year of their last screening mammogram.
Table 5. Associations between screening mammography date recall and socio-demographic, health behaviour and cancer screening characteristics at baseline for female relatives of the Ontario site of the Breast Cancer Family Registry (n = 516†)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Screening Mammography Recall [n (%)]</th>
<th>Adjusted OR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Accurate n = 317</td>
<td>Overestimated n = 95</td>
</tr>
<tr>
<td>Familial breast cancer risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>118 (37.0)</td>
<td>25 (26.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>85 (26.6)</td>
<td>25 (26.3)</td>
</tr>
<tr>
<td>Low</td>
<td>116 (36.4)</td>
<td>45 (47.4)</td>
</tr>
<tr>
<td>Age at interview</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td>224 (70.2)</td>
<td>65 (68.4)</td>
</tr>
<tr>
<td>40-49</td>
<td>78 (24.5)</td>
<td>26 (27.4)</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>17 (5.3)</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Bachelor’s degree</td>
<td>81 (25.4)</td>
<td>22 (23.2)</td>
</tr>
<tr>
<td>Some college, university or vocational/technical school</td>
<td>129 (40.4)</td>
<td>39 (41.0)</td>
</tr>
<tr>
<td>≤ High school</td>
<td>109 (34.2)</td>
<td>34 (35.8)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/common law</td>
<td>264 (82.8)</td>
<td>77 (81.0)</td>
</tr>
<tr>
<td>Single</td>
<td>55 (17.2)</td>
<td>18 (19.0)</td>
</tr>
<tr>
<td>Visits to health professional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1 time per year</td>
<td>92 (29.1)</td>
<td>40 (43.5)</td>
</tr>
<tr>
<td>2-3 times per year</td>
<td>145 (45.9)</td>
<td>32 (34.8)</td>
</tr>
<tr>
<td>≥ 4 times per year</td>
<td>79 (25.0)</td>
<td>20 (21.7)</td>
</tr>
<tr>
<td>Clinical breast examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>313 (98.1)</td>
<td>90 (94.7)</td>
</tr>
<tr>
<td>No</td>
<td>6 (1.9)</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td>BRCA1/2 genetic test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58 (19.5)</td>
<td>13 (14.1)</td>
</tr>
<tr>
<td>No</td>
<td>239 (80.5)</td>
<td>79 (85.9)</td>
</tr>
<tr>
<td>Perceived risk of breast cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above average</td>
<td>192 (64.0)</td>
<td>44 (47.8)</td>
</tr>
<tr>
<td>Below/same as average</td>
<td>108 (36.0)</td>
<td>48 (52.2)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Screening Mammography Recall [n (%)]</td>
<td>Adjusted OR (95% CI)†</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td>Accurate n = 317</td>
<td>Overestimated n = 95</td>
</tr>
<tr>
<td>Time since last mammogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12 months</td>
<td>271 (84.9)</td>
<td>73 (76.8)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>48 (15.1)</td>
<td>22 (23.2)</td>
</tr>
<tr>
<td>Mammographic finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/benign</td>
<td>268 (84.0)</td>
<td>86 (90.5)</td>
</tr>
<tr>
<td>Abnormal/incomplete</td>
<td>51 (16.0)</td>
<td>9 (9.5)</td>
</tr>
</tbody>
</table>

* p < 0.05.
** p < 0.0001.
† Women who reported the month and year of their last screening mammogram.
‡ Models adjusted for familial breast cancer risk, age at interview, number of days since last mammogram, and corrected for familial clustering.
Chapter 5
Discussion and Conclusions

This chapter adds to the discussion section of each manuscript contained in Chapters 3 and 4, by providing a summary of main results, a detailed discussion of methodological issues, clinical implications and contribution to the fields of public health and epidemiology, and suggestions for future research. For detailed discussion of findings for Objective 1 (impact of mammography screening and familial risk on breast outcomes) see Manuscript 2 in Chapter 4, Section 4.2. For detailed discussion of findings for Objective 2 (relationship between perceived risk and breast cancer screening use) see Manuscript 1 in Chapter 2, Section 2.3.4 and Manuscript 3 in Chapter 4, Section 4.3. For detailed discussion of Objective 3 (validity of self-reported screening mammogram data) see Manuscript 4 in Chapter 4, Section 4.4.

5.1 Summary of Key Findings

Study Cohort

This prospective, population-based cohort study followed 1114 women with a family history of breast and/or ovarian cancer from the Ontario site of the Breast Cancer Family Registry over two years. Data on breast cancer risk factors, breast outcomes, and breast cancer screening behaviours were collected by telephone-administered questionnaires, and abstracted from surgical, pathology, and imaging reports. The 1114 women in the FHS were from 677 unique families, and ranged in age from 25 to 73 years over the study period. Nearly half (48.7%) of the women in the cohort were classified as low familial risk, while 23.5% and 27.8% were classified as moderate and high familial risk, respectively. Over the study period, 38 cases of pathologically-confirmed breast cancer with an invasive component developed in 37 unique
families (two cases in one family), 6 cases of pathologically-confirmed DCIS developed in 6 unique families, and 56 cases of pathologically-confirmed BBD developed in 54 unique families (two families with two cases each).

Manuscript 2

This study found that women with high familial risk are nearly three times more likely to be diagnosed with invasive breast cancer compared with women with low/moderate familial risk. These findings are in line with the results of two previous meta-analyses (Collaborative Group on Hormonal Factors in Breast Cancer, 2001; Pharoah et al., 1997). Women with high familial risk were nearly twice as likely to be diagnosed with BBD compared to women at low/moderate familial risk, and the association was more pronounced in women below age 50 years. To our knowledge, ours is the first study to examine diagnoses of BBD by gradients of familial risk.

Significant associations between level of familial risk and prognostic features of cases of invasive breast cancer or benign breast disease were not detected. While differences were not statistically significant, women with high familial risk had proportionally fewer tumors that were larger than 15mm, diagnosed at stage II or above, histologic grade III, or demonstrated lymphovascular invasion compared to women with low/moderate familial risk, after adjusting for age. Tumors among unscreened women were significantly larger, and diagnosed at a later stage compared to screen-detected tumors, irrespective of level of familial risk. A similar trend was observed with the other prognostic features examined; tumors in unscreened women were more often node-positive, had a higher histologic grade, had a higher mitotic activity index, demonstrated lymphovascular invasion, and were ER- and PR-, however these differences were not statistically significant. Similar to our results, several studies in women with average risk of
breast cancer have found screen-detected invasive breast cancers are significantly smaller in size (Nagtegaal & Duffy et al., 2013; Chiarelli et al., 2012; Burke et al., 2008; Clayforth et al., 2005; Dillon et al., 2004), node-negative (Nagtegaal & Duffy et al., 2013; Chiarelli et al., 2012; Burke et al., 2008; Dillon et al., 2004), diagnosed at an earlier stage (Nagtegaal & Duffy et al., 2013; Chiarelli et al., 2012), and lower grade (Chiarelli et al., 2012; Burke et al., 2008; Clayforth et al., 2005; Dillon et al., 2004), compared with symptomatic cancers.

Manuscripts 1 and 3

The relationship between perceived risk of breast cancer and breast cancer screening in women with familial risk has been widely studied, but never reviewed. Findings of our systematic review suggest there is a weak positive relationship between higher levels of perceived risk and adherence to mammography screening guidelines in women with a family history of breast and/or ovarian cancer. Consistent associations were not observed for CBE or BSE. Our review identified a number of important limitations, including the lack of consistency in measurement of perceived risk, limited generalizability, and the lack of prospective research.

In our prospective study, perceived risk did not predict use of breast cancer screening or genetic testing in the overall cohort. Two previous meta-analyses in women at average-risk suggest there is a small but significant positive relationship between perceived risk and mammogram use (Katapodi et al., 2004; McCaul et al., 1996). In contrast to our study, many of these studies were cross-sectional and measured ever-use of mammography. The results of this study suggest the findings of previous cross-sectional studies may be explained by temporal bias. We observed some evidence which suggests the relationship between perceived risk and breast cancer screening use may be modified by level of familial risk. Among women at low familial risk, women who perceived their risk as greater than 50% were non-significantly more
likely to have a mammogram, CBE or genetic test compared with women who perceived their risk as 50%. In women at moderate/high familial risk, women who perceived their risk as greater than 50% were non-significantly less likely to have a mammogram and genetic test, and significantly less likely to have a CBE compared to women who perceived their risk as 50%.

Manuscript 4

To our knowledge, ours is the first study to examine the accuracy of self-reported mammogram use in women with varying levels of familial risk. Our validation study found that over 95% of women accurately reported their screening mammogram use in the previous 12 months. Over 70% of women were able to provide the month and year of their examination. These high rates of recall accuracy differ from the rates observed in studies of women at average-risk of breast cancer; two studies reported that only 70% of women who reported a mammogram in the last 12 months had actually had a mammogram (McGovern et al., 1998; Armstrong et al., 2004), and lower rates have also been reported (Champion et al., 1998; Suarez et al., 1995). We found that the proportions of women who overestimated and underestimated the time since their last mammogram were approximately equal. These findings also contrast with findings from studies conducted in average-risk women, which have consistently found that women underestimate the time since their last mammogram (Rauscher et al., 2008; Howard et al., 2009). Recall was significantly poorer in women with low familial breast cancer risk, lower perceived risk, those who visited health care professionals less frequently, and when the screening episode occurred more than 12 months prior.
5.2 Limitations and Methodological Issues

5.2.1 Selection Bias

Subjects who participate in research often differ from those who do not on important socio-demographic, lifestyle and medical characteristics (Gordis, 2014; Elwood, 2007), which may be related to the exposure and outcome of interest. Selection bias occurs when individuals have different probabilities of being selected for or participating in a study, and those probabilities are dependent on both the exposure and outcome (Szklo & Nieto, 2007).

One method of reducing potential selection bias is ensuring nonresponse and attrition is minimal. Numerous methods for obtaining high response rates have been developed and proven effective (Dillman et al., 2008). The women identified as eligible for the FHS were motivated to participate; they were all members of the Ontario site of the BCFR, had given permission to be contacted for related research, and due to their family history of cancer likely had a vested interest in participating in research on this topic. Several methods described by Dillman et al. (2008) were employed to maximize participation in the FHS, including: pre-notification of eligible women about the research project using letters with original signatures from the PI (Dr. Anna Chiarelli), providing hard-copies of the questionnaire by mail in advance to being contacted over the telephone, using coloured questionnaires instead of black-and-white, providing stamped return envelopes for consent forms, and attempting several rounds of follow-up contact during various days of the week and times of the day when subjects could not be contacted on first attempt. As shown in Figure 3.2, we obtained high response rates. Of women in the sampling frame, 73.6% participated. Rates of attrition over the study period were also relatively low (9.0% at year 1, and 8.9% at year 2). While there is no consensus on what constitutes an acceptable follow-up rate, rates of 50% to 80% have been suggested as acceptable.
by several authors in the context of observational epidemiologic studies (Kristman et al., 2004; Babbie, 1973). Some suggest that 80% should be used as the minimum acceptable follow-up (Altman, 2000). While follow-up in our study well exceeded these minimal acceptable rates, the validity of these thresholds for follow-up is not known. Kristman et al. (2004), conducted a simulation study to investigate whether varying rates of attrition are associated with biased odds ratios in cohort studies. While rates of attrition from 5% to 60% did not bias true odds ratios (OR) when observations were missing completely at random (MCAR), or missing at random (MAR), ORs were biased even at low rates of attrition (5% to 20%) where data were missing not at random (MNAR) (Kristman et al., 2004). For example, with 20% attrition, the OR was underestimated by approximately 50% of its true value when observations were MNAR (Kristman et al., 2004).

In many studies, no information is available for non-participants, so assessing whether participation or attrition occurs differentially or at random is not possible. As we identified women eligible for the FHS from a pre-existing cohort of women, we had access to data from the Ontario site of the BCFR for our full sampling frame, and were able to examine factors associated with non-participation and loss to follow-up. We compared both women who were unreachable (lost to follow-up), and women who refused to participate, to women who participated in the FHS on a number of socio-demographic factors, breast cancer risk factors, medical/health behaviours, and lifestyle characteristics (Appendix E). Compared to women who participated, women who refused to participate were significantly more likely to be 50 years or older, have a personal history of cancer (any type), or be a current smoker. Compared to women who participated, women who were lost to follow-up were significantly more likely to be less than 40 years of age, single, post-menopausal or current drinkers. Despite high response rates, and the relatively few differences between participants and non-participants, selection bias
cannot be excluded as we do not have outcome data for women who did not participate. For example in Objective 1, if those who were exposed (high familial risk, or not screened with mammography prior to diagnosis) and had the outcome (diagnosed with breast cancer/BBD, or had less favourable prognostic features, respectively) were more likely to be non-participants or lost to follow-up, our results would be biased toward the null. Alternatively, if non-participation or loss to follow-up occurred disproportionately among those who were not exposed (low/moderate familial risk, or screened with mammography prior to diagnosis) and had the outcome (diagnosed with breast cancer/BBD, or had less favourable prognostic features, respectively), our estimates would be biased upward. Encouragingly, FHS participation status did not differ by level of familial risk, or history of ever use of mammography prior to the FHS. Furthermore, the nearly three-fold increase in breast cancer risk for women with high familial risk compared to women with low to moderate risk reported in Manuscript 2, and rates of mammography screening (55.8%) and CBE (68.8%) reported in Manuscript 3, are consistent with previous literature, suggesting selection bias is likely minimal.

Survival bias (Neyman bias) may lead to biased estimates where non-surviving individuals are excluded at the outset of a study, and exposure status is linked to mortality (Szklo & Nieto, 2007; Delgado-Rodríguez & Llorca, 2004). Participants of the FHS were limited to women from the Ontario site of the BCFR still alive at the start of the study. Thus, it is possible that the associations observed were subject to survival bias. For example, if women with high familial risk and a breast diagnosis were more likely to experience mortality during the period between recruitment to the Ontario site of the BCFR and start of the FHS, our results would be biased toward the null. Alternatively, if women with low familial risk and a breast diagnosis were more likely to be non-survivors, our results would be biased upwards. Survival bias was likely minimal in this study, as the time between recruitment to the Ontario site of the
BCFR and being contacted to participate in the FHS ranged from two to seven years, and the 5-year survival rate for breast cancer in Ontario from 2006 to 2010 was 86.5% (Cancer Quality Council of Ontario, 2014).

Self-selection bias is of particular concern when evaluating observational research which investigates the benefits of screening. Many studies have shown those who choose to participate in screening tend to be healthier and more likely to comply with medical recommendations compared to the general population (Gordis, 2014). As a result, more favourable outcomes may be observed in the screened group even if there is no causal relationship between screening and prognosis. Alternatively, people at high risk of disease may self-select into the screening group more often than those at lower or average risk. It is difficult to estimate how this type of selection bias might potentially bias results.

Length bias

Length bias occurs because diseases which exist for a longer period of time in the preclinical phase before progressing to the clinical phase are more likely to be detected by periodic screening compared with diseases which rapidly progress from the point of biologic onset to the clinical phase. Diseases with a long preclinical phase are thought to be less biologically aggressive and have more favourable prognosis than diseases with a short preclinical phase, irrespective of screening status. Length bias has the greatest effect for cases detected at initial screening (Herman et al., 2002). We did not exclude prevalent cases (women diagnosed with breast cancer following an abnormal index screening mammogram) from our analyses in Objective 1, thus length bias cannot be excluded, which may have led to the overestimation of the association between screening and prognostic characteristics. However, as
the majority of screened women in our study (88.8%) had undergone two or more screening mammograms prior to diagnosis, the effect of length bias was likely minimal.

5.2.2 Information Bias

Misclassification

Information bias is present when the means for obtaining data about study subjects are inadequate, and information gathered regarding exposure and outcome status is incorrect (Gordis, 2014). Two types of misclassification (or measurement error), exist. Non-differential misclassification, when measurement error is not different for the groups being compared, is generally considered less of a concern because it typically (for dichotomous variables) biases study results toward the null. Differential misclassification, when measurement error is different for the groups being compared, can bias results either toward or away from the null.

Measurement error in exposure and outcome measures was minimized by using data abstracted from medical records for a number of variables in this thesis project. Cases of breast cancer and BBD were identified initially by self-report. For all women who self-reported a breast outcome, diagnoses were pathologically-confirmed by obtaining pathology and surgical reports. Data on prognostic features of cases of breast cancer and BBD were largely obtained from pathology and surgical reports. Medical charts contained extensive pathology data that were consistently complete, and these data were also supplemented with stage data obtained from the OCR. Historically, only regional cancer centers submitted TNM stage data to Cancer Care Ontario for patients diagnosed and/or treated within those centers, thus stage data was not routinely available from the OCR prior to 2007 (Cancer Care Ontario, 2012). A province-wide stage capture project was initiated by Cancer Care Ontario in 2007, and the stage capture rate for breast cancer across Ontario has met or exceeded the Cancer Care Ontario target of 90% of
cases from 2007 onwards (Cancer Quality Council of Ontario, 2014). In our study, cases on invasive breast cancer with missing data on cancer stage were diagnosed prior to 2007.

Furthermore, while it is possible that some women may have been misclassified as being free of breast cancer or BBD if they did not report an outcome, high rates of sensitivity and specificity (>90%) for self-reported breast cancers have been demonstrated (Bergmann et al., 1998; Parikh-Patel et al., 2003; Stavrou et al., 2011; Dominguez et al., 2007), and one study found higher sensitivity for women with a family history of breast cancer compared to women without a family history (Abraham et al., 2009). We used women’s self-reported use of mammography screening prior to diagnosis to initially determine whether their breast outcome was screen-detected or symptomatic. We confirmed self-reports using data abstracted from imaging reports obtained from the imaging departments of hospitals or Independent Health Facilities (IHF). For women who were not diagnosed with a breast outcome, self-reported screening mammogram use was used. As demonstrated by our results in Manuscript 4, women’s self-report of their screening mammogram use in the previous year is highly accurate. Furthermore, women are unlikely to falsely report the non-use of mammography (Caplan et al., 2003a; Gordon et al., 1993; Etzi et al., 1994).

Where medical records were not used, previously-referenced and validated measures were used wherever possible for the measurement of variables. Classifications for familial breast and/or ovarian cancer risk are based on data collected from the FHQ, which was completed by the relative’s proband during the period of recruitment to the Ontario site of the BCFR, as well as updated information from ongoing contact with the family. Studies have previously demonstrated that patient-reported family cancer histories for first-degree relatives are highly accurate for breast cancer risk assessments (Murff et al., 2004). The classification of women as low, moderate, or high was based on previously referenced groups for familial breast
cancer risk (Eccles et al., 2000; Cortesi et al., 2006), with minimal modifications based on key evidence (Collaborative Group on Hormonal Factors in Breast Cancer et al., 2001; Bevier et al., 2011; Vencken et al., 2013; NICE, 2013; Egan et al., 1996; Toniolo et al., 1996), to ensure that women with the wide range of family histories in our study cohort were accurately classified. Familial risk was defined at baseline of the FHS and was not updated over the course of the study, so it is possible that some women may have moved to a higher risk classification if there were additional diagnoses of breast or ovarian cancer in their families during the study period. Given the short period of follow-up, this misclassification was likely minimal.

**Temporal bias**

The appropriate temporal sequence, that is, that the risk factor proceeds the outcome of interest, is needed to establish causality. Temporal bias occurs when inference about the appropriate temporal sequence of cause and effect is erroneous, and is often a major concern in cross-sectional research (Delgado-Rodríguez & Llorca, 2004). In our prospective cohort study, we can definitively establish that the exposures of interest did precede the outcomes. In Objective 1, through the use of medical records, we can be certain about whether women were screened with mammography prior to diagnosis of breast cancer or BBD. We were particularly interested in prospectively evaluating the relationship between perceived risk and use of screening mammography, CBE, and genetic testing to address the limitations of previous research. By using baseline measurements of perceived risk, and looking at subsequent screening behaviours, we limited temporal ambiguity.

**Hawthorne effect**

The Hawthorne effect was originally observed during studies undertaken at the Hawthorne plant of the Western Electric Company in Illinois in the 1920s (Roethlisberger &
Dickson, 1939). In the context of epidemiologic research, the Hawthorne effect refers to the phenomenon wherein subject’s knowledge that they are taking part in an experiment or being studied alters their behavior (McCambridge et al., 2014; Delgado-Rodríguez & Llorca, 2004). A recent review of experimental and observational studies evaluated the presence of the Hawthorne effect in health sciences research, finding that the majority (63.1%) of studies reported some evidence of the Hawthorne effect (McCambridge et al., 2014). As described in Section 3.5.4, we examined the frequency of reporting that participating in the FHS influenced the use of screening mammography or CBE. When asked to list the main reasons for having mammogram, no women at year 1, and only 2 women at year 2 reported ‘being part of this study’ as the only reason they had a mammogram. However, 45 (8.0%) women at year 1, and 53 (9.7%) women at year 2 reported that it was one of the main reasons they had a mammogram (in addition to ‘routine screening’). Women who reported that being part of the study was one of the main reasons for having a mammogram were significantly older (p = 0.041), had high familial risk (p = 0.011), were less educated (p = 0.024), and had a higher number of annual health care visits (p = 0.036). When asked to list factors which encouraged them to have a mammogram, 6 (1.1%) women at year 1, and 9 (1.6%) women at year 2 reported that ‘being a part of this study’ was the only encouragement to have a mammogram, while 71 (12.7%) women at year 1, and 84 (15.3%) women at year 2 reported it as one of several encouragements. Women who reported that being part of the study encouraged them to have a mammogram were significantly older (p = 0.005).

When asked to list the main reasons they had a CBE, 26 (3.6%) women at year 1, and 26 (4.1%) women at year 2 reported that ‘being part of this study’ was the only reason they had a CBE. A similar proportion of women at year 1 (3.9%) and year 2 (3.2%) reported it as one of the main reasons they had a CBE (in addition to ‘routine screening’). Women who reported that
being part of the study was one of the main reasons they had a CBE had significantly higher levels of breast cancer worry \((p = 0.0004)\), and higher number of health care visits \((p = 0.03)\).

Encouragingly, few women reported that the only reason they had a mammogram or CBE was because they were part of the FHS. However, 8-10\% of women reported that being part of the FHS was one of the main reasons they had a mammogram, and 3-4\% of women reported that study participation was one of the main reasons they had a CBE. These findings suggest that the rates of annual participation in mammography and CBE observed in the FHS at year 1 (57.4% for mammography, 72.9% for CBE) and year 2 (62.1% for mammography, 71.3% for CBE) may be slightly elevated compared to rates of screening in the target population.

**Publication bias**

The findings of our systematic review (Manuscript 1) were based solely on data published in peer-reviewed, English-language publications. Publication bias may lead to an over-representation of positive and statistically significant results, as these studies are more likely to be published than studies with null, or non-statistically significant findings (Elwood, 2007). Furthermore, studies with positive results are more likely to be published in English-language journals (Khan et al., 2003), which are often easiest to find (language bias) (Elwood, 2007). Thus, the studies included in our review might not be reflective of all studies conducted that have examined the relationship between perceived risk and breast cancer screening behaviours. It is worthy of note that differences in study results also exist across different electronic databases for scientific literature. The two primary databases of scientific literature in health are Medline and Embase. These databases differ in their coverage; Embase covers European journals more comprehensively than Medline (Elwood, 2007). One study examined
all RCTs included in both Medline and Embase, and found that trials reported in Embase had 29% smaller effects on average than the trials reported in Medline (Sampson et al., 2003), suggesting that only searching Medline could bias a meta-analysis or systematic review by only including studies that show larger estimates. To ensure we maximized the number of relevant studies included in our review, we searched a number of databases including Medline, Embase, PsychInfo, and the Cochrane Library, as well as conducted thorough hand-searches of bibliographies of numerous manuscripts.

5.2.3 Confounding

Confounding occurs when a noncausal association is observed or causal association is not observed between an exposure and outcome as a result of the influence of a third variable, or group of variables (Szklo & Nieto, 2007). To be classified as a confounder, the variable must be related to both the risk factor and outcome under study, and not be an intermediate step on the causal pathway between the exposure and outcome (Rothman et al., 2008). Confounding can result when known and/or unknown confounders are not adjusted for, or when included confounders are not adequately measured (Szklo & Nieto, 2007).

Despite adjusting for important potential confounders in our analyses, it is possible that our results are affected by residual confounding. Studies that have previously examined the association between perceived risk and breast cancer screening behaviours have adjusted for having a usual source of medical care, and physician recommendation to screen (Price et al., 2010; Diefenbach et al., 1999; Bowen et al., 2003). Not having a regular source of medical care (Shields & Wilkins, 2009; Rakowski et al., 2010; Scheuler et al., 2008; Maxwell et al., 2001) and physician recommendation (Scheuler et al., 2008; Hanson et al., 2009) have shown to be the most important predictors of mammography. It is likely that differences in screening
recommendations women received from physicians or other sources accounted for some of the variability in screening behaviours observed in the FHS. We did not collect follow-up data for all women on whether they had a regular source of medical care, or whether they received a physician recommendation to screen, so could not adjust our models for these potential confounders. In the PHSQ, women who reported that they did not have a mammogram were asked to report the reasons for not having an examination. At year 1, 42.5% of non-screening women said they did not have a mammogram because their doctor did not recommend it. While the majority of these women were younger than 50 years (80.8%), and had low familial risk (67.1%), it is noteworthy that nearly 20% of women who reported not screening because their doctor didn’t recommend it were 50 or older, and almost 17% had high familial risk.

Knowledge about breast cancer and breast cancer screening, along with beliefs regarding the efficacy of screening, appropriate age to begin and stop screening, and screening intervals may also be important in influencing screening behaviours. While these factors were not adjusted for, a previous study of the women in the FHS cohort demonstrated that 92% of women believed they should start screening with mammography prior to age 50 years, and 77% women believed they should screen annually (Ritvo et al., 2012).

Women aged 50 years or older who have a family history of breast cancer and are part of the OBSP receive annual reminder letters when screening is due, and may be more likely to attend screening than women who are not part of the OBSP. As we did not conduct a linkage to OBSP data, we could not adjust for participation in the OBSP. Several Canadian studies in women with population risk of breast cancer have also reported that women residing in rural areas are significantly less likely to report having a mammogram in the previous two years compared with women residing in urban areas (McDonald & Sherman, 2010; Shields &
Wilkins, 2009; Mah & Bryant, 1997; Bryant & Mah, 1992). As we did not conduct a linkage to Statistics Canada data holdings, we could not adjust for place of residence.

In our examination of the relationship between familial risk and prognostic features of invasive breast cancers, we did not adjust for screening history. As shown in Manuscript 1, women at high familial risk had a significantly higher number of lifetime mammograms ($p = 0.003$). Therefore, it is highly plausible that the trend of more favourable prognostic features we observed in women at high familial risk is partially explained by having more lifetime mammograms. However, certain types of breast cancer with a favourable prognosis have been reported to be more common in women with a family history of breast cancer, including medullary, tubular and lobular carcinoma (Vainio & Bianchini, 2002; Pereira et al., 1995). A study by Malone et al. (2011) also observed that women with a first-degree family history of breast cancer had more favourable prognostic profiles compared with women with no family history or a second-degree family history, and these differences were not explained by screening.

5.2.4 Effect Modification & Statistical Interaction

In contrast to quantitative interaction (when the association between risk factor and outcome is of the same direction within each stratum of the potential effect modifier, but the strength of association varies across strata), qualitative interaction is present when the effects of the risk factor on the outcome are in opposite directions (crossover) within each stratum of the potential effect modifier (Szklo & Nieto, 2007). When qualitative interaction is present, it can always be seen in both the additive and multiplicative scale (Szklo & Nieto, 2007). The results presented in Manuscript 3, which examine whether level of familial risk modifies the relationship between perceived breast cancer risk and breast cancer screening use, are
suggestive of qualitative interaction. Among women at low familial risk, a curvilinear u-shaped relationship was observed with mammography; women were more likely to screen if they perceived their risk as <50% (OR = 1.48) or >50% (OR = 1.13) vs. 50%. No consistent relationship between perceived risk and use of CBE or genetic testing was observed in women at low familial risk. In contrast, in women at moderate/high familial risk, a curvilinear inverted u-shaped relationship was observed; women were less likely to screen with mammography, CBE and genetic testing if they perceived their risk as <50% or >50% vs. 50% (ORs ranging from 0.52-0.84).

The statistical significance of interaction terms entered into regression models is often used to assess the presence of interaction. While we observed marked heterogeneity in the strata-specific ORs for level of familial risk (crossover), the product terms entered into the regression models to assess interaction between perceived risk and familial risk were not statistically significant at $p < 0.05$. Statistical testing of homogeneity of effects, while of value, is not sufficient to comprehensively assess the presence or absence of interaction (Szklo & Nieto, 2007). When sample size is very large, even minimal heterogeneity which has little or no clinical or biological relevance may be statistically significant. In contrast, estimates that demonstrate marked heterogeneity may not be significant at the statistical cut-point chosen in small samples (Szklo & Nieto, 2008). Ideally, results which demonstrate marked heterogeneity across strata of a potential effect modifier that are unaccompanied by statistically significant interaction terms (such as the findings from our study), should be confirmed in subsequent studies which have ample statistical power to detect this interaction. As such, future studies with larger sample sizes of women with varying levels of familial breast cancer risk are needed to confirm our findings.
5.2.5 Analytical Issues

Missing data

The magnitude of missing data for variables used in each of the three manuscripts is shown in Appendix G. In Manuscript 1, missing data was minimal (<5%) for the overall cohort. Missing data was greatest for prognostic features of invasive breast cancer; 23.5% of cases were missing data on lymph node status, 18.4% of cases were missing data on ER/PR receptor status, and 7.9% of cases were missing data on TNM stage, as well as lymphovascular invasion and mitotic score. As the majority (57.9%) of data on HER-2/neu were missing, it was not included in analyses. As such, we could not examine the distribution of tumor subtypes (i.e. luminal A, luminal B, and triple-negative) by level of familial risk or mammography screening status. Phipps et al. (2011) demonstrated that women with stronger family histories are at increased risk of having triple-negative breast tumors, which is associated with poorer survival (Bauer et al., 2007; Carey et al., 2006). It should also be noted that while we received pathological confirmation for 44 of 46 cases (95.6%) of self-reported breast cancer, we only received pathological confirmation for 56 of 75 cases (74.7%) of self-reported BBD. For Objective 2 analyses, missing data was minimal (<4%) for all variables. For Objective 3 analyses, missing data was greatest for genetic test use at baseline (6.4%), and perceived risk measured on the verbal Likert-type scale (5.3% at baseline, 4.7% at year 1). The majority of other variables were missing <1% of data.

Analyses were conducted on subjects with complete exposure, outcome and covariate data using a complete case analysis approach. Multiple imputation was not used to replace missing data for several important reasons: bias may be introduced where data are not MCAR or
MAR, the majority of multiple imputation procedures assume data are normally distributed, and the performance of multiple imputation is unclear for small samples (Sterne et al., 2009).

With regards to Objective 1, data from the pre-diagnosis mammogram was used to classify all women with a diagnosis of breast cancer into the screened (routine screening) and unscreened (symptomatic) groups. An additional limitation of this study is that interval cancers could not be systematically identified because the full mammogram history (including date, indication, and/or mammographic finding for mammograms prior to the pre-diagnosis mammogram) was not available for all breast cancer cases.

With regard to Objective 3, some data limitation was present. Data abstracted from imaging reports was used as the ‘gold standard,’ and these reports were obtained from the imaging centers in hospitals or IHFs which were self-reported by women in the PHSQ. In Ontario, screening mammography is available through over 260 OBSP and non-OBSP sites. As it was not possible to verify with each of these facilities that women did not have a mammogram when they self-reported that they did not, we could not validate the non-use of screening mammography. Thus, standard measures of validity including sensitivity, specificity, and Cohen’s kappa could not be tabulated, as true-negative and false-negative values were not available. Fortunately, previous evidence suggests women are unlikely to falsely report the non-use of mammography (Caplan et al., 2003a; Gordon et al., 1993; Etzi et al., 1994).

Statistical Methods

When prospective data are available, relative risk is typically estimated because it is a more easily understood measure of association than the odds ratio (Szklo & Nieto, 2007). For Objective 1, we used the OR as an estimate of the RR of being diagnosed with breast cancer or benign breast disease. Due to the complexity of the FHS design (clustered sample), ORs were
estimated instead of RRs, because more tailored techniques for robust variance estimation (i.e. small sample size correction) are available for the logistic regression model than for other regression models which can directly estimate RR (i.e. log-binomial or modified Poisson) in the statistical software package used. While in many cases the OR offers an accurate approximation of RR, the OR can overestimate the true RR (Szklo & Nieto, 2007). When the incidence of the outcome is rare (4.9% of women had breast cancer and 6.2% had BBD in our study) this bias is negligible, however it can be substantial when incidence is not rare (≥10%) (Szklo & Nieto, 2007). While incidence of the outcome was not rare in Manuscript 3 (55.8% women reported a mammogram, 68.8% reported a CBE, and 14.7% reported a genetic test), ORs were estimated to ensure comparability with previously conducted studies.

Study Power

During the design phase of the FHS, power was calculated for Objective 1 using PS (Dupont & Plummer, 1997), and it was estimated that the study would have 80% power to detect a RR of 3.3 comparing women with moderate familial risk to women with low familial risk, and 80% power to detect a RR of 3.7 comparing women with high familial risk to women with low familial risk. It was initially estimated that 90 breast cancers would be diagnosed over the study; however, only 44 breast cancers (38 invasive, 6 DCIS only) were diagnosed. This could be related to the higher likelihood of non-participation for women 50 years of age or older, and post-menopausal women noted in Section 5.2.1. The magnitude of missing data for lymph node status, and ER/PR receptor status for invasive cancers further reduced sample size and power for these sub-group analyses. While we observed a similar trend across prognostic features (symptomatic cancers were more likely to have poorer prognostic profiles compared with screen-detected cancers, and women with high familial risk were more likely to have favourable prognostic features compared with women at low and moderate familial risk), type II
error was a concern. Our ability to detect these differences was limited due to the small overall numbers of invasive cancers, and missing data. We were also unable to examine features of DCIS (architectural type, nuclear grade, necrosis, lesion size) due to the small number of cases of DCIS without invasive component.

For Objectives 2 and 3, power was calculated using Power, Version 3.0.0 (Lubin & Gail, 1990; Garcia-Closas & Lubin, 1999). As discussed in Section 3.5.3, the clustered design of the FHS, and resulting intracluster correlation of observations, led to a reduction in statistical power. It is necessary to account for clustering during both the design and analysis phases of the study (Liu & Liang, 1997). To account for clustering during the design phase, power was calculated with the total sample size equal to both the number of families, and number of relatives. True statistical power was likely situated between these conservative (families) and liberal (relatives) estimates. For Objective 2, we estimated that we would have 79.3% to 90.3% power (given a range of outcome probabilities) to detect an OR of 1.65 among relatives, and 69.5 to 82.7% power to detect an OR of 1.65 among families. However, it is important to note that these calculations reflected pre-study assumptions regarding expected probabilities of exposure and outcome based on estimates from previous literature, as well as a binary categorization of perceived risk. These assumptions did not reflect the observed exposure or outcome probabilities. Given the lower true exposure probabilities in our data, our decision to use a 3-level exposure variable given the distribution of our data, and the smaller observed effect sizes, the power of our study for this objective was likely substantially lower than the initial estimate. As post-hoc power calculations based on observed effect sizes which are smaller for those for which the study was originally designed will always underestimate prospective study power (Goodman & Berlin, 1994; Smith & Bates, 1992), post hoc power was not
calculated. For Objective 3, we estimated that we would have 77.3 to 88.2% power to detect an OR of 2.00 among relatives, and 67.8 to 80.1% power to detect an OR of 2.00 among families.

5.2.6 General Limitations

Perhaps the most important limitation of the thesis project was that we could not obtain complete pedigree data (full family history of breast and ovarian cancers, including age at diagnosis and/or death, and BRCA1/2 mutation carrier status) in a useable format to allow the use of one of the validated, widely-used breast cancer risk estimation tools discussed in Section 3.4.1, such as the BOADICEA (Lee et al., 2014) or IBIS (Tyrer et al., 2004) models, to calculate numeric lifetime breast cancer risk for each of the women in our study cohort. While the classification system of familial breast cancer risk that we employed was rigorously developed based on pre-existing models, and revised according to subsequent seminal studies and resources in the field, deriving a numeric breast cancer risk using one of the standard risk estimation algorithms would allow us to validate our measure. Importantly, this also would have allowed a comparison of women’s perceived numeric breast cancer risk and objective numeric breast cancer risk. As such, it would be possible to identify how accurate women with familial breast and/or ovarian cancer risk in Ontario are with regard to numerically estimating their personal risk, and identify specific sub-populations where risk management and messaging efforts may need to be focused to bring perceived breast cancer risk in line with actual risk.

Another limitation of the thesis was the short follow-up period of the FHS. The prospective cohort design afforded a number of important advantages for our research objectives, including the ability to investigate multiple exposures and outcomes, and the ability to definitively establish the appropriate temporal sequence (critical to both Objectives 1 and 2). However, the limited follow-up of only two years precluded our ability to examine long-term
outcomes for Objective 1. While our results from Objective 1 are an important starting point, to determine whether mammography screening is beneficial for all women with varying levels of familial breast cancer risk, the examination of long-term outcomes is needed.

5.2.7 External Validity

Our findings on the influence of level of familial breast cancer risk, and screening mammography status on prognostic features of invasive breast cancer and benign breast disease likely apply to most women with a family history of breast cancer, thus our findings can likely be extended to a much broader population of women with familial risk. It is unclear how our findings may generalize specifically to younger women, and women with BRCA1/2 mutations, as the mutation carrier prevalence in the FHS was estimated to be approximately 10% (Ontario Cancer Genetics Network, Internal Communication, 2012). Few studies have examined the effectiveness of mammography screening specifically in younger women with a family history of breast cancer; however, one study reported interim findings which predict a 10-year mortality reduction of 20% from annual mammography for women younger than 50 years with a moderate or high familial breast cancer risk (FH01 collaborative teams, 2010). Some studies have suggested BRCA1/2-associated breast cancers are more likely to be of a higher grade and ER- compared to sporadic cancers (Goodwin et al., 2012; Mavaddat et al., 2012; Breast Cancer Linkage Consortium, 1997). These histological differences may suggest a different natural history for breast cancers due to BRCA mutations, which has important implications for screening. If breast cancers in BRCA1 or BRCA2 mutation carriers spend a shorter amount of time than sporadic cancers in the preclinical phase, they are less likely to be detected by periodic screening mammography. Furthermore, a few studies have demonstrated that African-American and Hispanic women are significantly more likely to have basal-like, or triple-negative breast tumors compared with Caucasian women (Howlader et al., 2014; Carey et al., 2006), which may
partially account for the increased risk of mortality in these populations. Given that over 96% of women in our study were Caucasian, future studies should include varying ethnic groups to determine if our findings are applicable to these populations.

Our findings regarding the relationship between perceived risk and breast screening use likely apply to the broader population of women with familial breast cancer risk, with several limitations. All women in our study were Ontario residents, where universal healthcare coverage is available, and an organized breast cancer screening program is in place. While healthcare coverage is universal in Canada, and all provinces and territories have organized breast screening programs (with the exception of Nunavut), our findings may not apply to populations where health care is not universal or breast cancer screening sites are more difficult to access. Factors such as the cost of mammography, not having health insurance, long wait-times or distance of the screening facility may impose barriers to attending screening that Canadian women do not generally experience. Additionally, there may be differences in breast cancer screening guidelines, specifically for women under 50 years of age with familial breast cancer risk outside of Canada.

5.3 Study Strengths

This thesis project has a number of notable strengths. Participants of the FHS were identified from a large, population-based cohort of relatives of cases of breast cancer. The population-based nature of the study allows for broad generalizability to women with a family history of breast and/or ovarian cancer, and limits self-selection bias. The population-based design also allowed for the inclusion of women with a very wide range of familial breast or ovarian cancer histories, allowing for us to examine potential differences among women with varying levels of increased breast cancer risk. While many studies have compared women with a
family history of breast cancer to women without a family history, few studies have compared women with varying levels of familial breast cancer risk. Another major strength of this study is the prospective design, which limited reverse causality in assessing the relationship between perceived risk and breast cancer screening use.

The high initial response rate obtained (73.6%) limited selection bias within the cohort. Furthermore, our analyses which demonstrated that participation status was not associated with familial breast cancer risk, or screening mammogram history suggest that the women in our study are likely similar to women in the target population on these main exposure and outcome measures. We collected detailed baseline and follow-up data for a large number variables, thus were able to adjust for a number of important confounders. Our ability to validate self-reported mammogram use and diagnoses of breast cancer and benign breast disease using data from imaging and pathology/surgical reports ensured that misclassification was kept to a minimum. Our familial risk classification scheme was also rigorously developed using the most recent and seminal evidence to ensure all women were accurately classified.

5.4 Implications for Epidemiology and Public Health, and Future Directions

This thesis project provides new evidence regarding prognostic features of breast cancer and risk of BBD in women with varying levels of familial breast cancer risk. While much is known about the risk and prognosis of breast cancer in average-risk women and women at very high risk of breast cancer (BRCA1/2 mutation carriers), much less is known about women with intermediate levels of familial risk. In our cohort, symptomatic invasive breast cancers were significantly larger in size and diagnosed at a later stage compared with screen-detected cancers. While our results suggest that all women with a first-degree family history of breast and/or ovarian cancer may benefit from annual mammography screening, a mortality benefit cannot be
inferred. Breast cancers which exist in the preclinical phase for a longer period (and may have more favourable prognosis) are more likely to be detected during screening compared with cancers that progress rapidly to the symptomatic phase (length bias). It is possible then, that the increased likelihood of small, localized invasive cancers detected by mammography screening in the FHS is partially representative of overdiagnosed cases. However, the overall magnitude of overdiagnosis may be less in women with familial risk, given that some of these women may experience poorer prognosis relative to average-risk women. Having a first-degree relative diagnosed with breast cancer before age 50 years is a strong risk factor for early-onset breast cancer (Althuis et al., 2003), and 5-year breast cancer survival rates are lowest in women diagnosed prior to age 40 years (Freedman & Partridge, 2013). Women with strong family histories also have higher risk of triple-negative breast tumors (Phipps et al., 2011), which demonstrate poorer survival. A study combining data from several high-risk screening studies also found the rate of tumor growth in BRCA mutation carriers was double that of non-carriers (Tilanus-Linthorst et al., 2007).

To determine whether mammography screening is effective for all women with a family history of breast and/or ovarian cancer, studies with extensive periods of follow-up that assess the effect of mammography screening on breast cancer mortality are necessary. Future research should also include larger samples of women to be able to detect small differences in prognostic features between familial risk groups, focus specifically on younger women with familial breast cancer risk, and include women of different ethnic backgrounds. A recent US study found that the rate of breast MRI for breast cancer screening increased from 1.5 per 10,000 women in 2003, to 32.3 per 10,000 women in 2011 (Stout et al., 2014). While 82.0% of women screened with breast MRI had a family history of breast cancer, only 5.9% had a known BRCA mutation (Stout et al., 2014). Studies which examine the efficacy and cost-effectiveness of screening for
breast cancer using MRI in addition to mammography in women with varying levels of familial risk are also critical, given the increased use of breast MRI within broader populations of women at intermediate and high breast cancer risk. Several countries have revised breast cancer screening protocols for carriers of BRCA1/2 mutations to exclude mammography, in response to the concerns about increased radiosensitivity and risk of radiation-induced breast cancer due to accumulated exposure to ionizing radiation in this population (Pijpe et al., 2012). As such, investigation of the efficacy of breast screening with MRI alone compared with combined MRI and mammography in women at very high risk may be warranted. This evidence is needed before definitive risk-based breast cancer screening guidelines can be developed. Developing tailored risk-based screening strategies for women with varying levels of breast cancer risk may maximize detection of early-stage breast cancers, which may ultimately improve breast cancer prognosis.

This thesis project also provides an important contribution to the body of literature concerning the relationship between perceived risk and breast cancer screening behaviours in women with a family history of breast cancer. As discussed, the majority of studies in this area are cross-sectional, and it is highly plausible that their results are explained by temporal bias. In our overall cohort, perceived risk did not predict breast cancer screening in the following year. We hypothesized that level of familial risk may moderate this relationship, and our stratified findings suggested some evidence to support this. Importantly, women at moderate/high familial risk were less likely to screen with any modality if they perceived their risk as greater than 50%, compared to women who perceived their risk as exactly 50%, suggesting that highly-elevated levels of perceived risk may deter regular screening use. Notably, nearly half (47%) of the women who perceived their lifetime breast cancer risk to be greater than 50% were classified as low familial risk, suggesting many of these women greatly overestimated their risk. Women
with such elevated risk perceptions may disproportionately experience anxiety about developing cancer, which may in turn promote avoidance of regular screening. Given that rates of annual mammography screening in North American women with familial risk are lower than 60% (Campitelli et al., 2011; Madlensky et al., 2005), understanding the factors which influence screening is critical to developing strategies to increase participation. Further clarification of how women with a family history perceive their risk, the accuracy of perceived risk estimates, and the influence of perceived risk on screening will guide the development of risk education and management strategies to promote informed decision-making regarding optimal breast screening use, and to identify populations where these strategies should be targeted. Due to the lack of statistical significance of our results, studies with larger samples of women with varying levels of perceived risk are needed to confirm our findings.

Finally, this project also provided some of the first evidence of the accuracy of self-reported mammogram use in women with varying levels of familial risk, and identified subgroups of women with reduced recall accuracy. Understanding the validity of self-reported mammogram data is essential for researchers given the wide use of these data for measuring adherence to breast screening guidelines in epidemiologic research studies. These findings may also be important in the clinical setting, where patient’s self-reported use of cancer screening examinations may be considered during the process of medical decision-making and referral.

Taken together, the studies that form this thesis contribute significantly to the body of knowledge regarding the effectiveness and use of breast cancer screening in women with familial risk. Understanding the differences in screening participation and effectiveness, as well as breast cancer prognosis that exist for women with varying levels of familial risk is critical, as we shift towards models of medicine and healthcare that are increasingly personalized. The potential harms of breast cancer screening must always be weighed against the potential clinical...
benefits, and robust evidence that allows women and their physicians to make informed decisions regarding the modalities they are screened with, the optimal age to begin screening, and appropriate screen intervals is needed. Future research which builds upon our results will guide the continued development of risk-tailored screening strategies, along with interventions to increase regular use of breast cancer screening in women with familial risk, with the ultimate goal of reducing the burden of breast cancer in this high-risk population. As breast cancer is the leading incident cancer and second leading cause of cancer death among Canadian women, and given that as many as 1 million Canadian women aged 20 years or older are estimated to have a first-degree family history of breast cancer, developing screening strategies which more effectively detect early-stage cancers, and increasing breast cancer screening participation in this population is essential.
Chapter 6
Contribution to the Design and Conduct of the Thesis Project

The FHS was designed and data collection underway prior to the candidate’s initial involvement in the project. However, the candidate was responsible for explicitly developing the thesis objectives in collaboration with the PhD advisory committee. The candidate also secured a two-year Doctoral Fellowship from the Canadian Breast Cancer Foundation - Ontario Region to support completion of the project, and was responsible for initially obtaining and maintaining ethical approval. The idea to conduct a systematic review (Objective 2), to identify important methodological issues and limitations which our original study would subsequently address, was that of the candidate. Upon completion of data collection in March 2011, the candidate assumed full responsibility for managing the FHS database, and all study materials. The candidate was independently responsible for creating a final, complete dataset incorporating data files from all years of FHS follow-up, data from the Ontario site of the BCFR, as well as pathology and imaging data. The candidate also undertook a comprehensive quality assessment of the FHS database, and partially re-abstracted and re-entered data from imaging reports. The candidate also updated the familial risk classification scheme based on emerging seminal evidence. The candidate was responsible for processing data from raw database format to cleaned and derived versions of data, and independently responsible for conducting all statistical analyses in the thesis project. The candidate drafted all versions of the manuscripts in full, and made all revisions as suggested by the manuscript co-authors. The candidate also submitted all resulting manuscripts for peer-review, made appropriate revisions as suggested by peer-reviewers, and presented all results at relevant scientific meetings locally, nationally and internationally.


Statistics Canada. Table 051-0001 - Estimates of population, by age group and sex for July 1, Canada, provinces and territories, annual (persons unless otherwise noted), CANSIM (database). Accessed December 5, 2013 from: http://www4.hrsdc.gc.ca/.3ndic.1t.4r@-eng.jsp?iid=35.


Appendix A. Family History Study Grant Abstract

CBCRA / ACRC 801/04 – page 5

10. DETAILED SCIENTIFIC ABSTRACT / RÉSUMÉ SCIENTIFIQUE DÉTAILLÉ

Responses must be limited to one page. Refer to the 2004 Grant Application Guide for specific instructions regarding the format to be used for this section. / Las respuestas deben estar limitadas a una página. Consulte el Guía de demanda de subvención de 2004 para obtener las directivas específicas para este apartado.

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Screening behaviours and outcomes among relatives of women with breast cancer

Keywords/Technical Terms: breast cancer, benign breast disease, family history, screening behaviours, knowledge, attitudes

Background: Although there is substantial evidence for the efficacy of screening mammography for women 50-69 years of age, the impact of screening on reducing mortality from breast cancer in women with a family history of breast cancer is unknown. This evidence is required for the development of definitive breast cancer screening guidelines for women with varying levels of family history risk of breast cancer.

Objectives: 1) To compare breast screening outcomes (high risk types of benign breast disease and prognostic features of breast cancers) among women with high, moderate and low risk family history of breast cancer 2) To compare breast screening behaviours among women with high, moderate and low risk family history of breast cancer 3) To compare knowledge, attitudes and beliefs on breast cancer risk and screening among women with high, moderate and low risk family history of breast cancer. 4) To determine the difference in association between breast screening outcomes and breast screening behaviours among women with high, moderate and low risk family history of breast cancer 5) To determine the difference in association between breast screening behaviours and knowledge, attitudes and beliefs on breast cancer risk and screening among women with high, moderate and low risk family history of breast cancer

Study design: A retrospective cohort study is proposed. The study cohort will be identified from female relatives of cases of invasive breast cancer (probands) who were diagnosed in Ontario between 1996-1998 in the Ontario Familial Breast Cancer Registry. Breast screening behaviours among women with high, moderate and low risk family history of breast cancer will be compared. In addition, the determinants of these behaviours will be examined and the outcomes will be followed until December 31, 2008. Information on breast screening behaviours and knowledge, attitudes and beliefs about breast cancer risk and screening will be collected by a telephone-administered questionnaire. The cohort will be followed for two years by annual questionnaires to collect data on subsequent screening behaviours and identify breast screening outcomes. Data on benign breast disease and prognostic features of breast cancer will be obtained from tissue specimens and mammography and breast cancer treatment data will be abstracted from medical records.

Analysis: As women are selected from families, all analyses will adjust for the effect of clustering of individuals within families. Multivariate associations between screening behaviours and family history and screening outcomes and family history will be examined using generalized estimating equations extension of logistic regression modeling. Knowledge, attitude and beliefs will be examined as potential predictor variables of screening behaviours.

Significance: This study will evaluate the effectiveness of breast screening in women with different risk levels of family history of breast cancer. In addition, the determinants of screening behaviours will be examined.
Several years ago you completed a personal history questionnaire (PHQ) about factors that may relate to a person’s risk of developing breast cancer. It is important to update this information and collect additional information for scientific research. We encourage you to answer all questions.

Should you wish to speak with someone about this questionnaire, please call 416-217-1228 or our toll-free number 1-866-989-0031.

An interviewer will be calling you to record your answers. You can keep this questionnaire for your records.
Although an interviewer will be calling to record your answers, you may find it helpful to fill out the questionnaire ahead of time. You may write your answers in the space provided or check the appropriate circles.

If you come to a question that you do not want to answer, please skip that question and continue to answer the remaining questions.

We last heard from you when you completed a Personal History Questionnaire (PHQ) for this study on_________________________.  Where appropriate, please think back to that date and age when answering the questions below.

Background Information

1. What is your date of birth? _____/_____/19_____
   month   day   year

2. How much do you currently weigh? If you are currently pregnant please give your pre-pregnancy weight.

   _______ pounds  or  _______ kilograms

3. What is the highest level of education you have completed?

   ○ Less than high school
   ○ Some or all of high school
   ○ Vocational or technical school
   ○ Some college or university
   ○ Bachelor's degree or higher

4. What is your current marital status?

   ○ Married or common law
   ○ Widowed
   ○ Divorced or separated
   ○ Never married
Breast Investigation

5. Since you last completed the PHQ, has a doctor ever told you that you had breast cancer (a malignant or in situ tumour)?

- Yes
- No ➔ Please go to question 10
- Don't know ➔ Please go to question 10

6. Did you have a breast biopsy (breast tissue removed by a core needle biopsy or open surgical biopsy) to find your breast cancer (a malignant or in situ tumour)?

- Yes, the right breast
- Yes, the left breast
- Yes, both breasts
- No ➔ Please go to question 8
- Don't know ➔ Please go to question 8

7. Where and when did you have your breast biopsy (ies) done? Please indicate your age and/or date of surgery (ies).

- Biopsy No. 1
  Hospital: __________________________/ Age_____ or Date_____ /_____
             years      month   year
- Biopsy No. 2
  Hospital: __________________________/ Age_____ or Date_____ /_____
             years      month   year
- Don't know
8. Did you have a **lumpectomy** (breast lump removed by surgery) to find or treat your **breast cancer** (a malignant or in situ tumour)?

- Yes, the right breast
- Yes, the left breast
- Yes, both breasts
- No  ➔  Please go to question 10
- Don't know  ➔  Please go to question 10

9. Where and when did you have your lumpectomy (ies) done? *Please indicate your age and/or date of surgery (ies).*

- Lumpectomy No. 1
  
  Hospital: ___________________________ / Age____ or Date____ /____

- Lumpectomy No. 2
  
  Hospital: ___________________________ / Age____ or Date____ /____

- Don't know

10. **Since you last completed the PHQ**, has a doctor ever told you that you had **benign breast disease** (non-cancerous cyst or breast lump) that was **not breast cancer**?

- Yes
- No  ➔  Please go to question 13
- Don't know  ➔  Please go to question 13

11. Did you have a **breast biopsy** (breast tissue removed by a core needle biopsy or open surgical biopsy) to find your **benign breast disease** (non-cancerous cyst or breast lump), that was **not breast cancer**?

- Yes, the right breast
- Yes, the left breast
- Yes, both breasts
- No  ➔  Please go to question 13
- Don’t know  ➔  Please go to question 13
12. Where and when did you have your surgical breast biopsy (ies) done? Please indicate your age and/or date of surgery (ies).

- Biopsy No. 1
  Hospital: ______________________ / Age____ or Date____ /____
  years   month   year
- Biopsy No. 2
  Hospital: ______________________ / Age____ or Date____ /____
  years   month   year
- Don't know

**Surgical and Medical History**

13. Since you last completed the PHQ, has a doctor told you that you had a disease such as cancer, leukemia or malignant tumour, other than breast cancer?

- Yes → Type of cancer ______________________ and _____ years of age
  Type of cancer ______________________ and _____ years of age
  Type of cancer ______________________ and _____ years of age
- No
- Don’t know

14. Since you last completed the PHQ, have you had one or both breasts completely removed?

- Yes, the right breast → At what age was this? _____ years of age
- Yes, the left breast → At what age was this? _____ years of age
- Yes, both breasts → At what age was this? _____ years of age
- No → Please go to question 16
- Don’t know → Please go to question 16
15. Why did you have your breast(s) removed? *Please check all that apply.*
- To treat breast cancer
- To prevent breast cancer
- Other, please specify ____________________________
- Don't know

16. Have you ever had a hysterectomy (uterus or womb removed)?
- Yes, At what age was this? _____ years of age
- No
- Don't know

17. Since you last completed the PHQ, has a doctor told you that you had cysts in one or both ovaries?
- Yes, At what age was this first diagnosed? _____ years of age
- No
- Don't know

18. Since you last completed the PHQ, have you had one or both ovaries completely removed? *If your ovaries were removed at different times, please give your age at the most recent operation.*
- Yes, one ovary, At what age was this? _____ years of age
- Yes, both ovaries, At what age was this? _____ years of age
- Yes, unsure if 1 or both ovaries, At what age was this? _____ years of age
- No, Please go to question 20
- Don't know, Please go to question 20
19. Why did you have one or both of your ovaries removed? Please check all that apply.

- Gynecological problem (abnormal bleeding, missed periods, cysts)
- To treat ovarian cancer
- To prevent ovarian cancer
- As part of treatment of breast cancer
- As part of prevention of breast cancer
- Other, please specify ________________________________
- Don't know

Breast Examination

20. Since you last completed the PHQ, have you had a mammogram (x-ray examination of the breasts)?

- Yes             → How many mammograms did you have in total?____
- No              → Please go to question 24
- Don't know      → Please go to question 24

21. Where and when did you have your last mammogram done? Please indicate your age and/or date of your last mammogram.

Hospital/Clinic:_____________________/ Age____ or Date____ /____

- years          month     year

- Don't know

22. What was the main reason you had your last mammogram? Please check all that apply.

- Part of a regular check-up or routine screening
- Part of the Ontario Breast Screening Program
- Family history of breast cancer
- Breast problem or symptom
- Other, please specify ________________________________
- Don't know
23. Did anyone or anything encourage you to have a mammogram? Please check all that apply.

- Family physician
- Familial cancer genetic clinic (genetic counselor, geneticist)
- Family member
- Friend
- Family member with breast cancer
- Someone with breast cancer
- Media (television, radio, magazine)
- Community presentation
- Other, please specify ________________________________

Please go to question 25

24. What are your reasons for not having a mammogram? Please check all that apply.

- Not old enough
- Have not gotten around to it
- Not needed or no problems
- Doctor has not recommended it
- Personal or family responsibilities
- Transportation problems
- Language problems
- Hate or dislike having one done
- Fear (painful, embarrassing, may find something wrong)
- Other, please specify ________________________________

25. Have you ever had your breasts examined (physical breast exam) for lumps (tumours or cysts) by a doctor, nurse or other health professional?

- Yes
- No Please go to question 28
- Don't know Please go to question 28

26. When did you have your last physical breast exam? Please indicate your age and/or date of your last physical breast exam.

_____ years of age or _____/_____

- month year
- Don't know
27. What was the main reason you had your last physical breast exam? Please check all that apply.

- Part of a regular check-up or routine screening
- Part of the Ontario Breast Screening Program
- Family history of breast cancer
- Breast problem or symptom
- Other, please specify ________________________________

→ Please go to question 29

28. What are your reasons for not having a physical breast exam? Please check all that apply.

- Not old enough
- Have not gotten around to it
- Not needed or no problems
- Doctor has not recommended it
- Personal or family responsibilities
- Transportation problems
- Language problems
- Hate or dislike having one done
- Fear (painful, embarrassing, may find something wrong)
- Other, please specify ________________________________

29. Have you ever examined your own breasts (breast self exam or BSE) for lumps (tumours, cysts)?

- Yes
- No → Please go to question 31
- Don’t know → Please go to question 31

30. On average, how often do you examine your own breasts (breast self exam or BSE) for lumps (tumours, cysts)?

- Once a month or more
- Every 2-3 months
- Every 4-6 months
- Once a year
- Other, please specify ________________________________
- Don’t know
31. Have you ever had any other tests to check for breast cancer? Please check all that apply.

<table>
<thead>
<tr>
<th>Test</th>
<th>If yes, what was the main reason for having the test? Please check all that apply.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast ultrasound</td>
<td>☐ Yes</td>
</tr>
<tr>
<td></td>
<td>☐ Part of a regular check-up or routine screening</td>
</tr>
<tr>
<td></td>
<td>☐ No</td>
</tr>
<tr>
<td></td>
<td>☐ Follow-up of past problem</td>
</tr>
<tr>
<td></td>
<td>☐ Don’t know</td>
</tr>
<tr>
<td></td>
<td>☐ Breast problem or symptom</td>
</tr>
<tr>
<td></td>
<td>☐ Family history of breast cancer</td>
</tr>
<tr>
<td></td>
<td>☐ Other, please specify</td>
</tr>
<tr>
<td></td>
<td>☐ Don’t know</td>
</tr>
<tr>
<td>MRI Scan (Magnetic Resonance Imaging)</td>
<td>☐ Yes</td>
</tr>
<tr>
<td></td>
<td>☐ Part of a regular check-up or routine screening</td>
</tr>
<tr>
<td></td>
<td>☐ No</td>
</tr>
<tr>
<td></td>
<td>☐ Follow-up of past problem</td>
</tr>
<tr>
<td></td>
<td>☐ Don’t know</td>
</tr>
<tr>
<td></td>
<td>☐ Breast problem or symptom</td>
</tr>
<tr>
<td></td>
<td>☐ Family history of breast cancer</td>
</tr>
<tr>
<td></td>
<td>☐ Other, please specify</td>
</tr>
<tr>
<td></td>
<td>☐ Don’t know</td>
</tr>
<tr>
<td>Other test, please specify</td>
<td>☐ Yes</td>
</tr>
<tr>
<td></td>
<td>☐ Part of a regular check-up or routine screening</td>
</tr>
<tr>
<td></td>
<td>☐ Follow-up of past problem</td>
</tr>
<tr>
<td></td>
<td>☐ Breast problem or symptom</td>
</tr>
<tr>
<td></td>
<td>☐ Family history of breast cancer</td>
</tr>
<tr>
<td></td>
<td>☐ Other, please specify</td>
</tr>
<tr>
<td></td>
<td>☐ Don’t know</td>
</tr>
</tbody>
</table>
32. Have you ever had an appointment at a specialist clinic to discuss your family history of cancer and the possibility of genetic testing?
- Yes
- No
- Don’t know

33. Have you ever had a genetic test for the breast cancer genes BRCA1 or BRCA2?
- Yes
- No
- Don’t know

**Awareness about Breast Cancer or Screening**

*Screening for breast cancer means having tests to check for breast cancer when you do not have any symptoms or problems.*

34. **Since you last completed the PHQ**, have you found out anything more about breast cancer?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read about it in the newspaper</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Read about it in a magazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heard about it on the radio or television</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Searched for it on the Internet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discussed it with a friend or relative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discussed it with a health care professional</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
35. **Since you last completed the PHQ**, have you found out anything more about **breast screening** (mammography, physical breast exam, or breast self exam)?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read about it in the newspaper</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Read about it in a magazine</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Heard about it on the radio or television</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Searched for it on the Internet</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Discussed it with a friend or relative</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Discussed it with a health care professional</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

36. Some factors have been suggested to increase the risk of developing breast cancer. For each factor, please check the answer that best describes how important you feel it is in causing breast cancer.

<table>
<thead>
<tr>
<th>Not at all important</th>
<th>Somewhat important</th>
<th>Very important</th>
<th>Extremely important</th>
</tr>
</thead>
<tbody>
<tr>
<td>High fat diet</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Lack of exercise</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Stress</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Family history of breast cancer</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Hormone replacement therapy (HRT)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

37. On a scale from 0 to 100, where 0= **certain not to happen**, and 100= **certain to happen**, how likely are you to get breast cancer in your lifetime? **Please place a cross (X) on the horizontal line.**
38. The next few questions ask about any thoughts or worries you may have about your risk of developing breast cancer. For each question, please check the answer that best describes how often you have felt this way during the past month.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all or rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost all the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often have you thought about your own chances of developing breast cancer?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often have you worried about your own chances of developing breast cancer?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often have your thoughts about your own chances of getting breast cancer affected your mood?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often have your thoughts about your own chances of getting breast cancer affected your ability to perform your daily activities?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

39. There are different screening tests to check for breast cancer when you do not have any symptoms or problems. How likely do you think the following tests could find breast cancer in your breasts?

<table>
<thead>
<tr>
<th>Test</th>
<th>Not at all likely</th>
<th>Not very likely</th>
<th>Somewhat likely</th>
<th>Very likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical breast exam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast self exam (BSE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

40. How often do you think you should have a screening mammogram? Please check only one.

- Once every six months
- Once a year
- Once every two years
- Once every three years
- Other, please specify ________________________________
- Don’t know
41. At what age do you think you should start having screening mammograms? Please check only one.

- Less than 30
- 30 to 39
- 40 to 49
- 50 to 59
- Other, please specify ________________________________
- Don’t know

42. At what age do you think you should stop having screening mammograms? Please check only one.

- 50 to 59
- 60 to 69
- 70 and over
- Other, please specify ________________________________
- Never
- Don’t know

43. Compared to other women your age, how likely are you to get breast cancer in your lifetime? Please check only one.

- Much below average
- Below average
- Same average risk
- Above average
- Much above average
- Don’t know

---

**Cancer Screening**

*Screening for cancer means having tests to check for cancer when you do not have any symptoms or problems.*

44. Doctors have many screening tests to check for cancer. Have you ever had a **Pap test** to check for cervical cancer, a **trans-vaginal ultrasound** or **CA-125 blood test** to check for ovarian cancer or a **stool blood test** to check for colorectal cancer? Check all that apply.

<table>
<thead>
<tr>
<th>Test</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap test (cervical cancer)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trans-vaginal ultrasound (ovarian cancer)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA-125 blood test (ovarian cancer)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool blood test (colorectal cancer)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If you answered no or don’t know to all of the above, please go to question 46.
45. For the screening test(s) you answered **yes** to in question 44, indicate when you had your last test(s) and the main reason for having your test(s).

<table>
<thead>
<tr>
<th>Test Description</th>
<th>When did you have your last test?</th>
<th>What was the main reason for having your test? Please check only one.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pap test (cervical cancer)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When did you have your last test?</td>
<td>o Less than 1 year ago</td>
<td>o Part of a regular check-up or routine screening</td>
</tr>
<tr>
<td></td>
<td>o 1 year to less than 2 years ago</td>
<td>o Follow-up of past problem</td>
</tr>
<tr>
<td></td>
<td>o 2 years to less than 3 years ago</td>
<td>o Health problem or symptom</td>
</tr>
<tr>
<td></td>
<td>o 3 or more years ago</td>
<td>o Family history</td>
</tr>
<tr>
<td></td>
<td>o Don’t know</td>
<td>o Other, please specify _________________________________</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Don’t know</td>
</tr>
<tr>
<td><strong>Trans-vaginal ultrasound (ovarian cancer)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When did you have your last test?</td>
<td>o Less than 1 year ago</td>
<td>o Part of a regular check-up or routine screening</td>
</tr>
<tr>
<td></td>
<td>o 1 year to less than 2 years ago</td>
<td>o Follow-up of past problem</td>
</tr>
<tr>
<td></td>
<td>o 2 years to less than 3 years ago</td>
<td>o Health problem or symptom</td>
</tr>
<tr>
<td></td>
<td>o 3 or more years ago</td>
<td>o Family history</td>
</tr>
<tr>
<td></td>
<td>o Don’t know</td>
<td>o Other, please specify _________________________________</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Don’t know</td>
</tr>
<tr>
<td><strong>CA-125 blood test (ovarian cancer)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When did you have your last test?</td>
<td>o Less than 1 year ago</td>
<td>o Part of a regular check-up or routine screening</td>
</tr>
<tr>
<td></td>
<td>o 1 year to less than 2 years ago</td>
<td>o Follow-up of past problem</td>
</tr>
<tr>
<td></td>
<td>o 2 years to less than 3 years ago</td>
<td>o Health problem or symptom</td>
</tr>
<tr>
<td></td>
<td>o 3 or more years ago</td>
<td>o Family history</td>
</tr>
<tr>
<td></td>
<td>o Don’t know</td>
<td>o Other, please specify _________________________________</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Don’t know</td>
</tr>
<tr>
<td><strong>Stool blood test (colorectal cancer)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When did you have your last test?</td>
<td>o Less than 1 year ago</td>
<td>o Part of a regular check-up or routine screening</td>
</tr>
<tr>
<td></td>
<td>o 1 year to less than 2 years ago</td>
<td>o Follow-up of past problem</td>
</tr>
<tr>
<td></td>
<td>o 2 years to less than 3 years ago</td>
<td>o Health problem or symptom</td>
</tr>
<tr>
<td></td>
<td>o 3 or more years ago</td>
<td>o Family history</td>
</tr>
<tr>
<td></td>
<td>o Don’t know</td>
<td>o Other, please specify _________________________________</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Don’t know</td>
</tr>
</tbody>
</table>
46. For the screening test(s) you answered no to in question 44, indicate your reason(s) for not having the test(s) done. Please check all that apply.

<table>
<thead>
<tr>
<th>Pap test (cervical cancer)</th>
<th>Trans-vaginal ultrasound or CA-125 blood test (ovarian cancer)</th>
<th>Stool blood test (colorectal cancer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Not old enough</td>
<td>☐ Not old enough</td>
<td>☐ Not old enough</td>
</tr>
<tr>
<td>☐ Not needed or no problems</td>
<td>☐ Not needed or no problems</td>
<td>☐ Not needed or no problems</td>
</tr>
<tr>
<td>☐ Doctor didn’t recommend it</td>
<td>☐ Doctor didn’t recommend it</td>
<td>☐ Doctor didn’t recommend it</td>
</tr>
<tr>
<td>☐ Personal or family responsibilities</td>
<td>☐ Personal or family responsibilities</td>
<td>☐ Personal or family responsibilities</td>
</tr>
<tr>
<td>☐ Transportation problems</td>
<td>☐ Transportation problems</td>
<td>☐ Transportation problems</td>
</tr>
<tr>
<td>☐ Language problems</td>
<td>☐ Language problems</td>
<td>☐ Language problems</td>
</tr>
<tr>
<td>☐ Hate or dislike having it done</td>
<td>☐ Hate or dislike having it done</td>
<td>☐ Hate or dislike having it done</td>
</tr>
<tr>
<td>☐ Fear (painful, embarrassing, may find something wrong)</td>
<td>☐ Fear (painful, embarrassing, may find something wrong)</td>
<td>☐ Fear (painful, embarrassing, may find something wrong)</td>
</tr>
<tr>
<td>☐ Other, please specify</td>
<td>☐ Other, please specify</td>
<td>☐ Other, please specify</td>
</tr>
<tr>
<td>__________________________</td>
<td>_________________________</td>
<td>________________________________</td>
</tr>
</tbody>
</table>

**Reproductive History**

47. **Since you last completed the PHQ**, have you used hormonal contraceptives in the form of birth control pills, the patch, implants or injections?

☐ Yes
☐ No  ➔ Please go to question 49
☐ Don't know  ➔ Please go to question 49

48. Are you **currently** taking hormonal contraceptives in the form of birth control pills, the patch, implants or injections?

☐ Yes
☐ No  ➔ At what age did you stop? _____ years of age
### Pregnancy History

49. Since you last completed the PHQ, have you been pregnant?

- Yes
- No → Please go to question 56

50. Since you last completed the PHQ, how many pregnancies have you had? Please include live births, stillbirths, tubal (ectopic) pregnancies, miscarriages, and therapeutic abortions.

- _____ pregnancy (ies)
- Don't know

**Please complete questions 51-55 for each pregnancy.**

If you have had more than 5 pregnancies, this information will be collected at the time of the interview.

<table>
<thead>
<tr>
<th>1st Pregnancy</th>
<th>2nd Pregnancy</th>
<th>3rd Pregnancy</th>
<th>4th Pregnancy</th>
<th>5th Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What was the outcome of this pregnancy?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Currently pregnant</td>
<td>- Single live birth</td>
<td>- Multiple birth</td>
<td>- Stillbirth</td>
<td>- Induced abortion</td>
</tr>
<tr>
<td>- Currently pregnant</td>
<td>- Single live birth</td>
<td>- Multiple birth</td>
<td>- Stillbirth</td>
<td>- Induced abortion</td>
</tr>
<tr>
<td>- Currently pregnant</td>
<td>- Single live birth</td>
<td>- Multiple birth</td>
<td>- Stillbirth</td>
<td>- Induced abortion</td>
</tr>
<tr>
<td>- Currently pregnant</td>
<td>- Single live birth</td>
<td>- Multiple birth</td>
<td>- Stillbirth</td>
<td>- Induced abortion</td>
</tr>
<tr>
<td>- Currently pregnant</td>
<td>- Single live birth</td>
<td>- Multiple birth</td>
<td>- Stillbirth</td>
<td>- Induced abortion</td>
</tr>
</tbody>
</table>

| **On what date did your pregnancy end?** | | | | |
| _____/_____ month year | _____/_____ month year | _____/_____ month year | _____/_____ month year | _____/_____ month year |
53. **How long was this pregnancy?**

- 3 months or under
- 4 - 6 months
- 7 or more months

For live births only:

54. **What was the sex of each child delivered from this pregnancy?**

- ___number of males
- ___number of females

For live births only:

55. **Did you breast feed this child?**

- Yes
- No
- Under 1 month
- 1 - 5 months
- 6 - 11 months
- 12 - 24 months
- Over 24 months
Menopause and Hormone Replacement Therapy

56. **Since you last completed the PHQ,** have your menstrual periods stopped for **one year or more?** Please include only menstrual bleeding. **Do not include bleeding that results from hormone replacement therapy or progesterone, progestin or withdrawal bleeding.**

- Yes
- No → **Please go to question 59**
- Don’t know → **Please go to question 59**

57. When was your **last** menstrual period? **Please indicate your age and/or date of your last period.**

____ years of age  or  ____/_____  
month  year

- Don’t know

58. Why did your menstrual periods stop? **Please check only one.**

- Natural menopause (periods stopped by themselves)
- Surgery (hysterectomy and/or ovary (ies) removed)
- Radiation or chemotherapy
- Other, please specify ________________________________
- Don’t know

59. **Since you last completed the PHQ,** have you taken **hormone replacement therapy (HRT),** prescribed by a doctor (for menopausal symptoms, surgical removal of ovaries, osteoporosis or heart disease prevention) for **at least 3 months?** Please do not include hormone therapy that was used for birth control, or infertility, or hormone therapy that was delivered by injections, herbal or soy products.

- Yes → At what age did you start? _____ years of age
- No → **Please go to question 61**
- Don’t know → **Please go to question 61**

60. Are you currently taking **hormone replacement therapy (HRT)?**

- Yes
- No → At what age did you stop? _____ years of age
- Don’t know
61. Overall, how would you rate your general health compared to other women your age?

- Poor  - Fair  - Good  - Very good  - Excellent

62. Below is a list of the ways you might have felt or behaved. For each statement, please check the answer that best describes how often you have felt this way during the past week.

<table>
<thead>
<tr>
<th>Feeling</th>
<th>Rarely or None of the time (less than 1 day)</th>
<th>Some or a little of the time (1-2 days)</th>
<th>Occasionally or Moderate amount of time (3-4 days)</th>
<th>Most or All of the time (5-7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I felt depressed</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>My sleep was restless</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>I felt lonely</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>I had crying spells</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>I could not ‘get going’</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

63. Is there a particular doctor's office, clinic, health centre, or other place that you usually go to when you are sick or need advice about your health (for yourself)?

- Yes
- No  ➔ Please go to question 65
- Don’t know  ➔ Please go to question 65

64. During the past 2 years, how many times on average, did you go to the doctor’s office, clinic, health centre, or other place that you usually go to when you were sick or needed advice about your health (for yourself)?

- Less than once a year
- Once a year
- 2-3 times a year
- 4-5 times a year
- 6 or more times a year
- Don’t know
65. **During the past 2 years**, have you seen any of the following health professionals about your physical, emotional or mental health? *Please check all that apply.*

- Family doctor
- Eye specialist (ophthalmologist or optometrist)
- Dentist or orthodontist
- Familial cancer genetic clinic staff (genetic counselor, geneticist)
- Other medical doctor (surgeon, allergist, orthopedist, gynecologist)
- Nurse
- Physiotherapist or chiropractor
- Psychiatrist or psychologist
- Homeopath or naturopath
- Other health professional, please specify____________________________
- None of them
- Don't know

66. **Since you last completed the PHQ**, have you consumed any alcoholic beverages, such as beer, wine or spirits, at least once a week, for 6 months or longer?

- Yes
- No
- Don’t know  → *Please go to question 69*
- Don’t know  → *Please go to question 69*

67. **Since you last completed the PHQ**, when you consumed alcohol at least once a week, how many drinks did you have in a week?

- Beer (12 oz can)  _____ drinks per week
- Wine or wine coolers (1 medium glass)  _____ drinks per week
- Liquor (1 shot)  _____ drinks per week
- Don't know

68. Are you currently consuming alcohol at least once per week?

- Yes
- No  → *At what age did you stop? _____ years of age*
- Don't know
69. **Since you last completed the PHQ,** have you smoked at least 1 cigarette a day for 3 months or longer?
   - Yes
   - No ➔ Please go to question 72
   - Don’t know ➔ Please go to question 72

70. **Since you last completed the PHQ,** when you smoked, how many cigarettes on average did you usually smoke in a day?
   
   _______ cigarettes per day
   - Don't know

71. Are you currently smoking at least 1 cigarette a day?
   - Yes
   - No ➔ At what age did you stop? _____ years of age
   - Don't know

72. **During the past 2 years,** how often on average did you participate in **strenuous physical activities or sports** that made you breathe much harder (vigorous housework, swimming, aerobics, jogging or running, cycling, racquet sports, skiing or skating)?

<table>
<thead>
<tr>
<th>Average hours per week</th>
<th>Average months per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>None ½ hr</td>
<td>1-3 mths</td>
</tr>
<tr>
<td>1 hr</td>
<td>4-6 mths</td>
</tr>
<tr>
<td>1½ hrs</td>
<td>7-9 mths</td>
</tr>
<tr>
<td>2 hrs</td>
<td>10-12 mths</td>
</tr>
<tr>
<td>3 hrs</td>
<td></td>
</tr>
<tr>
<td>4-6 hrs</td>
<td></td>
</tr>
<tr>
<td>7-10 hrs</td>
<td></td>
</tr>
<tr>
<td>11 hrs</td>
<td></td>
</tr>
</tbody>
</table>

73. **During the past 2 years,** how often on average did you participate in **moderate physical activities or sports** (brisk walking, gardening, house or yard work, golfing, volleyball, bowling, curling or social dancing)?

<table>
<thead>
<tr>
<th>Average hours per week</th>
<th>Average months per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>None ½ hr</td>
<td>1-3 mths</td>
</tr>
<tr>
<td>1 hr</td>
<td>4-6 mths</td>
</tr>
<tr>
<td>1½ hrs</td>
<td>7-9 mths</td>
</tr>
<tr>
<td>2 hrs</td>
<td>10-12 mths</td>
</tr>
<tr>
<td>3 hrs</td>
<td></td>
</tr>
<tr>
<td>4-6 hrs</td>
<td></td>
</tr>
<tr>
<td>7-10 hrs</td>
<td></td>
</tr>
<tr>
<td>11 hrs</td>
<td></td>
</tr>
</tbody>
</table>

Thank you for your participation.
Authorization For Release of Medical Information/Tissue

I, ___________________________ hereby authorize the Ontario Cancer Registry or Medical Record Department at

Name of Hospital where surgery was performed

Street address of Hospital where surgery was performed

City                     Province                  Postal Code

to release information/tissue pertaining to the diagnosis of cancer or a benign breast condition to Dr. Irene Andrulis, Principal Investigator, Cancer Care Ontario, 610 University Ave, Toronto, ON M5G 2M9.

Name of Patient: ___________________________ Date of Birth: ___________________________

Date of diagnosis/surgery: ___________________________

Type of cancer/surgery: ___________________________

**Please sign and date this form**

Signature: ___________________________ Date: ___________________________

Witness: ___________________________ Date: ___________________________

RE: Patient File #: ___________________________ Study ID#: ___________________________

For Medical Department ➔ **Please return a copy of this authorization form with the medical records**
Authorization For Release of Imaging Information

I, ______________________________ hereby authorize the Medical/Radiology Record Department at

Name of Hospital/clinic where a mammogram was performed

Street address of Hospital/clinic where mammogram was performed

City          Province          Postal Code

to release any imaging information pertaining to mammography examination to Dr. Anna Chiarelli, Principal Investigator, Cancer Care Ontario, 610 University Ave, Toronto, ON M5G 2M9.

Name of Patient: ___________________________ Date of Birth: ___________________________

Date of Mammogram: ___________________________

**Please sign and date this form**

Signature: ___________________________ Date: ___________________________

Witness: ___________________________ Date: ___________________________

RE: Patient File #: ___________________________ Study ID#: ___________________________

For Medical Department ➔ **Please return a copy of this authorization form with the medical records**
Appendix E. Factors Associated with Participation in the Family History Study

Table 1. Odds ratios and 95% confidence intervals for associations between socio-demographic characteristics, breast cancer risk factors, cancer screening practices and study participation status for eligible female relatives from the Ontario site of the BCFR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participated</th>
<th>Refused</th>
<th>Unreachable</th>
<th>Refused vs. Participated OR (95% CI)</th>
<th>Unreachable vs. Participated OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 1114</td>
<td>n = 201</td>
<td>n = 162</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at interview</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td>315 (28.28)</td>
<td>58 (28.86)</td>
<td>30 (18.52)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>40-49</td>
<td>335 (30.07)</td>
<td>37 (18.41)</td>
<td>35 (21.60)</td>
<td>0.60 (0.38-0.95)</td>
<td>1.10 (0.66-1.83)</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>464 (41.65)</td>
<td>106 (52.74)</td>
<td>97 (59.88)</td>
<td>1.24 (0.86-1.78)</td>
<td>2.19 (1.44-3.35)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Bachelor’s degree</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some college, university or vocational/technical school</td>
<td>423 (37.97)</td>
<td>88 (43.78)</td>
<td>56 (34.57)</td>
<td>1.45 (0.96-2.18)</td>
<td>1.03 (0.66-1.62)</td>
</tr>
<tr>
<td>≤ High-school</td>
<td>374 (33.57)</td>
<td>67 (33.33)</td>
<td>64 (39.50)</td>
<td>1.32 (0.84-2.07)</td>
<td>1.71 (1.08-2.71)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/common law</td>
<td>833 (75.38)</td>
<td>141 (71.21)</td>
<td>87 (54.04)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Single</td>
<td>272 (24.62)</td>
<td>57 (28.79)</td>
<td>74 (45.96)</td>
<td>1.17 (0.79-1.73)</td>
<td>2.13 (1.45-3.13)</td>
</tr>
<tr>
<td>Birth place</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>1007 (90.39)</td>
<td>173 (86.07)</td>
<td>141 (87.04)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Other</td>
<td>107 (9.61)</td>
<td>28 (13.93)</td>
<td>21 (12.96)</td>
<td>1.58 (0.99-2.52)</td>
<td>1.51 (0.85-2.67)</td>
</tr>
<tr>
<td>Ethnic background</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1071 (96.14)</td>
<td>195 (97.01)</td>
<td>150 (92.59)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Other</td>
<td>43 (3.86)</td>
<td>6 (2.99)</td>
<td>12 (7.41)</td>
<td>1.34 (0.55-3.25)</td>
<td>1.77 (0.80-3.90)</td>
</tr>
<tr>
<td>Familial breast cancer risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>527 (48.66)</td>
<td>95 (50.00)</td>
<td>80 (50.63)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Moderate</td>
<td>255 (23.55)</td>
<td>41 (21.58)</td>
<td>41 (25.95)</td>
<td>0.92 (0.59-1.43)</td>
<td>1.18 (0.76-1.84)</td>
</tr>
<tr>
<td>High</td>
<td>301 (27.79)</td>
<td>54 (28.42)</td>
<td>37 (23.42)</td>
<td>1.06 (0.71-1.58)</td>
<td>1.06 (0.66-1.70)</td>
</tr>
<tr>
<td>Ashkenazi Jewish descent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1052 (97.50)</td>
<td>182 (96.30)</td>
<td>153 (96.84)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>27 (2.50)</td>
<td>7 (3.70)</td>
<td>5 (3.16)</td>
<td>1.50 (0.55-4.06)</td>
<td>1.17 (0.41-3.32)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Participated n = 1114</td>
<td>Refused n = 201</td>
<td>Unreachable n = 162</td>
<td>Refused vs. Participated OR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Unreachable vs. Participated OR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>-----------------------</td>
<td>-----------------</td>
<td>---------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>Personal history of cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1063 (95.94)</td>
<td>184 (91.54)</td>
<td>150 (94.94)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>45 (4.06)</td>
<td>17 (8.46)</td>
<td>8 (5.06)</td>
<td>2.35 (1.29-4.29)</td>
<td>1.69 (0.78-3.68)</td>
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<tr>
<td><strong>Personal history of benign breast disease (BBD)</strong></td>
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<td>Yes</td>
<td>273 (24.98)</td>
<td>39 (19.90)</td>
<td>30 (18.87)</td>
<td>1.00</td>
<td>1.00</td>
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<td>No</td>
<td>820 (75.02)</td>
<td>157 (80.10)</td>
<td>129 (81.13)</td>
<td>1.30 (0.88-1.92)</td>
<td>1.12 (0.72-1.77)</td>
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<td><strong>Personal history of ovarian cysts</strong></td>
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<td>Yes</td>
<td>219 (20.13)</td>
<td>33 (16.67)</td>
<td>26 (16.56)</td>
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<td>No</td>
<td>869 (79.87)</td>
<td>165 (83.33)</td>
<td>131 (83.44)</td>
<td>1.23 (0.81-1.86)</td>
<td>1.10 (0.67-1.79)</td>
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<td><strong>Parous</strong></td>
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<td>Yes</td>
<td>855 (76.82)</td>
<td>141 (70.15)</td>
<td>107 (66.05)</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>No</td>
<td>258 (23.18)</td>
<td>60 (29.85)</td>
<td>55 (33.95)</td>
<td>1.35 (0.88-2.05)</td>
<td>1.10 (0.70-1.73)</td>
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<tr>
<td><strong>Menopausal status</strong></td>
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<tr>
<td>Pre-/peri-menopausal</td>
<td>775 (69.76)</td>
<td>143 (71.50)</td>
<td>116 (72.05)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>336 (30.24)</td>
<td>57 (28.50)</td>
<td>45 (27.95)</td>
<td>1.15 (0.76-1.74)</td>
<td>2.44 (1.44-4.11)</td>
</tr>
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<td><strong>Body Mass Index (BMI)</strong></td>
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<tr>
<td>&lt; 25</td>
<td>597 (53.59)</td>
<td>113 (56.22)</td>
<td>98 (60.49)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>25-29</td>
<td>301 (27.02)</td>
<td>60 (29.85)</td>
<td>38 (23.46)</td>
<td>1.10 (0.78-1.58)</td>
<td>0.95 (0.61-1.47)</td>
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<td>≥ 30</td>
<td>216 (19.39)</td>
<td>28 (13.93)</td>
<td>26 (16.05)</td>
<td>0.73 (0.45-1.16)</td>
<td>0.89 (0.56-1.42)</td>
</tr>
<tr>
<td><strong>Ever use of hormone replacement therapy</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>159 (47.60)</td>
<td>27 (47.37)</td>
<td>19 (42.22)</td>
<td>1.00</td>
<td>1.00</td>
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<td>Yes</td>
<td>175 (52.40)</td>
<td>30 (53.63)</td>
<td>26 (57.78)</td>
<td>0.91 (0.51-1.63)</td>
<td>1.64 (0.86-3.13)</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
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</tr>
<tr>
<td>No</td>
<td>919 (82.87)</td>
<td>152 (75.62)</td>
<td>118 (68.52)</td>
<td>1.00</td>
<td>1.00</td>
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<td>Yes</td>
<td>190 (17.13)</td>
<td>49 (24.38)</td>
<td>51 (31.48)</td>
<td>1.55 (1.08-2.24)</td>
<td>2.28 (1.57-3.32)</td>
</tr>
<tr>
<td><strong>Current drinker</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>744 (67.57)</td>
<td>127 (64.14)</td>
<td>114 (70.37)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>357 (32.43)</td>
<td>71 (35.86)</td>
<td>48 (29.63)</td>
<td>1.18 (0.85-1.63)</td>
<td>1.09 (0.76-1.55)</td>
</tr>
<tr>
<td><strong>Previous mammogram</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>773 (69.39)</td>
<td>123 (61.50)</td>
<td>84 (51.85)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>341 (30.61)</td>
<td>77 (38.50)</td>
<td>78 (48.15)</td>
<td>1.44 (0.88-2.34)</td>
<td>1.37 (0.84-2.25)</td>
</tr>
</tbody>
</table>
Appendix F. Ethical Approval

PROTOCOL REFERENCE # 27102

December 5, 2011

Dr. Anna Maria Chiarelli
DALLA LANZA SCHOOL OF PUBLIC HEALTH
FACULTY OF MEDICINE

Ms. Meghan J. Walker
DALLA LANZA SCHOOL OF PUBLIC HEALTH
FACULTY OF MEDICINE

Dear Dr. Chiarelli and Ms. Meghan J. Walker,

Re: Your research protocol entitled, "The role of family history and perceived risk in breast cancer screening behaviours"

ETHICS APPROVAL

Original Approval Date: December 5, 2011
Expiry Date: December 4, 2012
Continuing Review Level: 1

We are writing to advise you that the Health Sciences Research Ethics Board (REB) has granted approval to the above-named research protocol under the REB's delegated review process. Your protocol has been approved for a period of one year and ongoing research under this protocol must be renewed prior to the expiry date.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events in the research should be reported to the Office of Research Ethics as soon as possible.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 15 to 30 days prior to the expiry date of your current ethics approval. Note that annual renewals for studies cannot be accepted more than 30 days prior to the date of expiry.

If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your research.

Yours sincerely,

Judith Friedland, Ph.D.
REB Chair

Daniel Gyewu
REB Manager
Dear Dr. Chiarelli and Ms. Meghan J. Walker,

Re: Your research protocol entitled, "The role of family history and perceived risk in breast cancer screening behaviours"

We are writing to advise you that you have been granted annual renewal of ethics approval to the above-referenced research protocol through the Research Ethics Board (REB) delegated process. Please note that all protocols involving ongoing data collection or interaction with human participants are subject to re-evaluation after 5 years. Ongoing research under this protocol must be renewed prior to the expiry date.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 15 to 30 days prior to the expiry date of your protocol. Note that annual renewals for protocols cannot be accepted more than 30 days prior to the date of expiry as per our guidelines.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events should be reported to the Office of Research Ethics as soon as possible. If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your research.

Yours sincerely,

Judith Friedland, Ph.D.
REB Chair

Daniel Gyewu
REB Manager
### Table 1. Missing data for variables used in Objective 1 analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Missing n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All women (n = 899)</strong></td>
<td></td>
</tr>
<tr>
<td>Familial breast cancer risk</td>
<td>0</td>
</tr>
<tr>
<td>Age at interview</td>
<td>0</td>
</tr>
<tr>
<td>Age at menarche</td>
<td>10 (1.1%)</td>
</tr>
<tr>
<td>Parity</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Hormone replacement therapy use&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Mammogram use since the PHQ</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>Months since last mammogram&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21 (2.8%)</td>
</tr>
<tr>
<td>Number of lifetime mammograms&lt;sup&gt;c&lt;/sup&gt;</td>
<td>27 (4.2%)</td>
</tr>
<tr>
<td>Self-reported diagnosis of breast cancer</td>
<td>0</td>
</tr>
<tr>
<td>Self-reported diagnosis of benign breast disease</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td><strong>Cases of breast cancer (n = 46)</strong></td>
<td></td>
</tr>
<tr>
<td>Pathological confirmation</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Screening mammography use prior to diagnosis</td>
<td>0</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cases of invasive breast cancer (n = 38)</strong></td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>0</td>
</tr>
<tr>
<td>Nodal involvement</td>
<td>9 (23.7%)</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td>3 (7.9%)</td>
</tr>
<tr>
<td>Histologic grade</td>
<td>0</td>
</tr>
<tr>
<td>Mitotic score</td>
<td>3 (7.9%)</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>3 (7.9%)</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>7 (18.4%)</td>
</tr>
<tr>
<td>Progesterone receptor</td>
<td>7 (18.4%)</td>
</tr>
<tr>
<td>Her2-neu</td>
<td>22 (57.9%)</td>
</tr>
<tr>
<td><strong>Cases of benign breast disease (n = 75)</strong></td>
<td></td>
</tr>
<tr>
<td>Pathological confirmation</td>
<td>19 (25.3%)</td>
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<tr>
<td>Screening mammography use prior to diagnosis</td>
<td>4 (7.1%)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>0</td>
</tr>
<tr>
<td>Severity</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>: Among 444 post-menopausal women only  
<sup>b</sup>: Among 740 women who reported having a mammogram since the PHQ  
<sup>c</sup>: Among 640 women who reported at the PHQ that they had ever had a mammogram
Table 2. Missing data for variables used in Objective 2 analyses (n = 913)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Missing n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposures</strong></td>
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</tr>
<tr>
<td>Numeric-scale perceived breast cancer risk (baseline)</td>
<td>22 (2.4%)</td>
</tr>
<tr>
<td>Likert-type scale perceived breast cancer risk (baseline)</td>
<td>29 (3.2%)</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Screening mammogram use (year 1)</td>
<td>12 (1.3%)</td>
</tr>
<tr>
<td>Clinical breast examination use (year 1)</td>
<td>11 (1.2%)</td>
</tr>
<tr>
<td>Ever use of genetic testing (year 1)</td>
<td>13 (1.4%)</td>
</tr>
<tr>
<td><strong>Potential confounders/effect modifiers</strong></td>
<td></td>
</tr>
<tr>
<td>Familial breast cancer risk</td>
<td>0</td>
</tr>
<tr>
<td>Age at interview</td>
<td>0</td>
</tr>
<tr>
<td>Education</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Annual frequency of health care visits</td>
<td>20 (2.2%)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>History of benign breast disease</td>
<td>15 (1.6%)</td>
</tr>
<tr>
<td>History of genetic counselling use</td>
<td>0</td>
</tr>
<tr>
<td>Worry about breast cancer</td>
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</tr>
<tr>
<td>Mammogram use at baseline</td>
<td>16 (1.7%)</td>
</tr>
<tr>
<td>Clinical breast examination use at baseline</td>
<td>22 (2.4%)</td>
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Table 3. Missing data for variables used in Objective 3 analyses

<table>
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<tr>
<th>Variable</th>
<th>Baseline (n = 699)</th>
<th>Year 1 (n = 469)</th>
<th>Year 2 (n = 456)</th>
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</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
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<tr>
<td>Screening mammogram date</td>
<td>14 (2.0%)</td>
<td>1 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td><strong>Characteristics associated with recall</strong></td>
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</tr>
<tr>
<td>Familial risk</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age at interview</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Education</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Marital status</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Annual frequency of health care visits</td>
<td>11 (1.6%)</td>
<td>5 (1.1%)</td>
<td>7 (1.5%)</td>
</tr>
<tr>
<td>Clinical breast examination use</td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td>6 (1.3%)</td>
</tr>
<tr>
<td>Genetic test use</td>
<td>45 (6.4%)</td>
<td>8 (1.7%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Perceived breast cancer risk (Likert-type scale)</td>
<td>37 (5.3%)</td>
<td>22 (4.7%)</td>
<td>11 (2.4%)</td>
</tr>
<tr>
<td>Months since last mammogram</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Mammographic finding (BI-RADS)</td>
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<tr>
<td><strong>Potential confounders</strong></td>
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<tr>
<td>Age at interview</td>
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<tr>
<td>Days since last mammogram</td>
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<td>0</td>
<td>0</td>
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</tbody>
</table>

a: 31 (3.5%) women at baseline, 21 (3.7%) women at year 1, and 28 (5.1%) women at year 2 did not provide consent to release their imaging report, thus were not included in any analyses.