On the Clinical Importance of Benign Breast Disease: Causal Intermediary or Susceptibility Marker?

Laura Reimers Iadeluca

Submitted in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy
under the Executive Committee
of the Graduate School of Arts and Sciences

COLUMBIA UNIVERSITY
2015

Abstract

On the Clinical Importance of Benign Breast Disease: Causal Intermediary or Susceptibility Marker?

Laura Reimers Iadeluca

Breast cancer is thought to develop through progression of benign breast lesions, atypical hyperplasia (AH) and/or carcinoma *in situ* (CIS). Benign breast disease (BBD) is a group of heterogeneous breast abnormalities. This dissertation investigated the association between BBD and breast cancer risk in order to determine whether BBD should be considered a causal intermediary or susceptibility marker of breast cancer risk. We addressed BBD as a modifier of risk in four parts: a comprehensive review of previous cohort studies examining the association between BBD and mammographic density, an analysis of interactions between BBD and established breast cancer risk factors, and validation of currently used risk assessment models in a population of women with BBD. We used two longitudinal cohorts to assess these relationships, the Early Determinants of Mammographic Density study and Woman At Risk registry. Mammographic density and BBD are both important risk factors of breast cancer. We found that women with a history of BBD on average had 3.5% higher percent density on their mammograms than women without a history of BBD. Women diagnosed with BBD prior to first pregnancy had 8.6% higher density than nulliparous women without a history of BBD. Few prior cohort studies have examined interactions between BBD and other breast cancer risk factors and all those that did only assessed multiplicative interactions, not additive interactions. BBD modified the association with parity and alcohol consumption. Nulliparous women with BBD had an almost 5-fold higher risk of breast cancer than nulliparous women without BBD. We found both multiplicative and additive interaction between alcohol use and BBD. Women with BBD who consumed alcohol had 2-fold higher risk of breast cancer compared to women without BBD who did not consume alcohol. We compared three widely used breast cancer risk assessment models, the Gail model, the International Breast Cancer Intervention Study (IBIS), and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA). Mean estimated breast cancer risk based on IBIS model was significantly higher for women with any BBD as compared to mean predicted risk in Gail and BOADICEA models (IBIS 5.84%, Gail 4.79%, and BOADICEA 3.71%; $p<0.001$ for all pairwise comparisons). All three models tended to under predict the

number of breast cancer events in our cohort. Discrimination was also poor in all three models, for the total population, women with BBD and women with atypical hyperplasia. Overall, we found an association between BBD and mammographic density, as well as interactions between BBD and parity, and BBD and alcohol use. Furthermore, current breast cancer risk models have moderate calibration and discrimination in a population of women with BBD, and we saw that differences in calibration depended on type of BBD. Risk assessment models should include not only BBD, but also the interactions between BBD and other risk factors in order to adequately predict subsequent risk of breast cancer. Current breast cancer screening guidelines recommend against MRI or conclude there is insufficient evidence to make decisions regarding MRI screening in women with BBD, even though these women are known to be at a higher risk of breast cancer. Improving breast cancer risk models by including BBD, mammographic density, and their interaction could improve risk assessment and as a result improve screening and clinical care of these women. Results from this dissertation support that BBD is more likely to be a susceptibility marker of breast cancer risk than a true precursor lesion. This suggests that changes in the BBD tissue that occur are more likely due to genetic or epigenetic factors that cause the breast to be more susceptible to the effects of other breast cancer risk factors.

T**able of Contents**

List of Tables & Figures

Acknowledgments

The road to completing this dissertation has been quite a journey, I could not have successfully travelled it without the guidance and support of so many people. First and foremost I would like to thank Dr. Mary Beth Terry for being an amazing mentor over the past few years. Not only have I learned a tremendous amount from you about epidemiologic methods, but I also enjoyed working with you on answering a number of important questions related to breast cancer. You have shown me what it means to do good epidemiologic research.

I would also like to thank my dissertation committee. To Dr. Kathy Crew, who agreed to work with me when I first arrived at Columbia and helped me get involved in a number of interesting clinical projects as well as shadowing residents during breast cancer clinic. Dr. Al Neugut to accepting me as part of the Cancer Training Program and providing me guidance. My outside committee members, Dr. Ying Wei and Dr. Anne Zeleniuch-Jacquotte, I would like to thank for their thoughtful comments during my dissertation defense. To all the participants of the both the Early Determinants of Mammographic Density and Women At Risk studies without their participation this research would not be possible.

Many thanks go to all my family and friends who have been there for me over the many years of my education. To my parents for never giving up on me, no matter how many times I told them “I’m not as smart as you think I am”. My sister for being a great support during my masters’ years and being a wonderful older sibling to look up to for your own determination. Finally, to my husband, Andrew, without you as my cheerleader all these years I don’t know if I could’ve been as dedicated and diligent in my studies. Thank you for always being my number one fan.

Chapter 1:

Epidemiology of benign breast disease and breast cancer risk: a review and synthesis

1.1 Introduction

Mammography use in the United States is steadily increasing since the introduction of breast cancer screening in the 1980s; the percentage of women getting a mammogram increased by 30.4% for women 40-49 years of age, 40.9% for women 50-64 years of age, and 41.8% for women 65 years of age or older [1]. Although screening has made early detection of breast cancer easier, it has also resulted in more women receiving breast biopsies. Approximately 18.7 million mammograms were ordered or provided, either through physician office visits or hospital outpatient department visits in the United States in 2010 (**Figure 1.1**) [2, 3]. Studies suggest that 5-10% of all screening mammograms are abnormal, requiring additional diagnostic testing [4-6]. The percent of abnormal findings is highest among women 40-49 years of age and decreases with age. An estimated 1.6 million breast biopsies are performed each year in the United States [7]. The cumulative risk of having at least one biopsy due to a false positive mammogram is 61.3% after 10 screening mammograms. The probability of receiving a false-positive biopsy after 10 years is 7.0% for women who initiate screening at 40 years and is 9.4% for women who initiate screening at 50 years of age [8]. Approximately 5 to 7 million women over the age of 50 undergo a breast biopsy for benign disease, and a quarter of these women have biopsies with proliferative changes [9].

Frequently breast biopsies result in a diagnosis of benign breast disease (BBD). BBD is a group of premalignant lesions that include fibroadenoma, fibrocystic disease, atypical ductal hyperplasia (ADH), and atypical lobular hyperplasia (ALH). Criteria developed by Dupont and Page [10], classify benign breast disease into three groups: non-proliferative disease, proliferative disease without atypia, and hyperplasia with atypia (**Table 1.1**). Non-proliferative disease includes fibroadenoma, cysts, fibrosis and mild hyperplasia. Proliferative disease without atypia includes intraductal papilloma, radial scar, sclerosing adenosis, and epithelial hyperplasia. Atypical hyperplasia includes both ductal and lobular types. Women with non-proliferative disease, proliferative disease without atypia, and atypical hyperplasia have gradually increasing risk of breast cancer compared to women with normal breast ducts [11].

The prevalence of BBD is unknown and difficult to measure. Not all BBD come to physician attention; some remain undetected [12]. In addition, not all women with palpable lesions or abnormal

mammograms undergo a breast biopsy. Nonetheless, we can estimate the frequency of BBD from autopsy and reduction mammoplasty studies. Prevalence estimates for proliferative disease and atypical hyperplasia range from 1.5-13% [13-17]; for nonproliferative changes, estimates are as high as 67.4% [18]. Autopsy and reduction mammoplasty studies show that BBD is a common occurrence in women [13-18]. However, we are still unable to predict which of these lesions will progress to invasive breast cancer.

Preceding the development of invasive carcinoma are a series of intermediate stages, through BBD and *in situ* carcinoma, representing a stepwise model of carcinogenesis within the breast [19, 20]. BBD are potential precursor lesions to breast cancer or they could just be susceptibility markers. Precursor lesions are distinguishable from susceptibility markers. If a lesion is frequent, as in the case of BBD, then it must also frequently result in an invasive diagnosis for it to be a precursor lesion, which is not the case for BBD. Susceptibility markers differ from precursor lesions in that they are variables associated with increased risk of disease, through making the tissue more susceptible to other risk factors.

Part of the difficulty in epidemiologic studies relates to how risk factors for breast cancer are being analyzed in association with BBD risk. Epidemiologic studies established that reproductive, hormonal, nutritional/lifestyle, and other factors are associated with breast cancer risk (reviewed in [21]). However, extensive research on many of these same risk factors on risk of BBD show a reduced or null association (reviewed in [22]). Discrepant risk estimates are primarily reproductive, hormonal, and lifestyle factors (**Table 1.2**). Selection and information bias may partly account for these discrepant results. However, in this dissertation, we will argue that if certain exposures are not a common cause of both BBD and breast cancer, than BBD is not a mediator of their relationship (*i.e.,* not a precursor lesion). Meaning that they are part of a causal pathway that works with BBD, not through BBD, to cause breast cancer (*i.e.,* BBD as a susceptibility marker). One way to assess this is through effect modification, as risk factors that are not related to the risk of BBD may modify the association between BBD and breast cancer.

Management of most BBD varies by institution with no standard follow-up guidelines for prevention and screening of subsequent disease. Follow-up of other high risk women is based on having a greater than or equal to 1.7% 5-year risk of invasive breast cancer based on the Gail model [23, 24] or for women with a strong family history and lifetime risk of breast cancer greater than 20% based on models that rely

on family history, such as International Breast Cancer Intervention Study (IBIS) [25] and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) [26]. Women in the first high-risk group (≥1.7%) are typically followed with annual screening mammography, whereas women with a >20% lifetime risk of breast cancer are recommended to have annual mammography and be considered for annual screening breast MRI [23]. The issue with using these risk models in women with BBD is that these models were developed in average risk women. In addition, only two of these models (Gail and IBIS) include presence of atypical hyperplasia. Although these models are used to determine screening and prevention decisions, they may not accurately reflect breast cancer risk in women with BBD.

This chapter reviews and synthesizes existing literature on progression to breast cancer after diagnosis with BBD, focusing on those studies that examine interaction between BBD and established breast cancer risk factors. Each chapter of this dissertation will develop on this premise, first establishing an association between mammographic density and BBD (Chapter 2), then examining interactions between BBD, family history, and other factors (Chapter 3). Despite the individual contributions of these three risk factors, little is known about how the three factors interact to affect risk. Part of establishing the link between BBD and subsequent risk is the ability to have risk models that are validated within high-risk women with a history of BBD and using this information to inform clinical management (Chapter 4). The final part of this dissertation is validation of current risk assessment models in our BBD population; often times models do not include BBD or mammographic density, even though they are strong breast cancer risk factors.

1.2 Methods

1.2.1 Selection of articles

We selected articles through literature review to obtain articles on epidemiologic risk factors for breast cancer among women with BBD.

A. Articles assessing risk factors for progression to breast cancer

The focus of this review is cohort studies of women with a history of BBD published between 1944 and May 2014. Searches of electronic databases Scopus and OVID MEDLINE identified published peer-reviewed articles. Search terms for the risk search included: “benign breast disease”

or “benign proliferative breast disease” or “benign breast disorder” or “benign breast” and “risk” and “breast cancer”. We limited articles to studies published in English. In addition, in Scopus we removed review articles and limited results to peer-reviewed articles or conference papers. A search of citations from relevant papers yielded an additional 5 papers for review.

After removal of duplicates that overlapped between Scopus and OVID MEDLINE, we reviewed an initial set of 1,000 abstracts. Inclusion criteria for this review are cohort studies among women with BBD, and, specifically, cohort studies that evaluated effect modification between BBD and another risk factor. For this review, studies of only ductal carcinoma *in situ* and lobular carcinoma *in situ* are excluded. We excluded approximately 956 studies for reasons shown in the search schematic **Figure 1.2**. The final number of articles included in this review is 44 articles from 15 different cohorts.

1.2.2 Defining benign breast disease

BBD is a heterogeneous disease composed of many different types of breast abnormalities. For this review, BBD is reviewed as a combination of different abnormalities, and, where possible, categorized into three groups, as shown in **Table 1.1**: nonproliferative (NonPD), proliferative disease without atypia (PDWA), and atypical hyperplasia (AH). Black and Chabon is another schema used to classify BBD; this system focuses on the classifying the extent of duct atypia [27]. However, none of the cohort studies included in this review used these criteria. Atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) are often grouped together in studies of benign breast disease. In larger cohorts that were able to stratify by type of AH differences in breast cancer risk between the two groups will be highlighted.

1.3 Risk factors for progression to breast cancer

1.3.1 Cohort studies

Fifteen cohorts examined effect modification of BBD with other established breast cancer risk factors; these are presented in **Table 1.3**. The majority of these cohorts are large (i.e. >5,000 women in the cohort) [28-39], however three are smaller cohorts [40-42]. Cohorts ranged in follow-up from 3.6 years to 21 years of follow-up [28, 29, 31-42], in six cohorts with follow-up time was less than 10 years [31-35, 37, 39]. Four of the cohorts were constructed from screening populations [28, 31, 35, 36]; within

these studies all women were being actively screened for breast cancer. Five cohorts are clinic-based cohorts [29, 30, 40-42] and six used existing cohorts [32-34, 36, 38, 39]. Exclusion criteria were similar across cohorts; most exclude diagnosis of breast cancer prior to baseline or at biopsy; a few had additional restrictions of no diagnosis of any prior cancer or diagnosis of breast cancer within 6 months of baseline. Five of the cohorts were specifically created with examination of BBD and breast cancer as one of their primary aims [28-30, 40, 41]. Most of the cohorts (7 cohorts [28-31, 33, 37, 42]) used Dupont and Page criteria to classify BBD diagnoses; six cohorts used self-reported BBD from baseline questionnaires [31, 32, 34, 36, 38, 39]; three cohorts used a unique form of classifying BBD [35, 40, 41]. Two of these cohorts were conducted prior to the publication of the Dupont and Page criteria [40, 41]. The third chose to separate out atypical hyperplasia, cytologic atypia, and lobular carcinoma in situ due to their established elevated breast cancer risk; all other histologic diagnoses were classified as low-risk [35]. This study [35], along with the self-reported studies [31, 32, 34, 36, 38, 39] did not have 100% prevalence of BBD. Four of the cohorts followed women up for both invasive breast cancer and carcinoma *in situ* [28, 35, 39, 40, 42], whereas all the other cohorts used invasive breast cancer as the outcome [29-34, 36, 38]. Person-time and incidence rate of breast cancer were often not stated in these cohorts, mainly due to the fact that BBD was not the primary aim of the study; for others, though, it is unclear why this information was not provided.

Histology has been established as the main predictor of risk of progression to breast cancer after diagnosis with BBD (reviewed in [43, 44]). The association between histology, specifically histologic type and breast cancer risk, was assessed in all but five cohorts [32, 34, 36, 38, 39]. In **Table 1.4**, breast cancer risk is shown by histology for each cohort to provide estimates of the main effect of the association between BBD and breast cancer. In a few of the earlier cohorts, all types of BBD were combined and compared to the risk in population-based cancer registries [11, 45-48]. Overall, risk of breast cancer in women with BBD is approximately 2-fold higher than population-based estimates for expected number of breast cancer cases [45, 46]. When stratifying based on BBD subtype, most studies have shown a 3 to 4-fold increase in breast cancer risk among women diagnosed with atypical hyperplasia (AH) [11, 47, 48], approximately 1.4 to 2-fold increase in risk among women with proliferative disease without atypia (PDWA) [11, 47, 48], and a null to 1.5-fold increase risk in nonproliferative disease (NonPD) as compared

to population-based estimates [11, 47, 48]. Variations in these estimates may be due to the lack of adjustment for any confounders in these studies. When the comparison group became women with NonPD the risk of breast cancer increased for both AH and PDWA in the one study that did not adjust for other confounders [47]. Overall, compared to women with NonPD, women with AH have a 2 to 5-fold increase in risk of breast cancer [28, 37, 49-51] and women with PDWA have a 1.2 to 2-fold increased risk of breast cancer [28, 37, 49-51].

1.3.2 Effect modification of BBD by breast cancer risk factors on breast cancer risk

A. Histologic characteristics

One study, not using the Dupont and Page criteria, reported stratum-specific risks for breast cancer by BBD, this study actually found slightly higher (2.4 No BBD vs. 2.0 BBD) risk of breast cancer in women with gross cystic disease and no BBD diagnosis (**Table 1.5**) [40]. This finding is not surprising given that these relative risks were calculated compared to expected rates relative to incidence rates from the state of Connecticut tumor registry, which only accounts for age and calendar year. Epidemiologic studies have also focused on additional histologic characteristics of BBD that may help further stratify risk beyond the Dupont and Page criteria [40]. The interaction between calcifications and BBD was examined by three studies; one study used the Third National Cancer Survey (TNCS) as the referent population [46], another used women with NonPD without calcifications as the referent group [52], and the third study examined results using both of these referent groups [10]. Compared to the TNCS, women with AH or PDWA and calcifications had a greater risk than women with AH or PDWA without calcifications [10, 46]. Using a common referent group, NonPD without calcifications, the cohort study showed evidence of effect modification of BBD by calcifications [10], however, a nested case-control study showed no evidence of effect modification [52]. The nested case-control study was also the only study to adjust for other risk factors, such as age at biopsy, year of biopsy, follow-up time, and study center.

In some cohorts, the presence of radial scar [29, 33, 48, 53], columnar cell lesions [54, 55], cysts [52], and sclerosing adenosis [56] were examined in addition to the focus of AH, PDWA, or NonPD (**Table 1.5**). With both radial scar and columnar cell lesions, the addition of these breast lesions increases risk in both women with PDWA or AH. Radial scar studies further showed having

more than one scar or a scar 4 mm or greater in size with AH has an 8-fold higher risk of breast cancer then NonPD without radial scar [53]. Including cysts and sclerosing adenosis with the diagnosis of AH or PDWA had no difference in risks. A study examining multiplicity further supports these data; women with AH and more than one other lesion with proliferative disease had 4-fold higher risk as compared to women with NonPD and no multiplicity [42]. However, all of these studies found a non-significant multiplicative interaction between these histologic characteristics and Dupont and Page criteria. Involution is the regression of lobules as women age and is another characteristic of histologic changes. One study examined the interaction between involution and Dupont and Page criteria and found a significant interaction between the two risk factors (p=0.003) [57]. However, breast cancer risk was greater in women with AH or PDWA without involution as compared to expected events based on Iowa Surveillance Epidemiology and End Results (SEER) data [57].

Tumor markers for breast cancer have also been examined for their association with BBD and subsequent breast cancer risk. One cohort investigated the multiplicative interaction between AH, divided by atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH), and found evidence of an interaction only for women with high intensity staining and ADH as compared to expected standardized incidence rates from Iowa SEER [58]. Another nested case-control study, within the same cohort, examined HER2/*neu* gene overexpression and BBD [59]. They did not report on multiplicative interaction, but they found that women with PDWA and AH had a 7-fold higher breast cancer risk compared to women with NonPD and no HER2/*neu* gene overexpression [59]. However, confidence intervals were wide and estimates were based on only 7 women who were both HER2/*neu* overexpressed and had PDWA or AH.

B. Age at biopsy, time since biopsy, and age at breast cancer

Age is an important risk factor for cancer and is associated with both age at BBD biopsy and age at breast cancer diagnosis. Only one study found evidence of multiplicative interaction between age at biopsy and histologic classification of BBD (p=0.05; **Table 1.6**) [30]. Risk of breast cancer was actually greatest among women who were diagnosed with BBD between ages 45-55 or <45 as compared to expected rates based on Iowa SEER [30]. Another cohort had similar results showing greatest risk in women diagnosed with AH at <50 years of age, however the multiplicative interaction

was non-significant (p=0.12) [28]. Only one other study evaluated the joint effects of age at biopsy and histologic diagnosis and found no association [10].

Risk for breast cancer based on histologic classification and time since biopsy is mixed; two studies show risk is greatest within 15 years of BBD biopsy [28, 60] and two others showing risk is greatest at 10 years or more after BBD biopsy (**Table 1.6**) [51, 61]. Interestingly, three of these studies are nested case-control studies within the Nurse's Health Study [51, 60, 61]. Differences in these results may be due to one study matching on year of birth and year of BBD biopsy [51] and/or differences in what other factors were adjusted for in final models. None of these studies found a significant multiplicative interaction between time since biopsy and histologic classification. Only the most recent nested case-control study found a significant multiplicative interaction between these two risk factors (p<0.01) [28].

Two studies examined the association between age at breast cancer diagnosis and histologic classification; both reported stratum specific estimations (**Table 1.6**). However, one showed risk highest in women diagnosed less than 55 years of age with previous diagnosis of AH [60] and the other showed an almost 18-fold increased risk of breast cancer in women 55 years of age or older with previous diagnosis of AH [62]. Both were compared to NonPD within the same age category. These differences could be due to the design (nested case-control versus prospective cohort) or adjustment factors (no adjustments versus adjustment for year of biopsy, year of birth, family history, age at menarche, age at first birth and parity).

C. Reproductive factors

In women with BBD, only one study examined multiplicative interaction between age at first birth and BBD (**Table 1.7**) [47]. This study found a non-significant multiplicative interaction, although risk estimates show that regardless of age at first birth, women with a higher histologic classification have a greater risk of breast cancer compared to population-based estimates and women with NonPD who were 20 years old or younger at first birth [47]. No other cohort had examined the association between age at first birth. The multiplicative interaction between breast size and BBD was also examined in this study. Similarly, the authors found that risk were higher in women who had both larger breasts and PDWA. However, the interaction was non-significant [47].

The only other reproductive factor examined in cohort studies for interaction with BBD is menopausal status. Several studies have examined BBD by menopausal status; all were nested case-control studies [28, 51, 52, 60, 61, 63] and four were all part of the same cohort [51, 60, 61, 63]. Most studies examined the stratum specific estimates of menopausal status by BBD [28, 51, 60, 61, 63]. Only one study used a common referent: NonPD and premenopausal. In this study, they found that women who were diagnosed with AH and postmenopausal had 12-fold higher risk of breast cancer [52]. They did not report whether the multiplicative interaction was significant or not. The other cohorts, (with two exceptions [61, 63], based on stratum specific estimates,) found that risk was highest in premenopausal women with AH as compared to premenopausal women with NonPD. Regardless of menopausal status, women with PDWA had similar risk estimates [28, 51, 60]. In addition, only one of these studies found a significant multiplicative interaction [28], however, no adjustment for other confounders was made. None of these studies assessed additive interaction, and two reproductive factors need to be examined, (specifically, age at menarche and breast feeding, both of which have different associations for BBD and breast cancer).

D. Hormonal factors

Exogenous estrogens, hormone replacement therapy (HRT), and oral contraceptive use, are examined in seven studies (**Table 1.8**) [31, 32, 41, 63-66]. Only one study examined exogenous estrogens, defined as use of estrogens or other hormone pills or injections at any time. In this study they did not state if there was a significant multiplicative interaction [64]. However, they found that exogenous estrogen combined with BBD reduced the risk of breast cancer [64]. Three studies examined the association between HRT use using a common referent group [41, 63, 65]. Most used NonPD with no HRT use as the referent, however, one used NonPD with HRT use [65]. Two studies found that HRT use did not increase risk of breast cancer among women with BBD [63, 65]. However, one study found use of estrogen after diagnosis with PDWA along with calcifications suggested increased risk on a multiplicative scale [41], though none of these studies reported the multiplicative interaction between these two factors. Two other studies examined the stratum-specific estimates of HRT use by BBD status, one a cohort study [32] and the other a nested case-control [31]. The authors of the nested case-control study found evidence of a multiplicative interaction

between BBD and duration of HRT use [31]. Similar to the cohort study that examined estrogen use and calcifications [41], 10 or more years of HRT use after diagnosis with BBD increased breast cancer risk [31].

Only one study examined the multiplicative interaction between oral contraceptive use and BBD, using stratum specific estimates for pre- and postmenopausal women [67]. This study found no multiplicative interactions between menopausal status and BBD use for either premenopausal or postmenopausal women [67]. The paucity of and mixed results reported suggests the need for additional cohort studies examining interactions between hormonal factors and BBD.

E. Nutritional and lifestyle factors

Surprisingly, only two nutritional and lifestyle factors have been examined for multiplicative interaction with BBD: alcohol and caffeine consumption (**Table 1.9**). Three studies have examined alcohol consumption [34, 38, 68]; of these, one study reported no association between alcohol consumption, BBD, and breast cancer risk [68]. Conversely, the two other studies found that a history of BBD increased the association between alcohol consumption and breast cancer risk. However, these increased effect sizes were not very strong [34, 38]. All of these studies reported non-significant multiplicative interactions. Given the fact that adolescent alcohol use has been found to be a strong predictor of BBD [69], the effects of alcohol consumption on BBD may only be important early in life and after BBD diagnosis alcohol may not have as large of an effect.

Caffeine consumption was only examined in two studies. One reported a non-significant multiplicative interaction ($p=0.12$), but did not provide either stratum-specific or common referent risk estimates (**Table 1.9**) [39]. Therefore, we only have one study to evaluate the interaction between caffeine consumption and BBD on breast cancer risk [36]. Using data from the Nurse's Health Study (NHS), Ishitani *et al.* found slight (approximately 20-30%) increases in breast cancer risk among women with a history of BBD [36]. They found significant multiplicative interactions between caffeine ($p=0.05$) and coffee ($p=0.05$) consumption and history of BBD [36]. A number of nutritional and lifestyle factors remain to be investigated for potential effect modification with BBD to increase or decrease breast cancer risk.

F. Family history

A combination of BBD diagnosis and first-degree family history of breast cancer appears to coincide with increased risk of subsequent breast cancer. In women with all BBD types combined, there are conflicting results as to whether or not a positive first-degree family history increases risk, one study showed a 5-fold increased risk with having two or more biopsies [66]; others show no difference in effect estimates between women with BBD and women without BBD with a family history [70, 71]. These differences however, may be due to differences in study design, with two cohort studies finding no differences [70, 71] and one nested case-control study finding the positive association between family history and BBD and breast cancer risk [66].

Five different cohorts stratified family history by Dupont and Page criteria (**Table 1.10**) [10, 28, 30, 52, 60]. Four of these found increasing risk of breast cancer with increasing severity of disease, specifically, the greatest risk was in women with AH and a positive family history as compared to women with NonPD and no family history [10, 30, 52, 60]. A similar increase with family history in addition to histology was also seen for those women with PDWA as compared to NonPD, however, risk estimates were not as strong. There may be multiplicative interaction between BBD histology and family history, however, these studies either did not report a p-value for interaction [10, 52] or reported a non-significant p-value [30, 60, 72]. One study that did not agree was the Kabat *et al.* study, likely due to the fact that they had to combine PDWA and AH due to the small number of women in the AH category [28]. Additional studies with a larger sample size of women with AH are needed to help further explore the interaction between BBD subtype and family history.

G. Mammographic density

An intermediate marker of breast cancer, mammographic density, may also interact with BBD to increase breast cancer risk. Four studies, three cohort [35, 37, 73] and one nested case-control [50], have examined multiplicative interaction between mammographic density and BBD. However, each used different methods of measuring mammographic density. Wolfe parenchymal patterns were used in one cohort and found that the combined effects of lobular involution and mammographic density increased breast cancer risk in women with BBD (p=0.006) [73]. Another cohort study compared the combination of fatty tissue and scattered breast densities to dense tissue, but it is unclear if they used any standard mammographic measurement such as Breast Imaging Reporting

and Data System (BIRADS) [35]. No multiplicative interaction was reported, but the authors concluded that BBD may be modified by breast density based on the increased risk of breast cancer in women with low-risk BBD and dense breasts [35]. In the last two studies, one used BIRADS categories [37] and the other used a computerized planimeter to calculate mammographic density, categorizing density into <50%, 50-74%, and ≥75% [50]. In the cohort study, a non-significant multiplicative interaction of p=0.28 was found, however, there was a trend showing increasing breast cancer risk with increasing severity of subtype of BBD and increasing density [37]. In the nested case-control study there was multiplicative interaction (p=0.006), yet it was in the opposite direction than expected [50]. The authors concluded that risk was no greater for women with both AH and high breast density [50]. Additional studies using a consistent measurement for mammographic density are needed. Also, if both factors are associated with an increased risk for breast cancer, then there should be interaction on the additive scale.

1.3.3 Methodologic issues for interpreting existing studies

A number of cohort studies have been conducted and have examined interactions between BBD and established breast cancer risk factors and subsequent breast cancer risk. However, besides the fact that so few breast cancer risk factors have been examined in relation to BBD, there are some methodological issues that should be considered in future studies of BBD and subsequent breast cancer risk.

Type of reference population: First, studies of subsequent risk of breast cancer have compared women with BBD to two different types of control populations. Studies either use population-based estimates of breast cancer risk, (comparing observed number of breast cancers to the expected number of breast cancers,) or they use women with BBD in the cohort who did not develop breast cancer, (the non-cases,) to assess subsequent risk comparing the risk in PDWA and AH to women with NonPD. The use of different comparison groups has resulted in different effect measures. Age at first birth is an excellent example of this, within the same study population. When having a first child after 20 years of age and a history of AH was compared to State of Connecticut Tumor Registry data, risk estimates were 4.5 [47], whereas, when an internal control group of NonPD and first birth less than or equal to 20 years was used, the risk estimate became 10-fold higher in the AH and first birth after 20 years [47]. In studies

using population-based estimates, differences may be due to the characteristics of these populations. For example, TNCS is from the San Francisco and Oakland metropolitan area, whereas the SEER data came from Iowa. These two different geographical locations could also have different underlying risk factors. In studies with internal controls, differences could be due to the prevalence of BBD and distribution of the subtypes of BBD in each cohort. One study that found no multiplicative interaction between BBD and mammographic density had only 3.6% prevalence of BBD in the cohort [35]. Effect estimates will differ based on the prevalence of the modifier. In addition, prevalence of AH ranged from 3%-13%. Results from these cohort studies suggest that an internal control is better to limit uncontrolled confounding. None of these studies assessed multiplicative interactions using both an internal control of non-BBD woman and NonPD without the modifying risk factor. Future studies should assess these interactions using both of these referent groups to see how the results may differ.

Classification of BBD: Second, these studies have inconsistently classified BBD. Almost half of the cohorts have been non-specific in classifying BBD and grouping them all together. However, studies using Dupont and Page Criteria for classification of BBD clearly show that risk varies by histologic type and that AH is 3-5 fold higher than NonPD. Relative risks were lower in studies that did not use Dupont and Page; for example, in assessing alcohol consumption and 1st degree family history, the effect sizes were much lower in studies that just compared within stratum of BBD. These studies provide important information on the association between BBD and breast cancer risk, but the potential for misclassification limits the ability to draw conclusions. BBD are a group of heterogeneous diseases that need to be classified by the extent of disease and atypia in order to better understand the risk associated with them.

Effect modification: Third, while all of these cohorts examined effect modification of BBD with other breast cancer risk factors, a number of established breast cancer risk factors have not been assessed for interaction. Age at menarche, breastfeeding, obesity, physical activity level, and others were not assessed in any of these studies. Each of the factors listed also have different strengths of association for the risk of breast cancer and for the risk of BBD. Therefore, if BBD is not on the pathway to disease for these factors, than potentially these factors interact with BBD to increase breast cancer risk. We are interested in how risk changes in women with both BBD and the risk factor of interest. To assess this, the interaction term must be included in the statistical models. Furthermore, none of these

studies examined additive interactions; all of the factors examined in these cohorts increased risk of breast cancer. If both BBD and the other risk factors increase breast cancer and there is no multiplicative interaction, then there must be additive interaction and this needs to be assessed.

Mammographic density: To date only four studies have examined the association between mammographic density, BBD, and breast cancer risk. Results were mixed with two finding multiplicative interaction [50, 73] and one other not [37]. The major issue with these studies is that they all defined mammographic density differently, either using Wolfe criteria, BIRADS, or computerized planimeter. It is not surprising that differing ways of measuring mammographic density would result in misclassification of exposure. Computer-assisted methods of measuring mammographic density, such as Cumulus [74], have become gold standard. Misclassification potentially explains the differences between studies. Additional studies using validated computerized methods in larger populations are needed to further explore the association between mammographic density and BBD.

1.4 Risk assessment models in women with BBD

A number of breast cancer risk models have been developed to predict a woman's risk of breast cancer (reviewed in [75]). The major breast cancer risk models include Gail model or Breast Cancer Risk Assessment Tool [24], BOADICEA [26], and IBIS [25]. All of these models were developed in average-risk women. The Gail model was developed from the Breast Cancer Detection and Demonstration Project [24]. The Gail model incorporates current age, age at menarche, age at first live birth, race, first-degree family history, BRCA1/2 mutation status, number of breast biopsies, and atypical hyperplasia [24]. The IBIS model incorporates these factors, except number of biopsies. In addition, it includes other factors, such as menopausal status, HRT use, height/weight, and personal history of hyperplasia, LCIS, and ovarian cancer [25]. The IBIS model improved upon the Gail model by also including extensive family history data [25]. The IBIS model calculated risk of developing breast cancer using incidence rates from the general United Kingdom population. BOADICEA is a risk model that used a combination of a population-based series of breast cancer cases and multiple-case families, incidence rates were constrained to agree with population incidence rates for England and Wales. BOADICEA is another risk prediction model that takes into account specific data from relatives [26, 76]. However, it does not include any of the reproductive characteristics in the other two models, nor does it include breast biopsies,

hyperplasia or atypical hyperplasia.

Clinically these models are used to help clinicians assess individual risks as to provide appropriate recommendations regarding prevention. In order to provide accurate individualized prevention, these models need to accurately reflect a woman's risk of breast cancer. These models are often used to make screening and chemopreventive decisions [23]. However, if these models have poor discriminatory accuracy this hinders decision making and appropriate screening.

These models have been validated in a number of populations, such as high-risk women, screening populations, and existing cohorts. To our knowledge, only two of these models have been validated in a population with atypical hyperplasia: Gail model and IBIS [77, 78]. Both of these were conducted in the same Mayo Benign Breast Disease (BBD) Cohort, as shown in **Table 1.3**, which is a clinic-based study. The authors found that the Gail model significantly underestimated and had poor discrimination of breast cancer risk in women with atypical hyperplasia [77], whereas the IBIS model overestimated the risk of breast cancer in women with atypia with poor concordance [78]. A limitation of these studies is incomplete family history data in many of the women, restricting calculation of accurate estimates in the IBIS model. In addition, the biopsies on these women occurred between 1967 and 1991, primarily before widespread mammographic screening, as well as improvements in biopsy procedures. These studies were limited by the fact that they only included data from open biopsies. Finally, to our knowledge, no study has examined these models in women with all types of BBD.

1.5 Summary

Increased detection of BBD through screening mammograms has led to increases in the number of women diagnosed with precursor lesions. Currently, there is no accurate way to determine which of these lesions will progress to breast cancer. Establishing BBD as precursor lesions will provide a platform to better understand breast carcinogenesis. Previous epidemiologic studies have failed to comprehensively evaluate a range of important risk factors and only a few of the cohorts had comprehensive questionnaires. Methodologic issues in prior studies, inconsistent in their use of comparison group, lack of stratification of risk by histologic type, and no evaluation of effect modification make it difficult to interpret associations between BBD and subsequent breast cancer risk. Large prospective cohorts with more epidemiologic data with an internal reference group using a uniform

classification scheme are needed.

Atypical hyperplasia has consistently been found to have a higher risk of invasive breast cancer compared to nonproliferative diseases [11, 47, 48]. However, studies stratifying by BBD type are lacking, and little is known about established breast cancer risk factors that can predict, within histology, which women will progress. Knowledge of potentially modifiable risk factors in women with BBD can help to tailor clinical and lifestyle interventions for the prevention of breast cancer. Lack of standardization of BBD has hindered the ability of studies to examine risk by type of BBD. In addition, few studies have validated risk assessment models in these women. Clinical decisions made based on these models can affect the screening and prevention of these women and impact their breast cancer risk.

This dissertation research will take the next steps to understand how breast cancer risk factors interact to affect risk. This research has been divided into three aims. First, in Chapter 2, we will use a longitudinal birth cohort to examine the association between BBD and mammographic density. Next, in Chapter 3, using the Woman At Risk (WAR) high-risk cohort, we will examine interactions between BBD and reproductive, hormonal, and lifestyle factors. Finally, Chapter 4 will address current breast cancer risk assessment models, evaluating calibration and discrimination in a high-risk population of women with BBD. This dissertation aims to provide support for interaction between BBD, family history and mammographic density, and how this information can be used to improve risk assessment and clinical management of women with BBD.

Figure 1.1. Algorithm for abnormal mammograms and breast biopsies in the United States (Adapted from Esserman LJ, et al., [3])

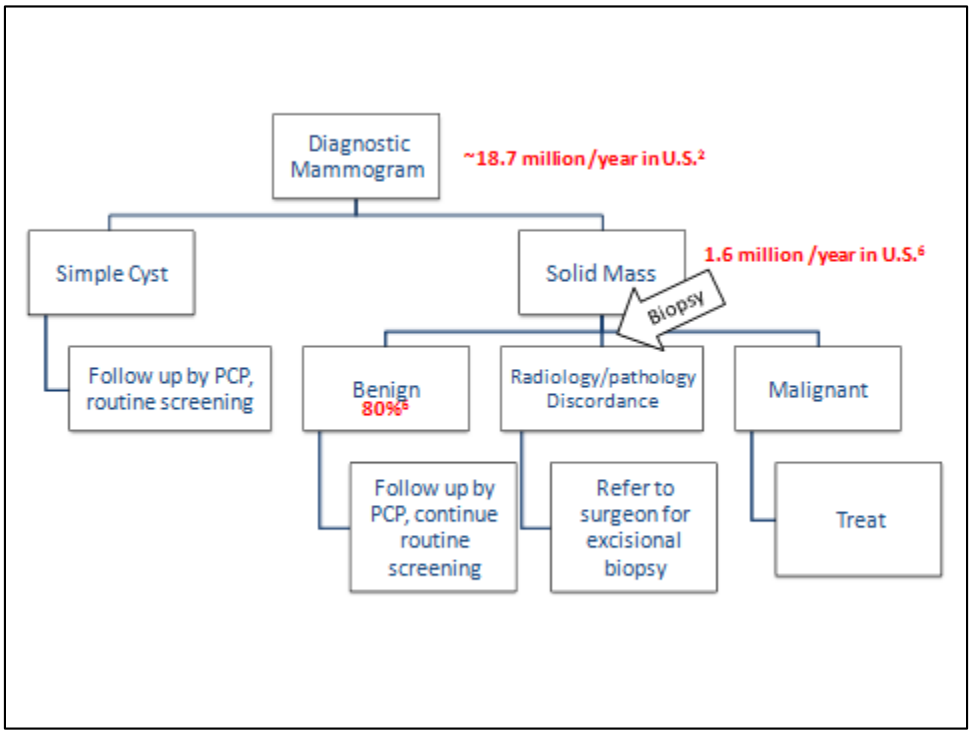

Figure 1.2. Search and article selection for review of BBD cohorts assessing breast cancer risk

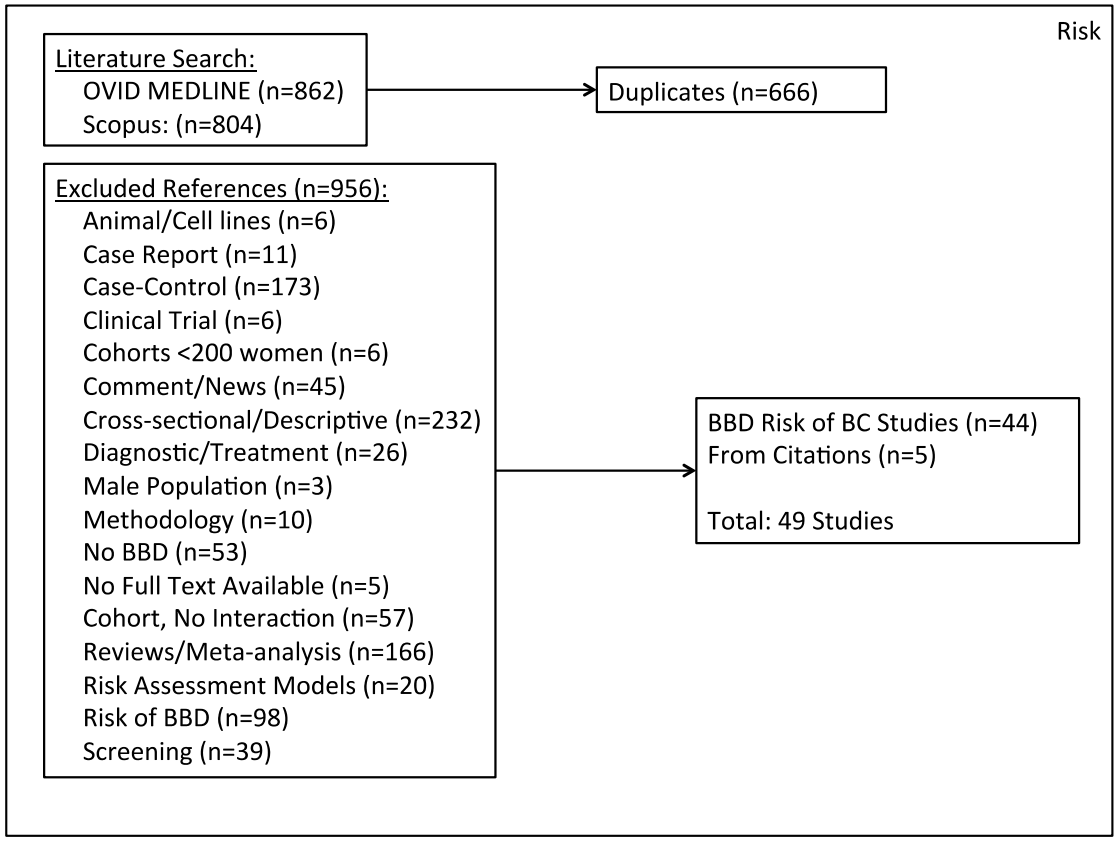

Table 1.1. Classification of benign breast disease

Non-proliferative
Fibroadenoma
Cysts
Epithelial-related calcification
Duct ectasia
Papillary apocrine change
Apocrine metaplasia
Mild hyperplasia
Fibrosis
Proliferative disease without atypia
Intraductal papilloma
Radial scar
Sclerosing adenosis
Moderate or florid ductal hyperplasia of the usual type
Epithelial hyperplasia without atypia
Columnar cell hyperplasia without atypia
Complex fibroadenoma without atypia
Atypical hyperplasia
Atypical ductal hyperplasia
Atypical lobular hyperplasia
Atypical columnar hyperplasia
Complex fibroadenoma with atypia
Adapted from Dupont et al. [10], London et al. [60], and Kabat et al. [28].

Table 1.2. Strength of association between risk factors for breast cancer as compared to risk factors for BBD

Risk Factor	Breast Cancer[a]	BBD[b]
Reproductive Factors		
Age at menarche	1.1-1.4	Null
Nulliparity	1.1-1.4	0.3, Null
Age at first birth	1.5-2.9	1.8-3, Null
Breastfeeding	0.7-0.8	Null
Age at menopause	1.1-1.4	4.0
Hormonal Factors		
Oral Contraceptive use	1.1-1.4	0.35-0.68, Null
Estrogen replacement	1.1-1.4	1.70, Null
Nutritional/Lifestyle Factors		
Obesity (postmenopausal)	1.1-1.4	0.27-0.9, 1.1-1.3
Adult weight gain	1.5-2.9	0.8
Alcohol consumption	1.1-1.4	0.2-0.46, Null
Height	1.1-1.4	Null
Physical Activity	0.7-0.8	Null
Monosaturated fat	0.7-0.8	2-3, Null
Other Factors		
Family History (1st degree)	1.5-2.9	1.3-4, Null

a. Reviewed in (Harris et al. [21])

b. Reviewed in (Silvera et al. [22])

Table 1.3. Cohorts investigating benign breast disease, interactions with other risk factors, and breast cancer risk by year of first enrollment

Cohort	Total cohort	Years	Average Follow-up	Person Time of Observation	Age at Enrollment	Breast Cancer	Incidence Rate	Breast Cancer Type	Type of Cohort	Exclusions	Controls	Follow-up Type	BBD Aims	BBD	Prevalence of BBD	Interactions
Dr. Haagensen Cohort	1,894	1930-1982	21 yrs	NS	43 yrs	157	NS	IBC/in situ	Clinic based	Slides unavailable for review, biopsy proven	CT general pop	Active	Primary	Biopsy, quasi D&P	100% (5.9% NP, 31.9% PDWA/AH 4.4% LN, 57.8% GCD)	Gross Cystic Disease
Fred Hutchinson Cancer Center	1,441	1940-1976	12.9 yrs	18,542	41 yrs	66	3.55 per 1,000	IBC	Clinic based	None	Non-breast cancer cases; Third NCS	Active	Primary	Biopsy, uncategorized	100% (42% epithelial hyperplasia or papillomatosis)	Calcifications, HRT Use
Kabat BBD Cohort	20,697	1946-2003	14.7 yrs	NS	49 yrs	665	NS	IBC/in situ	Screening based	Diagnosis of breast cancer prior to baseline or at time of biopsy	Non-breast cancer cases	Active	Primary	D&P	100% (36% NP, 61% PDWA, 3% AH)	Age at biopsy, 1st Degree Family History, Menopause, Time Since Biopsy

Nashville Breast Cohort (NBC)	16,946	1954-1992	17 yrs	NS	42 yrs	538	NS	IBC	Clinic based	Breast cancer prior to entry biopsy, carcinoma in situ at entry biopsy, both breasts removed within 6 months of entry, 2+ surgical procedures, age <15 yrs	Non-breast cancer cases; Third NCS	Active	Primary	D&P	100% (70% NP, 27% PDWA, 3% AH)	Age at biopsy, Age at breast cancer, Age at first birth, Breast size, Calcifications, Columnar cell lesions, Exogenous Estrogens, 1st Degree Family History, HRT use, Radial Scar
Mayo Benign Breast Disease Cohort	13,434	1967-2004	15.7 yrs	144,881	18-85 yrs	1,236	NS	IBC	Clinic based	Diagnosis of breast cancer or LCIS before or within 6 months of biopsy, mastectomy, or refusal of researc	Non-breast cancer cases; Iowa SEER	Active	Primary	D&P	100% (67% NP, 29% PDWA, 3% AH)	Age at biopsy, ER/PR status, Family History, HER2/neu, Involution, Mammographic Density, Radial Scar, Sclerosin

										h participation						g Adenosis
Breast Cancer Detection Demonstration Project (BCDDP)	61,433	1973-1995	8.3 yrs	NS	35-74 yrs	4,275	NS	IBC	Screening based	Diagnosis of breast cancer or in situ at, before or within 6 months of biopsy, incomplete pathology or risk factor information	Non-breast cancer cases; low a SEER	Active	Secondary	D&P; Self-reported	100% (44% NP, 49% PDWA, 7% AH)	Calcifications, Cysts, 1st Degree Family History, HRT use, Mammographic Density, Menopausal Status, Oral Contraceptives
Seventh-day Adventist	20,341	1974-1982	6 yrs	NS	55.4 yrs	215	NS	IBC	Existing cohort	None	Non-breast cancer cases	Active	Secondary	Self-reported (yes/no)	NS	HRT use

Nurses' Health Study	117,998	1976-1996	10 yrs	NS	30-55 yrs	2,389	NS	IBC	Existing cohort	Diagnosis of any prior cancer, slides available for review	Non-breast cancer cases; Self-reported	Active	Secondary	D&P	100% (36% NP, 51% PDWA, 13% AH)	Age at breast cancer, Alcohol use, Choline, Columnar Cell Lesions, 1st Degree Family History, HRT use, Menopausal Status, Radial Scar, Time Since Biopsy, Type of Lobules
Henry Ford BBD Cohort	4,537	1981-1994	10.7 yrs	44,700	≥18 yrs	202	452 per 100,000	IBC/in situ	Clinic based	Diagnosis of breast cancer prior to or within 6 months of biopsy, biopsy proven	Non-breast cancer cases	Active	Secondary	D&P	100% (28% NP, 56% PDWA, 6% AH)	Multiplicity

Netherlands Cohort Study	62,573	1986-1989	3.3 yrs	NS	55-69 yrs	553	NS	IBC	Existing cohort	Diagnosis of any prior cancer or in situ, or incident for other type of cancer	Non-breast cancer cases	Active	Secondary	Self-reported (yes/no)	7%	Alcohol use
New Mexico Mammography Project	215,283	1992-2000	6.8 yrs	NS	30-89 yrs	4,882	466 per 100,000 (based on low-risk BBD)	IBC/in situ	Screening based	Diagnosis of prior or within 90 days breast cancer or in situ, mastectomy, or breast implants	Non-breast cancer cases	Passive	Secondary	Biopsy, created categories	3.6% BBD	Mammographic Density
Women's Health Study	38,432	1992-2004	10 yrs	NS	54 yrs	1,188	NS	IBC	Existing cohort	Diagnosis of prior cancer, missing data on risk factors, implausible data, more than 70 items	Non-breast cancer cases	Active	Secondary	Self-reported (yes/no)	34%	Caffeine Consumption

										blank						
Breast Cancer Surveillance Consortium	41,459	1994-2009	6.1 yrs	NS	≥30 yrs	1,359	NS	IBC/in situ	Screening based	Diagnosis of breast cancer or DCIS prior or within 6 months of biopsy, LCIS on biopsy, one biopsy on pathology and density measurement	Non-breast cancer cases	Passive	Secondary	D&P	100% (70% NP, 25% PDWA, 5% AH)	Mammographic Density

California Teachers Study (CTS)	103,460	1995-2001	NS	NS	<85 yrs	1,742	NS	IBC (postmenopausal)	Existing cohort	Diagnosis of breast cancer prior to baseline or identified by California Cancer registry, non-residents of California at baseline, 85+ yrs at baseline, data missing or unreliable on breast cancer or risk factors	Non-breast cancer cases	Active	Secondary	Self-reported (yes/no)	28%	Alcohol use
NIH-AARP Diet and Health Study	198,404	1995-2006	5.2 yrs	1,906,185	50-71 yrs	9,915	NS	IBC/in situ	Existing cohort	Diagnosis of any prior cancer, nonepithelial breast tumors, missing	Non-breast cancer cases	Passive	Secondary	Self-reported (yes/no)	24%	Caffeine Consumption

or unreliable information on risk factors

IBC: Invasive Breast Cancer, NCS: National Cancer Survey, SEER: Surveillance Epidemiology and End Results, NP: Nonproliferative, PDWA: Proliferative disease without atypia, AH: Atypical Hyperplasia

Table 1.4. Comparison of benign breast disease cohorts and breast cancer risk by histology

Cohort	Histology vs. Population-based	Histology vs. Nonproliferative	Adjusted for
Dr. Haagensen Cohort	BBD vs State of Connecticut Tumor Registry: 2.1 (1.8-2.5) Proliferative disease vs. State of Connecticut Tumor Registry: 2.2 (1.9-2.6) Nonproliferative disease vs. State of Connecticut Tumor Registry: 1.6 (1.0-2.6)	N/A	None
Fred Hutchinson Cancer Center	BBD vs. Third National Cancer Survey: 2.16 (1.66-2.76)	N/A	None
Kabat BBD Cohort	N/A	AH: 5.27 (2.29-12.15) PDWA: 1.45 (1.10-1.90)	Age, age at BBD, age at menarche, age at first birth, number of pregnancies, menopausal status, family history
Nashville Breast Cohort (NBC)	AH vs. Third National Cancer Survey: 4.0 (2.8-5.8) PDWA vs. Third National Cancer Survey: 1.4 (1.2-1.8) NonPD vs. Third National Cancer Survey: 0.80 (0.57-1.1)	AH: 5.3 (3.1-8.8) PDWA: 1.9 (1.3-2.9)	None
Mayo Benign Breast Disease Cohort	AH vs. Iowa SEER: 3.75 (2.88-4.80) PDWA vs. Iowa SEER: 1.61 (1.42-1.82) NonPD vs. Iowa SEER: 1.16 (1.05-1.28)	AH: 3.69 (2.30-5.91) PDWA: 2.09 (1.51-2.89)	None (for histology vs. population-based) Age, BBD histology, BMI, parity, menopausal status, family history, parenchymal pattern, lobular

			involution
Breast Cancer Detection Demonstration Project (BCDDP)	AH vs. SEER: 3.0 (2.1-4.1) PDWA vs. SEER: 1.9 (1.5-2.4) NonPD vs. SEER: 1.5 (1.1-2.0)	AH: 2.1 (1.2-3.6) PDWA: 1.2 (0.8-1.8)	None (for histology vs. population-based) Age, race, breast density, family history, alcohol, nulliparity and age at first birth, education, weight, menopausal status, age at menopause, use of postmenopausal hormones
Seventh-day Adventist	N/A	N/A	N/A
Nurses' Health Study	N/A	AH: 3.4 (2.0-5.9) PDWA: 1.7 (1.2-2.6)	Age at diagnosis, year of BBD biopsy, family history, age at menarche, menopausal status, age at first birth, parity
Henry Ford BBD Cohort	N/A	AH: 3.75 (1.99-7.06) PDWA: 1.66 (1.13-2.42)	Age, race, fibroadenoma present
Netherlands Cohort Study	N/A	N/A	N/A
New Mexico Mammography Project	N/A	AH vs. Negative: 5.80 (3.29-10.24) Low-risk histologic diagnoses vs. Negative: 1.75 (1.53-2.00)	Breast density, ethnicity, family history

Women's Health Study	N/A	N/A	N/A
Breast Cancer Surveillance Consortium	N/A	AH: 2.45 (2.03-2.95) PDWA: 1.31 (1.16-1.48)	Age, race, registry
California Teachers Study (CTS)	N/A	N/A	N/A
NIH-AARP Diet and Health Study	N/A	N/A	N/A

SEER: Surveillance Epidemiology and End Results, NP: Nonproliferative, PDWA: Proliferative disease without atypia, AH: Atypical Hyperplasia

Table 1.5. Interaction between benign breast disease, histologic characteristics, and risk of breast cancer

Cohort	Study Design	Matching	Referent	Calcifications						Relative risk of entire population	Multiplicative Interaction	Adjustments
				AH w/ Calcifications	*AH w/o Calcifications*	*PDWA w/ Calcifications*	*PDWA w/o Calcifications*	*NonPD w/ Calcifications*	*NonPD w/o Calcifications*			
Fred Hutchinson Cancer Center (Hutchinson, 1980)	Prospective Cohort	None	Third National Cancer Survey	5.27 (2.72-9.21)	2.77 (1.43-4.84)	N/A	N/A	1.71 (0.35-5.00)	1.65 (0.88-2.81)	CAL vs. TNCS: 3.05 (1.8-4.71)	NS	None
Nashville Breast Cohort (NBC) (Dupont, 1985)	Retrospective Cohort	None	Third National Cancer Survey	N/A	N/A	2.4 (1.6-3.6)	1.8 (1.5-2.3)	0.80 (0.3-2.1)	0.90 (0.62-1.3)	NS	NS	None
Nashville Breast Cohort (NBC) (Dupont, 1985)	Retrospective Cohort	None	Nonproliferative w/o CAL	8.3 (3.5-19)	N/A	2.3 (1.2-4.3)	N/A	N/A	1.0	CAL vs. No CAL: 1.3 (0.87-2.0)	NS	None
Breast Cancer Detection	Nested Case-Control	1:2, age, year of	Nonproliferative w/o CAL	N/A	N/A	1.7 (0.89-3.2)	1.3 (0.71-2.4)	0.80 (0.29-2.2)	1.0	CAL vs. No CAL:	NS	Age at biopsy, year of

Demonstration Project (BCDDP) (Dupont, 1993)		bx, follow-up time								1.2 (0.75-2.1)		biopsy, study center
				Radial Scar (RS)								
				AH w/ RS	*AH w/o RS*	*PDWA w/ RS*	*PDWA w/o RS*	*NonPD w/ RS*	*NonPD w/o RS*			
Nurse's Health Study (NHS) (Jacobs, 1999)	Cohort	None	Nonproliferative w/o RS	5.3 (2.4-11.6)	3.7 (2.4-5.9)	2.7 (1.5-5.0)	1.5 (1.1-2.1)	N/A	1.0	NS	NS	Age, year of biopsy, follow-up cycle, age at menarche, family history, BMI, menopausal status, parity/age at first birth
Nurse's Health Study (NHS) (Jacobs, 1999)	Cohort	None	Nonproliferative w/o RS	1 scar: 3.5 (1.0-11.7) >1 scar: 8.4 (3.1-22.9)	3.8 (2.4-5.9)	1 scar: 2.5 (1.3-5.2) >1 scar: 4.3 (1.7-10.8)	1.5 (1.1-2.1)	N/A	1.0	NS	NS	Age, year of biopsy, follow-up interval
Nurse's Health Study (NHS) (Jacobs,	Cohort	None	Nonproliferative w/o RS	<4 mm: 2.0 (0.4-10.0) 4+ mm: 8.8 (3.5-	3.8 (2.4-5.9)	<4 mm: 2.4 (1.0-6.0) 4+ mm: 3.5 (1.7-	1.5 (1.1-2.1)	N/A	1.0	NS	NS	Age, year of biopsy, follow-up interval

1999)				22.0)		7.3)						
Nashville Breast Cohort (NBC) (Sanders, 2006)	Cohort	None	Nonproliferative w/o RS	≤10 yrs: 5.39 (2.6-11) >10 yrs: 2.14 (1.1-4.2)	≤10 yrs: 4.38 (2.5-7.7) >10 yrs: 1.88 (1.2-3.0)	≤10 yrs: 2.13 (1.3-3.5) >10 yrs: 1.14 (0.72-1.8)	≤10 yrs: 1.74 (1.2-2.5) >10 yrs: 1.47 (1.16-1.9)	≤10 yrs: 2.25 (0.5-9.2) >10 yrs: 1.11 (0.27-4.5)	1.0	RS vs. No RS, ≤10 yrs: 1.82 (1.2-2.7); >10 yrs: 1.11 (0.77-1.6)	NS	Age at biopsy, year biopsy, parity, age at first birth, age at menopause
Nashville Breast Cohort (NBC) (Sanders, 2006)	Cohort	None	Nonproliferative w/o RS (Age ≥50 yrs)	≤10 yrs: 4.66 (1.5-14) >10 yrs: 6.72 (2.5-18)	≤10 yrs: 3.39 (1.3-8.7) >10 yrs: 1.30 (0.39-4.3)	≤10 yrs: 2.03 (0.85-4.8) >10 yrs: 0.84 (0.25-2.8)	≤10 yrs: 1.09 (0.52-2.3) >10 yrs: 1.91 (1.1-3.4)	≤10 yrs: 3.50 (0.46-27) >10 yrs: 0	1.0	RS vs. No RS, ≤10 yrs: 1.82 (1.2-2.7); >10 yrs: 1.11 (0.77-1.6)	NS	Age at biopsy, year biopsy, parity, age at first birth, age at menopause
Mayo Benign Breast Disease Cohort (Berg, 2008)	Prospective Cohort	None	Iowa SEER	2.81 (1.29-5.35)	3.97 (2.99-5.19)	1.88 (1.36-2.53)	1.57 (1.37-1.79)	N/A	1.16 (1.05-1.28)	RS vs. Iowa SEER: 1.99 (1.49-2.61)	PWA p=0.29 AH p=0.33	Standardized incidence ratios - age and calendar year

Nurse's Health Study (NHS) (Aroner, 2013)	Nested Case-Control	None	Nonproliferative w/o RS	4.8 (2.6-8.9)	3.8 (2.7-5.3)	2.4 (1.5-3.9)	1.4 (1.0-1.8)	N/A	1.0	Radial Scar vs. No Radial Scar, adj: 2.0 (1.4-2.8)	p=0.38	Age, year of BBD dx, time since BBD dx, BMI at age 18, weight changes since age 18, family history of breast cancer, age at menarche, parity/age at first birth

				Columnar Cell Lesions (CCL)								
				AH w/ CCL	*AH w/o CCL*	*PDWA w/ CCL*	*PDWA w/o CCL*	*NonPD w/ CCL*	*NonPD w/o CCL*			
Nashville Breast Cohort (NBC) (Boulos, 2008)	Nested Case-Control	None	Nonproliferative w/o CCL	5.01 (2.7-9.1)	3.24 (1.6-6.5)	N/A	N/A	N/A	1.0	NS	NS	None
Nurse's Health Study (NHS) (Aroner, 2010)	Nested Case-Control	Year of birth, year of BBD diagnosis	Nonproliferative w/o CCL	4.20 (2.63-6.70)	4.04 (2.57-6.36)	1.63 (1.12-2.38)	1.38 (1.00-1.91)	1.24 (0.69-2.22)	1.0	CCL vs. No CCL, adj: 1.37 (1.06-1.76)	p=0.77	Age, year of BBD dx, time since BBD dx, BMI at age 18, weight

												changes since age 18, family history of breast cancer, postmenopausal hormone use, parity/age at first birth
				Cysts								
				AH w/ Cysts	*AH w/o Cysts*	*PDWA w/ Cysts*	*PDWA w/o Cysts*	*NonPD w/ Cysts*	*NonPD w/o Cysts*			
Breast Cancer Detection Demonstration Project (BCDDP) (Dupont, 1993)	Nested Case-Control	1:2, age, year of bx, follow-up time	Nonproliferative w/o Cysts	4.3 (0.89-21)	4.2 (1.5-12)	2.7 (1.1-6.5)	1.1 (0.61-1.9)	1.0 (0.29-3.4)	1.0	Cysts vs. No Cysts: 1.9 (0.99-3.5)	NS	Age at biopsy, year of biopsy, study center
				Sclerosing Adenosis (SA)								
				AH w/ SA	*AH w/o SA*	*PDWA w/ SA*	*PDWA w/o SA*	*NonPD w/ SA*	*NonPD w/o SA*			
Mayo Benign Breast Disease	Cohort	None	Iowa SEER	4.76 (3.82-5.86)	4.16 (3.18-5.36)	1.97 (1.76-2.21)	1.99 (1.70-2.31)	1.39 (1.06-1.79)	1.34 (1.23-1.45)	SA-: 1.52 (1.42-1.63)	NS	Age and calendar period

Cohort (Visscher, 2014)											SA+: 2.10 (1.91-2.30)		
				Gross Cystic Disease (GCD)									
				BBD	*No BBD*								
Haagensen Cohort (Bodian, 1992)	Prospective Cohort	None	State of Connecticut Tumor Registry	2.0	2.4						GCD vs. CT SEER, 1 aspiration: 1.9	NS	None
				Multiplicity									
				AH w/ Multiplicity (another PDWA lesion)	*AH w/o Multiplicity*	*PDWA w/ Multiplicity*	*PDWA w/o Multiplicity*	*NonPD w/ Multiplicity*	*NonPD w/o Multiplicity*				
Henry Ford BBD Cohort (Worsham, 2007)	Prospective Cohort	None	Nonproliferative w/o Multiplicity	4.90 (2.60-9.21)	6.26 (2.73-14.32)	2.87 (1.70-4.83)	2.06 (1.23-3.43)	1.79 (1.0-3.21)	1.0		Multiplicity vs. No Multiplicity: 3.22 (1.95-5.30)	NS	None
				Involution									
				AH w/ Involutio	*AH w/o Involutio*	*PDWA w/ Involutio*	*PDWA w/o Involutio*	*NonPD w/ Involutio*	*NonPD w/o Involutio*				

				n	*n*	*n*	*n*	*n*	*n*			
Mayo Benign Breast Disease Cohort (Milanese, 2006)	Prospective Cohort	None	Iowa SEER	Partial: 4.06 (3.0-5.3) Complete: 1.9 (0.4-3.8)	7.79 (3.6-14.8)	Partial: 1.62 (1.5-2.0) Complete: 1.11 (0.7-1.7)	2.94 (2.3-3.8)	Partial: 1.16 (1.0-1.4) Complete: 0.86 (0.6-1.1)	1.36 (1.1-1.8)	None: 1.88 (1.59-2.21) Partial: 1.47 (1.33-1.61) Complete: 0.91 (0.75-1.10)	p=0.003	None
				ER/PR Status on BBD Tissue								
				AH w/ ER/PR+	*AH w/o ER/PR+*	*PDWA w/ ER/PR+*	*PDWA w/o ER/PR+*	*NonPD w/ ER/PR+*	*NonPD w/o ER/PR+*			
Mayo Benign Breast Disease Cohort (Barr Fritcher, 2011)	Cohort	None	Iowa SEER	ADH, 80+ percent staining: 3.62 (1.51-8.71) ALH, 60-79 percent staining: 3.54 (1.14-11) ADH, 140+	ADH, 0-19 percent staining: 2.29 (0.32-16.3) ALH, 0-19 percent staining: 4.23 (2.34-7.64) ADH, 0-99	N/A	N/A	N/A	1.0	NS	ADH, percent staining: p=0.39 ALH, percent staining: p=0.80 ADH, intensity staining: p=0.01 ALH, intensity staining:	Age and calendar period

				intensity staining: 3.69 (1.76-7.74) ALH, 120-139 intensity staining: 3.45 (1.11-10.7)	intensity staining: 2.03 (0.29-14.4) ALH, 0-99 intensity staining: 3.93 (2.41-6.41)							p=0.71	
				HER2/neu on BBD Tissue									
				AH w/ HER2/neu+	*AH w/o HER2/neu+*	*PDWA w/ HER2/neu+*	*PDWA w/o HER2/neu+*	*NonPD w/ HER2/neu+*	*NonPD w/o HER2/neu+*				
Mayo Benign Breast Disease Cohort (Stark, 2000)	Nested Case-Control	Frequency: year of biopsy, age at biopsy, county of residence	Nonproliferative w/ not amplified	N/A	N/A	7.2 (0.9-60.8)[a]	1.0 (0.6-1.7)	1.4 (0.5-4.3)	1.0	HER2/ new amplified vs. Not amplified: 2.2 (0.9-5.8)	NS	None	

AH Atypical Hyperplasia; PDWA Proliferative Disease without Atypia; NonPD Nonproliferative; TNCS Third National Cancer Survey ; SEER Surveillance Epidemiology and End Results; NS: Not Stated

[a]Includes with and without atypia

Table 1.6. Interaction between benign breast disease, age at biopsy, time since biopsy, age at breast cancer, and risk of breast cancer

Cohort	Study Design	Matching	Referent	Age at Biopsy						Relative risk of entire population	Multiplicative Interaction	Adjustments
				AH w/ Age	*AH w/o Age*	*PDWA w/ Age*	*PDWA w/o Age*	*NonPD w/ Age*	*NonPD w/o Age*			
Nashville Breast Cohort (NBC) (Dupont, 1985)	Retrospective Cohort	None	Third National Cancer Survey	N/A	N/A	20-45: 1.9 (1.5-2.5) 46-55: 1.9 (1.3-2.6) >55: 2.2 (1.2-4.0)	N/A	20-45: 0.99 (0.66-1.5) 46-55: 0.83 (0.40-1.8) >55: 0.30 (0.04-2.2)	N/A	NS	NS	None
Nashville Breast Cohort (NBC)	Retrospective Cohort	None	Nonproliferative	N/A	N/A	20-45: 1.9 (1.2-3.2) 46-55: 1.4 (0.57-3.3) >55:	N/A	N/A	1.0	NS	NS	None

						5.6 (0.69-46)						
Mayo Benign Breast Disease Cohort (Hartman n, 2005)	Prospective Cohort	None	Iowa SEER	<45 yrs: 6.99 (3.0-15) 45-55 yrs: 5.02 (3.0-8.0) >55 yrs: 3.37 (2.1-4.2)	N/A	<45 yrs: 2.27 (1.8-3.0) 45-55 yrs: 2.00 (1.7-2.2) >55 yrs: 1.63 (1.4-1.8)	N/A	<45 yrs: 1.27 (1.1-1.8) 45-55 yrs: 1.23 (1.0-1.5) >55 yrs: 1.31 (1.2-1.6)	N/A	50-59 vs. <30: 1.56 (1.35-1.79)	p=0.05	None
Kabat BBD Cohort (Kabat, 2010)	Nested Case-Control	Age, age at BBD	Stratum specific: Nonproliferative, <50 vs. ≥50 yrs	<50 yrs: 7.54 (1.96-29.04) ≥50 yrs: 3.96 (1.26-12.40)	N/A	<50 yrs: 1.46 (1.03-2.08) ≥50 yrs: 1.55 (0.95-2.53)	N/A	1.0	N/A	NS	p=0.12	None

Time Since BBD Biopsy					
AH w/ Time	*AH w/o Time*	*PDWA w/ Time*	*PDWA w/o Time*	*NonPD w/ Time*	*NonPD w/o Time*

				Since Biopsy	*Since Biopsy*	*Since Biopsy*	*Since Biopsy*	*Since Biopsy*	*Since Biopsy*			
Nurse's Health Study (NHS) (London, 1992)	Nested Case-Control	None	Stratum specific: Nonproliferative, <10 yrs, 10-14 yrs, ≥15 yrs	<10 yrs: 4.2 (1.9-9.2) 10-14 yrs: 3.5 (0.9-12.7) ≥15 yrs: 4.1 (0.8-22)	N/A	<10 yrs: 1.5 (0.8-2.9) 10-14 yrs: 1.7 (0.6-4.8) ≥15 yrs: 1.5 (0.6-4.2)	N/A	1.0	N/A	NS	p=Non-significant	Year of biopsy, year of birth, family history, age at menarche, age at first birth, parity
Nurse's Health Study (NHS) (Marshall, 1997)	Nested Case-Control	1:4, Year of birth and year of BBD diagnosis	Stratum specific: Nonproliferative, ≤9 yrs or ≥10 yrs	≤9 yrs: 3.2 (1.6-6.4) ≥10 yrs: 3.6 (1.6-8.2)	N/A	≤9 yrs: 1.9 (1.0-3.4) ≥10 yrs: 1.6 (0.9-2.7)	N/A	1.0	N/A	NS	p=Non-significant	Age at diagnosis, year of BBD bx, family history of breast cancer, age at menarche, age at first birth, parity
Nurse's Health Study (NHS) (Collins, 2007)	Nested Case-Control	None	Stratum specific: Nonproliferative, <10 yrs vs. ≥10 yrs	<10 yrs: 3.31 (2.05-5.33) ≥10 yrs:	N/A	<10 yrs: 1.43 (0.98-2.08) ≥10 yrs:	N/A	1.0	N/A	NS	p=0.73	Age at breast cancer dx, year of BBD biopsy, years of follow-up, age at menarche,

				5.15 (2.81-9.43)		1.58 (1.07-2.35)						parity/age at first birth, BMI, menopausal status/type of menopause, recent/duration of HRT use
Kabat BBD Cohort (Kabat, 2010)	Nested Case-Control	Age, age at BBD	Stratum specific: Nonproliferative, <15 yrs vs. ≥15 yrs	<15 yrs: 9.71 (1.89-49.76) ≥15 yrs: 5.30 (0.84-33.42)	N/A	<15 yrs: 2.24 (1.21-4.16) ≥15 yrs: 1.46 (0.74-2.89)	N/A	1.0	N/A	NS	p<0.01	None
				Age at Breast Cancer								
				AH w/ Age	*AH w/o Age*	*PDWA w/ Age*	*PDWA w/o Age*	*NonPD w/ Age*	*NonPD w/o Age*			
Nurse's Health Study (NHS) (London, 1992)	Nested Case-Control	None	Nonproliferative, <55 or ≥55 yrs	<55 yrs: 4.5 (2.2-9.5) ≥55 yrs: 2.6 (0.9-	N/A	<55 yrs: 1.6 (0.9-2.9) ≥55 yrs: 1.6 (0.7-	N/A	1.0	N/A	NS	p=0.12	None

				7.8)		3.7)						
Nashville Breast Cohort (NBC) (Page, 2003)	Prospective Cohort	None	Nonproliferative, <55 or ≥55 yrs	<55 yrs: 6.5 (2.6-16) ≥55 yrs: 17.7 (2.3-140)	N/A	N/A	N/A	1.0	N/A	NS	NS	Year of biopsy, year of birth, family history, age at menarche, age at first birth, parity

AH Atypical Hyperplasia; PDWA Proliferative Disease without Atypia; NonPD Nonproliferative; TNCS Third National Cancer Survey ; SEER Surveillance Epidemiology and End Results; NS: Not Stated

Table 1.7. Interaction between benign breast disease, reproductive factors, and risk of breast cancer

Cohort	Study Design	Matching	Referent	Age at First Birth						Relative risk of entire population	Multiplicative Interaction	Adjustments
				AH w/ First Birth	*AH w/ Nulliparous*	*PDWA w/ First Birth*	*PDWA w/ Nulliparous*	*NonPD w/ First Birth*	*NonPD w/ Nulliparous*			
Nashville Breast Cohort (NBC) (Dupont, 1987)	Retrospective Cohort	None	State of Connecticut Tumor Registry	≤20 yrs: 1.6 (0.39-6.3) >20 yrs: 4.5 (2.7-7.3)	4.9 (2.7-8.9)	≤20 yrs: 0.95 (0.50-1.8) 21-29 yrs: 1.3 (0.90-1.9) ≥30 yrs: 1.5 (0.77-3.1)	1.4 (0.9-2.3)	≤20 yrs: 0.50 (0.19-1.3) 21-29 yrs: 0.71 (0.39-1.3) ≥30 yrs: 0.85 (0.27-2.6)	0.96 (0.50-1.8)	≤20 yrs: 0.80 (0.48-1.3) 21-29 yrs: 1.3 (1.0-1.7) ≥30 yrs: 1.4 (0.80-2.4) Nulliparous: 1.6 (1.1-1.2)	p=Non-significant	None
Nashville Breast Cohort (NBC) (Dupont, 1987)	Retrospective Cohort	None	Nonproliferative, ≤20 yrs	≥21 yrs: 10 (3.3-31)	11 (3.6-36)	21-29 yrs: 3.0 (1.0-8.5) ≥30 yrs: 3.5 (1.0-12)	3.3 (1.1-9.8)	≤20 yrs: 1.0 (ref) 21-29 yrs:1.5 ≥30 yrs: 1.9	N/A	≤20 yrs: 0.80 (0.48-1.3) 21-29 yrs: 1.3 (1.0-1.7) ≥30 yrs: 1.4 (0.80-2.4) Nulliparous: 1.6 (1.1-1.2)	p=Non-significant	None

				Breast Size								
				AH w/ Breast Size	*AH w/ Small Breasts*	*PDWA w/ Breast Size*	*PDWA w/Small Breasts*	*NonPD w/ Breast Size*	*NonPD w/ Small Breasts*			
Nashville Breast Cohort (NBC) (Dupont, 1987)	Retrospective Cohort	None	State of Connecticut Tumor Registry	N/A	N/A	Medium: 1.4 (1.1-1.9) Large: 2.1 (1.2-3.5)	1.2 (0.75-2.0)	Medium: 0.65 (0.38-1.1) Large: 0.80 (0.30-2.1)	0.75 (0.34-1.7)	Small: 1.0 (0.69-1.6) Medium: 1.1 (0.87-1.4) Large: 1.5 (0.96-2.4)	p=Non-significant	None
Nashville Breast Cohort (NBC) (Dupont, 1987)	Retrospective Cohort	None	Nonproliferative w/ Small	N/A	N/A	Medium: 2.1 (0.89-4.9) Large: 3.0 (1.2-7.9)	1.8	Medium: 0.90 Large: 1.2	1.0	Small: 1.0 (0.69-1.6) Medium: 1.1 (0.87-1.4) Large: 1.5 (0.96-2.4)	p=Non-significant	None
				Menopause								
				AH w/ Postmenopausal	*AH w/ Premenopausal*	*PDWA w/ Postmenopausal*	*PDWA w/ Premenopausal*	*NonPD w/ Postmenopausal*	*NonPD w/ Premenopausal*			
Nurse's Health Study (NHS) (London, 1992)	Nested Case-Control	Year of birth, year of BBD diagn	Stratum specific: Nonproliferative, pre or postmenopausal	2.3 (0.9-5.9)	5.9 (2.6-13.2)	1.5 (0.7-3.0)	1.7 (0.8-3.0)	1.0 (ref post)	1.0 (ref pre)	NS	p=0.20	Year of biopsy, year of birth, family history, age at menarch

		osis										e, age at first birth, parity
Breast Cancer Detection Demonstration Project (BCDDP) (Dupont, 1993)	Nested Case-Control	1:2, age, year of bx, follow-up time	Nonproliferative w/ menopause	12 (2.0-68)	3.3 (1.1-10)	1.6 (0.69-3.7)	1.4 (0.71-2.7)	1.3 (0.56-3.2)	1.0	Pre vs. Postmenopausal: 1.2 (0.67-2.2)	NS	Age at biopsy, year of biopsy, study center
Nurse's Health Study (NHS) (Marshall, 1997)	Nested Case-Control	1:4, Year of birth and year of BBD diagnosis	Stratum specific: Nonproliferative, pre or postmenopausal	2.6 (1.2-5.6)	4.6 (2.1-10.4)	1.8 (1.0-3.4)	1.8 (1.0-3.2)	1.0 (ref post)	1.0 (ref pre)	NS	p=0.59	Age at diagnosis, year of BBD bx, family history of breast cancer, age at menarche, age at first birth, parity
Nurse's Health Study (NHS) (Byrne, 2000)	Nested Case-Control	Year of birth, year of BBD diagnosis	Stratum specific: Nonproliferative, pre or postmenopausal	4.2 (1.4-12.5)	3.1 (1.4-6.6)	2.1 (0.8-5.9)	1.7 (1.0-2.9)	1.0 (ref post)	1.0 (ref pre)	NS	NS	Age, year of biopsy, follow-up cycle, age at menarche, parity, age at

												first birth, family history, menopause type, age at menopause, BMI
Nurse's Health Study (NHS) (Collins, 2007)	Nested Case-Control	None	Stratum specific: Nonproliferative, pre or postmenopausal	3.83 (1.72-8.52)	3.89 (2.47-6.12)	1.89 (0.94-3.77)	1.39 (1.02-1.90)	1.0 (ref post)	1.0 (ref pre)	NS	p=0.25	Age at breast cancer dx, year of BBD biopsy, years of follow-up, age at menarche, parity/age at first birth, BMI, menopausal status/type of menopause, recency/duration of HRT use
Kabat BBD Cohort	Nested Case-	Age, age at	Stratum specific: Nonprolif	2.54 (0.73-	5.84 (1.45-	1.97 (1.14-	1.18 (0.79-	1.0 (ref post)	1.0 (ref pre)	NS	p<0.01	None

(Kabat, 2010)	Control	BBD	erative, pre or postmen opausal	8.80)	23.58)	3.42)	1.75)

AH Atypical Hyperplasia; PDWA Proliferative Disease without Atypia; NonPD Nonproliferative; TNCS Third National Cancer Survey; SEER Surveillance Epidemiology and End Results; NS: Not Stated

Table 1.8. Interaction between benign breast disease, hormonal factors, and risk of breast cancer

Cohort	Study Design	Matching	Referent	Exogenous Estrogens (EE)						Relative risk of entire population	Multiplicative Interaction	Adjustments
				AH w/ EE	*AH w/o EE*	*PDWA w/ EE*	*PDWA w/o EE*	*NonPD w/ EE*	*NonPD w/o EE*			
Nashville Breast Cohort (NBC) (Dupont, 1989)	Retrospective Cohort	None	Nonproliferative w/EE	N/A	8.1 (3.7-17)	N/A	3.4 (1.9-6.2)	1.0	1.4 (0.66-3.1)	No EE vs. EE: 1.7 (1.2-2.6)	NS	Age at entry bx, length of folllow-up, first degree family history of breast cancer, proliferative disease, exogenous estrogen usage, age at first birth or nullipairty

HRT Use					
AH w/ HRT	*AH w/o HR*	*PDWA w/ HRT*	*PDWA w/o HRT*	*NonPD w/ HRT*	*NonPD w/o*

				T					*HRT*			
Fred Hutchinson Cancer Center (Thomas, 1982)	Prospective Cohort	None	Nonproliferative w/No Calcifications (CAL) & No Estrogen	N/A	N/A	No CAL/Estrogen: 2.49 CAL/Estrogen: 7.85	No CAL/No Estrogen: 1.48 CAL/No Estrogen: 3.20	No CAL/Estrogen: 1.68 CAL/No Estrogen: 0.97 CAL/Estrogen 1.63	1.0	Estrogen vs. No Estrogen: 1.84 (1.05-3.23)	NS	None
Nashville Breast Cohort (NBC) (Dupont, 1999)	Prospective Cohort	None	Nonproliferative w/ HRT Use	2.87 (1.3-6.3)	2.53 (1.0-6.3)	1.37 (0.88-2.1)	1.13 (0.69-1.9)	1.0	1.27 (0.89-1.8)	Yes vs. No: 0.91 (0.68-1.2)	NS	Age at bx, year of breast cancer diagnosis, pairty, length of follow-up
Nurse's Health Study (NHS) (Byrne, 2000)	Nested Case-Control	Year of birth, year of BBD diagnosis	Nonproliferative w/o duration of HRT use	<5 yrs: 3.7 (1.2-11.1) ≥5 yrs: 3.0 (0.9-9.5)	4.3 (1.8-9.8)	<5 yrs: 2.6 (1.2-5.4) ≥5 yrs: 1.5 (0.6-3.9)	1.7 (0.9-3.5)	<5 yrs: 1.1 (0.5-2.7) ≥5 yrs: 1.2 (0.4-3.2)	1.0	NS	NS	Age, year of biopsy, follow-up cycle, age at menarche, parity, age at first birth, family history, menopause type, age at menopaus

												e, BMI
Nurse's Health Study (NHS) (Byrne, 2000)	Nested Case-Control	Year of birth, year of BBD diagnosis	Nonproliferative w/o HRT use	Past use: 4.3 (1.4-12.9) Current use: 2.6 (0.8-8.0)	4.0 (1.7-9.5)	Past use: 2.1 (0.9-4.7) Current use: 1.9 (0.8-4.3)	1.6 (0.8-3.4)	Past use: 1.2 (0.4-3.1) Current use: 1.0 (0.4-2.5)	1.0	NS	NS	Age, year of biopsy, follow-up cycle, age at menarche, parity, age at first birth, family history, menopause type, age at menopause, BMI

				HRT Use				
				BBD	*No BBD*			
Breast Cancer Detection Demonstration Project (BCDDP) (Brinton, 1986)	Nested Case-Control	Center, race, age, time of entry, length of follow-up	Stratum specific: Nonuser; Among BBD hormone use before/after biopsy	<10 yrs: 1.23 10+ yrs: 1.50 Before, Ever vs. No HRT: 0.60 (0.4-0.9) Before, <10 vs. No HRT: 0.62 (0.4-1.1) Before, 10+ vs. No HRT: 0.62 (0.3-1.2) After, Ever vs. No HRT: 1.14 (0.8-1.6) After, <10 vs. No HRT: 0.93 (0.7-1.3) After, 10+ vs. No HRT: 3.01 (1.6-5.5)	<10 yrs: 0.96 10+ yrs: 0.85		<10 vs. Never: 1.03 (0.9-1.2) 10-14 vs. Never: 1.15 (0.9-1.4)	NS	Age, type of menopause, interval since oophorectomy
Seventh-day Adventist, California (Mills, 1989)	Cohort	None	Stratum specific: Past, Current, Ever vs. Never	Past vs. Never: 2.41 (0.86-6.76) Current vs. Never: 3.29 (1.10-9.88) Ever vs. Never: 2.69 (1.03-7.01)	Past vs. Never: 1.13 (0.69-1.84) Current vs. Never: 2.07 (1.25-3.44) Ever vs. Never: 1.50 (1.01-2.24)		Past vs. Never: 1.44 (0.95-2.17) Current vs. Never: 2.53 (1.62-3.98)	NS	Age

								Ever vs. Never 1.67 (1.17-2.39)	
				Oral Contraceptive (OC) Use					
				BBD	*No BBD*				
Breast Cancer Detection Demonstration Project (BCDDP) (Brinton, 1982)	Nested Case-Control	Center, race, age, time of entry, length of follow-up	Stratum specific: Ever vs. Never	Premenopausal: 1.24 (0.6-2.7) Postmenopausal: 0.93 (0.3-2.9)	Premenopausal: 1.11 (0.8-1.6) Postmenopausal: 1.05 (0.6-1.8)			Ever vs. Never, Pre: 1.11 (0.8-1.5) Ever vs. Never, Post: 1.02 (0.6-1.6) Ever vs. Never: 1.08 (0.8-1.4)	NS Age

AH Atypical Hyperplasia; PDWA Proliferative Disease without Atypia; NonPD Nonproliferative; TNCS Third National Cancer Survey; SEER Surveillance Epidemiology and End Results; NS: Not Stated

Table 1.9. Interaction between benign breast disease, nutritional and lifestyle factors, and risk of breast cancer

Cohort	Study Design	Matching	Referent	Alcohol Use						Relative risk of entire population	Multiplicative Interaction	Adjustments
				AH w/ Alcohol use	*AH w/ Nondrinkers*	*PDWA w/ Alcohol use*	*PDWA w/ Nondrinkers*	*NonPD w/ Alcohol use*	*NonPD w/ Nondrinkers*			
Nurse's Health Study (NHS) (Tamimi, 2005)	Nested Case-Control	Year of birth, year of BBD diagnosis	Nonproliferative w/ 0 g/day alcohol	<5 g/day: 6.48 (3.31-12.70) 5-15 g/day: 5.26 (2.30-12.04) ≥15 g/day: 3.46 (1.19-10.09)	0 g/day: 5.58 (2.74-11.38)	<5 g/day: 1.82 (1.05-3.16) 5-15 g/day: 2.40 (1.31-4.39) ≥15 g/day: 1.09 (0.45-2.62)	0 g/day: 1.99 (1.13-3.50)	<5 g/day: 1.42 (0.77-2.65) 5-15 g/day: 1.25 (0.60-2.60) ≥15 g/day: 1.67 (0.65-4.34)	1.0	>15 g/day vs. 0: 0.86 (0.50-1.46)	p=0.20	Age at diagnosis, year of BBD bx, follow-up interval, age at menarche, BMI, family history of breast cancer, parity/age at first birth, menopausal status/type of menopause, duration of HRT use
Nurse's Health Study (NHS) (Tamimi, 2005)	Nested Case-Control	Year of birth, year of BBD diagnosis	Stratum specific: 0 g/day	<5 g/day: 1.29 (0.60-2.78) 5-15 g/day: 1.02 (0.39-2.68) ≥15 g/day: 0.59 (0.19-1.89)	1.0	<5 g/day: 0.99 (0.62-1.56) 5-15 g/day: 1.14 (0.67-1.91) ≥15	1.0	<5 g/day: 1.46 (0.75-2.85) 5-15 g/day: 1.15 (0.53-2.53) ≥15	1.0	>15 g/day vs. 0: 0.86 (0.50-1.46)	p=0.20	Age at diagnosis, year of BBD bx, follow-up interval, age at menarche, BMI, family history of breast cancer, parity/age at

					g/day : 0.61 (0.26-1.41)	g/day : 1.90 (0.67-5.39)				first birth, menopausal status/type of menopause, duration of HRT use
				Alcohol Use						
				BBD	*No BBD*					
Netherlands Cohort Study (van den Brandt, 1995)	Case-Cohort	None	Stratum specific: g/day vs. Nondrinkers	Nondrinkers: 1.0 (ref) <15 g/day: 1.48 15+ g/day: 2.56	Nondrinkers: 1.0 (ref) <15 g/day: 1.17 15+ g/day: 1.18			<15 g/day: 1.21 15+ g/day: 1.28	NS	Age
California Teachers Study (CTS) (Horn-Ross, 2004)	Cohort	None	Stratum specific: Nondrinkers	Nondrinkers: 1.0 (ref) <20 g/day: 1.07 (0.82-1.40) ≥20 g/day: 1.44 (0.97-2.13)	Nondrinkers: 1.0 (ref) <20 g/day: 1.01 (0.85-1.19 ≥20 g/day: 1.26 (0.99-1.64)			≥20 g/day vs. Nondrinkers: 1.32 (1.06-1.63)	p=Non-significant	Age, race/ethnicity, caloric intake, age at menarche, family history, BMI, nulliparity/age at FFTP, physical activity, duration of ERT use
				Caffeine Consumption						
				BBD	*No BBD*					

Women's Health Study (Ishitani, 2008)	Cohort	None	Stratum specific: lowest grouping of consumption	Caffeine, >486.3 mg/d vs ≤68 mg/d: 1.32 (0.99-1.76) (p trend=0.10) Coffee, ≥4 cups/d vs. almost never: 1.35 (1.01-1.80) (p trend=0.08) Decaffeinated coffee, ≥2 cups/d vs. almost never: 0.96 (0.74-1.23) (p trend=0.78) Tea, ≥2 cups/d vs. almost never: 1.24 (0.92-1.66) (p trend=0.37)	Caffeine, >486.3 mg/d vs ≤68 mg/d: 0.84 (0.66-1.08) (p trend=0.71) Coffee, ≥4 cups/d vs. almost never: 0.91 (0.71-1.18) (p trend=0.96) Decaffeinated coffee, ≥2 cups/d vs. almost never: 0.90 (0.71-1.15) (p trend=0.16) Tea, ≥2 cups/d vs. almost never: 0.92 (0.72-1.18) (p trend=0.51)		Caffeine, >486.3 mg/d vs ≤68 mg/d: 1.02 (0.84-1.22) Coffee, ≥4 cups/d vs. almost never: 1.08 (0.89-1.30) Decaffeinated coffee, ≥2 cups/d vs. almost never: 0.92 (0.78-1.10) Tea, ≥2 cups/d vs. almost never: 1.03 (0.85-1.25)	Caffeine: p=0.05 Coffee: p=0.05	Age, randomized treatment assignment, BMI, physical activity, total energy intake, alcohol intake, multivitamin use, age at menopause, age at menarche, age at first pregnancy, number of pregnancies, menopausal status, postmenopausal hormone use, previous hysterectomy, previous bilateral oophorectomy, smoking status, family history
NIH-AARP Diet and Health Study (Gierach, 2012)	Cohort	None	Not presented				4+ cups/d vs. never drinkers: 0.98 (0.91-1.07)	p=0.10	Age, race/ethnicity, education, BMI, smoking status, alcohol, proportion of total energy

from fat, age at first live birth, HRT use, family history

AH Atypical Hyperplasia; PDWA Proliferative Disease without Atypia; NonPD Nonproliferative; TNCS Third National Cancer Survey; SEER Surveillance Epidemiology and End Results; NS: Not Stated

Table 1.10. Interaction between benign breast disease, 1st degree family history of breast cancer, and risk of breast cancer

Cohort	Study Design	Matching	Referent	1st Degree Family History						Relative risk of entire population	Multiplicative Interaction	Adjustments
				AH w/ Family History	*AH w/o Family History*	*PDWA w/ Family History*	*PDWA w/o Family History*	*NonPD w/ Family History*	*NonPD w/o Family History*			
Nashville Breast Cohort (NBC) (Dupont, 1985)	Retrospective Cohort	None	Third National Cancer Survey	N/A	N/A	3.2 (2.1-4.9)	1.7 (1.4-2.2)	1.2 (0.43-3.1)	0.86 (0.59-1.3)	FH: 2.5 (1.7-3.7) No FH: 1.4 (1.2-1.7)	NS	None
Nashville Breast Cohort (NBC) (Dupont, 1985)	Retrospective Cohort	None	Nonproliferative w/o FH	11 (5.5-24)	4.3 (2.4-7.8)	2.7 (1.4-5.3)	1.9 (1.2-3.0)	N/A	1.0	NS	NS	None
Nashville Breast Cohort (NBC) (Page, 1985)	Cohort	None	Nonproliferative w/ and w/o FH	ADH vs. w/o FH: 9.7 (3.7-25) ADH vs. w/ FH: 7.2 (1.9-27) ALH vs.	ADH vs. w/o FH: 3.9 (1.9-8.3) ALH vs. w/o FH: 4.8 (2.3-	N/A	N/A	1.0	1.0	NS	NS	None

				w/o FH: 13 (4.8-35) ALH vs. w/FH: 9.3 (2.4-35)	10)							
Nashville Breast Cohort (NBC) (Page, 1985)	Cohrot	None	Third National Cancer Survey	N/A	N/A	ALA III/IV 2.8 (0.69-11)	ALA III/IV 0.98 (0.41-2.4)	ALA I/II 1.9 (0.70-5.0)	ALA I/II 1.2 (0.82-1.8)	ALA I: 1.2 (0.74-2.0) ALA II: 1.4 (0.78-2.3) ALA III/IV: 1.2 (0.58-2.5)	NS	None
Nurse's Health Study (NHS) (London, 1992))	Nested Case-Control	None	Stratum specific: Nonproliferative, FH vs. No FH	7.3 (1.1-50.1)	3.7 (1.9-7.0)	4.5 (1.1-18.4)	1.3 (0.8-2.2)	1.0 (ref w/ FH)	1.0 (ref w/o FH)	NS	p=0.10	Year of biopsy, year of birth, family history, age at menarche, age at first birth, parity
Breast Cancer Detection Demonstration Project (BCDDP) (Dupont, 1993))	Nested Case-Control	1:2, age, year of biopsy, follow-up time	Nonproliferative w/o FH	22 (2.4-2003)	4.2 (1.4-1.2)	2.6 (1.0-6.4)	1.7 (0.92-3.2)	3.6 (1.5-8.6)	1.0	FH vs. No FH: 2.4 (1.4-4.3)	NS	Age at biopsy, year of biopsy, study center

Mayo Benign Breast Disease Cohort (Hartmann, 2005)[a]	Prospective Cohort	None	Iowa SEER	Weak: 4.18 (1.9-8.0) Strong: 4.00 (1.9-7.0)	2.95 (1.9-4.1)	Weak: 1.79 (1.3-2.3) Strong: 2.19 (1.8-2.8)	1.57 (1.3-2.0)	Weak: 1.12 (0.9-1.8) Strong: 1.62 (1.3-2.1)	0.89 (0.7-1.1)	None: 1.18 (1.01-1.37) Weak: 1.43 (1.15-1.75) Strong: 1.93 (1.58-2.32)	p=Non-significant	None
Nurse's Health Study (NHS) (Collins, 2006)	Nested Case-Control	None	Nonproliferative w/o FH	5.37 (3.01-9.58)	4.38 (2.93-6.55)	2.45 (1.61-3.70)	1.51 (1.12-2.06)	1.57 (0.94-2.62)	1.0	FH vs. No FH, adj: 1.51 (1.15-1.99)	p=0.74	Age at breast cancer dx, year of BBD biopsy, years of follow-up, age at menarche, parity/age at first birth, BMI, menopausal status/type of menopause, recent/duration of HRT use
Kabat BBD Cohort (Kabat, 2010)	Nested Case-Control	Age, age at BBD	Stratum specific: Nonproliferative, yes or no	N/A	N/A	1.05 (0.69-1.61)	2.00 (1.42-2.80)	1.0	N/A	NS	p=0.20	None

				1st Degree Family History					
				BBD	*No BBD*				
Breast Cancer Detection Demonstration Project (BCDDP) (Brinton, 1982)	Nested Case-Control	None	No BBD and No FH	No FH, 1 bx: 1.16 (0.9-1.5) No FH, 2+ bx: 1.49 (1.0-2.1) FH, 1 bx: 2.32 (1.4-3.9) FH, 2+ bx: 5.63 (2.6-12.3)	No FH: 1.0 (Ref) FH: 1.98 (1.6-2.5)		1st Degree vs. No FH: 2.08 (1.7-2.6)	NS	Age at diagnosis
Nurse's Health Study (NHS) (Colditz, 1993)	Cohort	None	Stratum specific: FH vs. No FH	1.62 (1.35-1.95)	1.85 (1.59-2.15)		FH vs. No FH 1.8 (1.5-2.0)	NS	None
Nurse's Health Study (NHS) (Colditz, 1996)	Cohort	None	No BBD, within stratum of FH	No FH: 1.49 (1.18-1.89) FH: 1.64 (1.49-1.81)	1.0		No FH: 0.75 (0.62-0.92) FH: 0.90 (0.55-1.49)	NS	Age, age at menarche, parity, menopause, age at menopause, history of BBD, oral contraceptives, HRT use, follow-up period

AH Atypical Hyperplasia; PDWA Proliferative Disease without Atypia; NonPD Nonproliferative; TNCS Third National Cancer Survey; SEER Surveillance Epidemiology and

End Results; NS: Not Stated

[a]Mayo cohort examined both 1st degree and 2nd degree family history, the difference is indicated by weak (2nd degree) and strong (1st degree)

Table 1.11. Interaction between benign breast disease, mammographic density, and risk of breast cancer

Cohort	Study Design	Matching	Referent	Mammographic Density (MD)						Relative risk of entire population	Multiplicative Interaction	Adjustments
				AH w/ MD	*AH w/o MD*	*PDWA w/ MD*	*PDWA w/o MD*	*NonPD w/ MD*	*NonPD w/o MD*			
Breast Cancer Detection Demonstration Project (BCDDP) (Byrne, 2001)	Nested Case-Control	Study center, age, race	Nonproliferative w/<50%	50-74%: 3.0 (1.3-7.0) ≥75%: 2.1 (0.6-7.0)	<50%: 4.1 (2.1-8.0)	50-74%: 2.5 (1.5-4.1) ≥75%: 3.2 (1.6-6.6)	<50%: 1.6 (1.0-2.5)	50-74%: 2.5 (1.3-5.1) ≥75%: 5.8 (1.8-18.6)	1.0	≥75% vs. <10%, adj: 4.4 (2.1-9.0)	p=0.002	Age, race, family history, alcohol use, nulliparity/age at first birth, years of education, weight, menopausal status, age at menopause, HRT use
Mayo Benign Breast Disease Cohort	Cohort	None	Complete Involution and N1/P1	No Involution and P2/DY: 4.08 (1.72-	No Involution and N1/P1:	Partial Involution and P2/DY: 2.70 (1.32-	Partial Involution and N1/P1:	Complete Involution and P2/DY: 1.66 (0.75-	1.0	DY vs. N1: 1.67 (1.03-2.73)	p=0.006	Age, BBD histology, BMI, menopause status,

(Ghosh, 2010)[a]				9.68)	3.24 (1.05-9.98)	5.53)	1.57 (0.73-3.36)	3.70)				family history
Breast Cancer Surveillance Consortium (Tice, 2013)	Cohort	None	Nonproliferative w/ scattered fibroglandular densities	Scattered: 2.57 (1.85-3.58) Heterogeneous: 3.37 (2.58-4.40) Extremely Dense: 5.34 (3.52-8.09)	Fatty: 0.68 (0.9-4.90)	Scattered: 1.37 (1.11-1.69) Heterogeneous: 2.02 (1.68-2.44) Extremely Dense: 2.05 (1.54-2.72)	Fatty: 0.67 (0.20-1.52)	Heterogeneous: 1.51 (1.28-1.78) Extremely Dense: 2.15 (1.73-2.68)	*	NS	p=0.28	Age, race/ethnicity, registry
				Mammographic Density								
				BBD	*No BBD*							
New Mexico Mammography Project (Ashbeck, 2007)	Cohort	None	No BBD and Fatty/scattered densities	Low-risk (PDWA and nonPD), Fatty/scattered: 2.09 (1.68-2.60) Low-risk, Dense: 3.36 (2.83-3.99)	1.0					Apocrine metaplasia: 3.89 (2.15-7.04) Cysts: 1.37 (0.71-2.65) Hyperplasia, ductal: 1.93 (1.22-3.06)	NS	Age and adjusted for concurrent low-risk diagnoses

AH Atypical Hyperplasia; PDWA Proliferative Disease without Atypia; NonPD Nonproliferative; TNCS Third National Cancer Survey; SEER

Surveillance Epidemiology and End Results; NS: Not Stated; MD: Mammographic density

[a]Used Wolfe Criteria for classifying breast density

1.6 References

1. Statistics NCfH. Health, United States, 2013: With Special Feature on Prescription Drugs. In: Services USDoHaH, (ed). Hyattsville, MD; 2014.

2. Centers for Disease C. National Ambulatory Medical Care Survey. In: Centers for Disease C, (ed). Atlanta, GA; 2010.

3. Esserman LJ, Wolverton D, Hylton N. Integration of breast imaging into cancer management. Curr Oncol Rep 2000;2(6):572-81.

4. May DS, Lee NC, Nadel MR*, et al.* The National Breast and Cervical Cancer Early Detection Program: report on the first 4 years of mammography provided to medically underserved women. AJR Am J Roentgenol 1998;170(1):97-104.

5. Kerlikowske K, Carney PA, Geller B*, et al.* Performance of screening mammography among women with and without a first-degree relative with breast cancer. Ann Intern Med 2000;133(11):855-63.

6. Kerlikowske K, Grady D, Barclay J*, et al.* Positive predictive value of screening mammography by age and family history of breast cancer. JAMA 1993;270(20):2444-50.

7. Silverstein M. Where's the outrage? J Am Coll Surg 2009;208(1):78-9.

8. Hubbard RA, Kerlikowske K, Flowers CI*, et al.* Cumulative probability of false-positive recall or biopsy recommendation after 10 years of screening mammography: a cohort study. Ann Intern Med 2011;155(8):481-92.

9. Vogel VG. High-risk populations as targets for breast cancer prevention trials. Prev Med 1991;20(1):86-100.

10. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312(3):146-51.

11. Carter CL, Corle DK, Micozzi MS*, et al.* A prospective study of the development of breast cancer in 16,692 women with benign breast disease. Am J Epidemiol 1988;128(3):467-77.

12. Goehring C, Morabia A. Epidemiology of benign breast disease, with special attention to histologic types. Epidemiol Rev 1997;19(2):310-27.

13. Nielsen M, Jensen J, Andersen J. Precancerous and cancerous breast lesions during lifetime and at autopsy. A study of 83 women. Cancer 1984;54(4):612-5.

14. Alpers CE, Wellings SR. The prevalence of carcinoma in situ in normal and cancer-associated breasts. Hum Pathol 1985;16(8):796-807.

15. Bhathal PS, Brown RW, Lesueur GC*, et al.* Frequency of benign and malignant breast lesions in 207 consecutive autopsies in Australian women. Br J Cancer 1985;51(2):271-8.

16. Bartow SA, Pathak DR, Black WC*, et al.* Prevalence of benign, atypical, and malignant breast lesions in populations at different risk for breast cancer. A forensic autopsy study. Cancer 1987;60(11):2751-60.

17. Nielsen M, Thomsen JL, Primdahl S*, et al.* Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. Br J Cancer 1987;56(6):814-9.

18. Kyriopoulos E, Kakagia D, Zapandioti P*, et al.* Pathologic findings in breast reduction specimens: detection of occult premalignant and cancerous lesions. Onkologie 2012;35(10):583-6.

19. Wellings SR, Jensen HM. On the origin and progression of ductal carcinoma in the human breast. J Natl Cancer Inst 1973;50(5):1111-8.

20. Lakhani SR. The transition from hyperplasia to invasive carcinoma of the breast. J Pathol 1999;187(3):272-8.

21. Harris JR. *Diseases of the breast*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2010.

22. Silvera SA, Rohan TE. Benign proliferative epithelial disorders of the breast: a review of the epidemiologic evidence. Breast Cancer Res Treat 2008;110(3):397-409.

23. Bevers TB, Anderson BO, Bonaccio E*, et al.* NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. In. 1.2014 ed: National Comprehensive Cancer Network (NCCN); 2014.

24. Gail MH, Brinton LA, Byar DP*, et al.* Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989;81(24):1879-86.

25. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004;23(7):1111-30.

26. Antoniou AC, Pharoah PP, Smith P*, et al.* The BOADICEA model of genetic susceptibility to breast and ovarian cancer. Br J Cancer 2004;91(8):1580-90.

27. Black MM, Barclay TH, Cutler SJ*, et al.* Association of atypical characteristics of benign breast lesions with subsequent risk of breast cancer. Cancer 1972;29(2):338-43.

28. Kabat GC, Jones JG, Olson N*, et al.* A multi-center prospective cohort study of benign breast disease and risk of subsequent breast cancer. Cancer Causes Control 2010;21(6):821-8.

29. Sanders ME, Page DL, Simpson JF*, et al.* Interdependence of radial scar and proliferative disease with respect to invasive breast carcinoma risk in patients with benign breast biopsies. Cancer 2006;106(7):1453-61.

30. Hartmann LC, Sellers TA, Frost MH*, et al.* Benign breast disease and the risk of breast cancer. New England Journal of Medicine 2005;353(3):229-237.

31. Brinton LA, Hoover R, Fraumeni JF, Jr. Menopausal oestrogens and breast cancer risk: an expanded case-control study. British Journal of Cancer 1986;54(5):825-32.

32. Mills PK, Beeson WL, Phillips RL*, et al.* Prospective study of exogenous hormone use and breast cancer in Seventh-day Adventists. Cancer 1989;64(3):591-7.

33. Aroner SA, Collins LC, Connolly JL*, et al.* Radial scars and subsequent breast cancer risk: results from the Nurses' Health Studies. Breast Cancer Research and Treatment 2013:1-9.

34. van den Brandt PA, Goldbohm RA, van 't Veer P. Alcohol and breast cancer: results from The Netherlands Cohort Study. American Journal of Epidemiology 1995;141(10):907-15.

35. Ashbeck EL, Rosenberg RD, Stauber PM*, et al.* Benign breast biopsy diagnosis and subsequent risk of breast cancer. Cancer Epidemiology, Biomarkers & Prevention 2007;16(3):467-72.

36. Ishitani K, Lin J, Manson JE*, et al.* Caffeine consumption and the risk of breast cancer in a large prospective cohort of women. Archives of Internal Medicine 2008;168(18):2022-31.

37. Tice JA, O'Meara ES, Weaver DL*, et al.* Benign Breast Disease, Mammographic Breast Density, and the Risk of Breast Cancer. J Natl Cancer Inst 2013;105(14):1043-9.

38. Horn-Ross PL, Canchola AJ, West DW*, et al.* Patterns of alcohol consumption and breast cancer risk in the California Teachers Study cohort. Cancer Epidemiology, Biomarkers & Prevention 2004;13(3):405-11.

39. Gierach GL, Freedman ND, Andaya A*, et al.* Coffee intake and breast cancer risk in the NIH-AARP diet and health study cohort. International Journal of Cancer 2012;131(2):452-60.

40. Bodian CA, Lattes R, Perzin KH. The epidemiology of gross cystic disease of the breast confirmed by biopsy or by aspiration of cyst fluid. Cancer Detection & Prevention 1992;16(1):7-15.

41. Thomas DB, Persing JP, Hutchinson WB. Exogenous estrogens and other risk factors for breast cancer in women with benign breast diseases. Journal of the National Cancer Institute 1982;69(5):1017-25.

42. Worsham MJ, Raju U, Lu M*, et al.* Multiplicity of benign breast lesions is a risk factor for progression to breast cancer. Clinical Cancer Research 2007;13(18 Pt 1):5474-9.

43. Bodian CA. Benign breast diseases, carcinoma in situ, and breast cancer risk. Epidemiol Rev 1993;15(1):177-87.

44. Pearlman MD, Griffin JL. Benign breast disease. Obstet Gynecol 2010;116(3):747-58.

45. Bodian CA, Perzin KH, Lattes R*, et al.* Prognostic significance of benign proliferative breast disease. Cancer 1993;71(12):3896-907.

46. Hutchinson WB, Thomas DB, Hamlin WB*, et al.* Risk of breast cancer in women with benign breast disease. Journal of the National Cancer Institute 1980;65(1):13-20.

47. Dupont WD, Page DL. Breast cancer risk associated with proliferative disease, age at first birth, and a family history of breast cancer. Am J Epidemiol 1987;125(5):769-79.

48. Berg JC, Visscher DW, Vierkant RA*, et al.* Breast cancer risk in women with radial scars in benign breast biopsies. Breast Cancer Research & Treatment 2008;108(2):167-74.

49. Ghosh K, Hartmann LC, Reynolds C*, et al.* Association between mammographic density and age-related lobular involution of the breast. J Clin Oncol 2010;28(13):2207-12.

50. Byrne C, Schairer C, Brinton LA*, et al.* Effects of mammographic density and benign breast disease on breast cancer risk (United States). Cancer Causes Control 2001;12(2):103-10.

51. Marshall LM, Hunter DJ, Connolly JL*, et al.* Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. Cancer Epidemiol Biomarkers Prev 1997;6(5):297-301.

52. Dupont WD, Parl FF, Hartmann WH*, et al.* Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. Cancer 1993;71(4):1258-65.

53. Jacobs TW, Byrne C, Colditz G*, et al.* Radial scars in benign breast-biopsy specimens and the risk of breast cancer. New England Journal of Medicine 1999;340(6):430-6.

54. Boulos FI, Dupont WD, Simpson JF*, et al.* Histologic associations and long-term cancer risk in columnar cell lesions of the breast: a retrospective cohort and a nested case-control study. Cancer 2008;113(9):2415-21.

55. Aroner SA, Collins LC, Schnitt SJ*, et al.* Columnar cell lesions and subsequent breast cancer risk: a nested case-control study. Breast Cancer Research 2010;12(4):R61.

56. Visscher DW, Nassar A, Degnim AC*, et al.* Sclerosing adenosis and risk of breast cancer. Breast cancer research and treatment 2014;144(1):205-12.

57. Milanese TR, Hartmann LC, Sellers TA*, et al.* Age-related lobular involution and risk of breast cancer. Journal of the National Cancer Institute 2006;98(22):1600-7.

58. Barr FEG, Degnim AC, Hartmann LC*, et al.* Estrogen receptor expression in atypical hyperplasia: lack of association with breast cancer. Cancer prevention research (Philadelphia, Pa.) 2011;4(3):435-44.

59. Stark A, Hulka BS, Joens S*, et al.* HER-2/neu amplification in benign breast disease and the risk of subsequent breast cancer. Journal of Clinical Oncology 2000;18(2):267-74.

60. London SJ, Connolly JL, Schnitt SJ*, et al.* A prospective study of benign breast disease and the risk of breast cancer.[Erratum appears in JAMA 1992 Apr 1;267(13):1780]. JAMA 1992;267(7):941-4.

61. Collins LC, Baer HJ, Tamimi RM*, et al.* Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia: results from the Nurses' Health Study. Cancer 2007;109(2):180-7.

62. Page DL, Schuyler PA, Dupont WD*, et al.* Atypical lobular hyperplasia as a unilateral predictor of breast cancer risk: a retrospective cohort study. Lancet 2003;361(9352):125-9.

63. Byrne C, Connolly JL, Colditz GA*, et al.* Biopsy confirmed benign breast disease, postmenopausal use of exogenous female hormones, and breast carcinoma risk. Cancer 2000;89(10):2046-52.

64. Dupont WD, Page DL, Rogers LW*, et al.* Influence of exogenous estrogens, proliferative breast disease, and other variables on breast cancer risk. Cancer 1989;63(5):948-57.

65. Dupont WD, Page DL, Parl FF*, et al.* Estrogen replacement therapy in women with a history of proliferative breast disease. Cancer 1999;85(6):1277-83.

66. Brinton LA, Hoover R, Fraumeni JF, Jr. Interaction of familial and hormonal risk factors for breast cancer. Journal of the National Cancer Institute 1982;69(4):817-22.

67. Brinton LA, Hoover R, Szklo M*, et al.* Oral contraceptives and breast cancer. International Journal of Epidemiology 1982;11(4):316-22.

68. Tamimi RM, Byrne C, Baer HJ*, et al.* Benign breast disease, recent alcohol consumption, and risk of breast cancer: a nested case-control study. Breast Cancer Res 2005;7(4):R555-62.

69. Berkey CS, Willett WC, Frazier AL*, et al.* Prospective study of adolescent alcohol consumption and risk of benign breast disease in young women. Pediatrics 2010;125(5):e1081-7.

70. Colditz GA, Willett WC, Hunter DJ*, et al.* Family history, age, and risk of breast cancer. Prospective data from the Nurses' Health Study. Journal of the American Medical Association 1993;270(3):338-43.

71. Colditz GA, Rosner BA, Speizer FE. Risk factors for breast cancer according to family history of breast cancer. For the Nurses' Health Study Research Group. Journal of the National Cancer Institute 1996;88(6):365-71.

72. Collins LC, Baer HJ, Tamimi RM*, et al.* The influence of family history on breast cancer risk in women with biopsy-confirmed benign breast disease: results from the Nurses' Health Study. Cancer 2006;107(6):1240-7.

73. Ghosh K, Vachon CM, Pankratz VS*, et al.* Independent association of lobular involution and mammographic breast density with breast cancer risk. Journal of the National Cancer Institute 2010;102(22):1716-23.

74. Boyd NF, Byng JW, Jong RA*, et al.* Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst 1995;87(9):670-5.

75. Amir E, Freedman OC, Seruga B*, et al.* Assessing women at high risk of breast cancer: a review of risk assessment models. J Natl Cancer Inst 2010;102(10):680-91.

76. Antoniou AC, Cunningham AP, Peto J*, et al.* The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer 2008;98(8):1457-66.

77. Pankratz VS, Hartmann LC, Degnim AC*, et al.* Assessment of the accuracy of the Gail model in women with atypical hyperplasia. Journal of Clinical Oncology 2008;26(33):5374-9.

78. Boughey JC, Hartmann LC, Anderson SS*, et al.* Evaluation of the Tyrer-Cuzick (International Breast Cancer Intervention Study) model for breast cancer risk prediction in women with atypical hyperplasia. J Clin Oncol 2010;28(22):3591-6.

Chapter 2:

Benign breast disease as a predictor of mammographic breast density

2.1 Abstract

Introduction: Mammographic density and benign breast disease (BBD) are both important risk factors of breast cancer. Understanding the association between these two factors is important to the clinical management and prevention of breast cancer. We evaluated changes in mammographic measures by BBD in a longitudinal birth cohort.

Methods: Using the Early Determinants of Mammographic Density (EDMD) study, a birth cohort of women born in the 1960s, we had data from adult interviews on women and mammographic films. Participants self-reported BBD and we assessed mammographic measures using computer-assisted thresholding program. We used generalized estimating equations (GEE) analysis with percent density, dense area, and non-dense area as the outcomes to assess the association with BBD.

Results: We had BBD and mammographic data for 681 women: 124 with a history of BBD and 557 without BBD. The median time from BBD diagnosis to first recorded mammogram was 9.1 years. We found that women with BBD on average had 3.54% higher percent density on their first mammogram than women without BBD (β: 3.54, p-value=0.04). We also found associations between age at BBD diagnosis and dense and non-dense area (β: 0.41, p-value=0.04 and β: 0.82, p-value=0.02, respectively). We found dense and non-dense area associated with time since BBD diagnosis. BBD diagnosis prior to pregnancy had 8.64% higher density than nulliparous women without BBD (β: 8.64, p-value=0.04).

Conclusions: Our results suggest a link between BBD and higher percent density and that the combination of BBD and parity may increase density. Improving the clinical care of women with BBD depends on understanding these relationships.

2.2 Introduction

Mammographic breast density is a strong risk factor for breast cancer, leading researchers consider it to be an intermediate marker. Researchers often use intermediate markers as surrogate endpoints for cancer risk; in the case of mammographic density women with higher breast density are at a greater risk of breast cancer. Women with 75% or greater dense tissue have a 4-6 fold risk of breast cancer compared to women with 25% or less dense tissue [1-3]. Benign breast disease (BBD) also increases breast cancer risk 2-3 fold, regardless of histologic subtype [4, 5]. Research suggest a link between histologic features and radiographic appearance [6]. In women with BBD, if they are at greater risk of breast cancer, it would be expected that a greater proportion of these women would also have higher breast density.

To our knowledge, few studies have examined BBD and mammographic density modeling breast density as the outcome (reviewed in [2]). Most of these studies used Wolfe classification criteria and/or were cross-sectional. An early study of risk of BBD found a reduced risk of BBD in women with mammographic homogenous density or large nodular densities, consistent in parous women, obese women, and women with a family history of breast cancer [7]. Other studies using continuous breast density divided into quintiles of mammographic density found increasing risk of BBD with increasing density [8, 9]. More recent studies have examined the interaction between BBD and mammographic density on subsequent breast cancer risk [10, 11]. No study using modern computerized measurements of breast density has examined the association between BBD and mammographic density. It is important to establish the relationship between BBD and mammographic density if a biological link exists, (such that mammographically dense tissue indicates histologic changes in breast tissue,) if this is true then the interaction between these two risk factors likely affects breast cancer risk.

It is established that mammographic density decreases with increasing age [1, 12-15]. Changes in mammographic density over time, specifically in women with BBD, could be clinically important to their management and prevention of breast cancer. However, no data shows changes in mammographic density over time in women with BBD compared to women without BBD. To evaluate whether changes in continuous mammographic measures share an association with BBD we used a longitudinal birth cohort.

2.3 Methods

Our population comes from the Early Determinants of Mammographic Density (EDMD) study, a follow-up of two birth cohorts: the Child Health and Development Study (CHDS) and the Collaborative Perinatal Project, (previously described [16]). Briefly, from 1960 to 1967 researchers conducted CHDS in California and we used two sites, Boston and Providence, from the Collaborative Perinatal Project, conducted from 1959 to 1966. Each cohort recruited pregnant women receiving prenatal care at one of the participating hospitals. We included a sibling sample in order to reduce bias due to family-level confounders. We successfully traced 1134 women in the EDMD study, 521 singletons and 296 sibling sets with 613 individuals [16]. We collected childhood data by direct measurement and maternal reports during exam visits. We later contacted women as adults and asked them to participate in a 45-min computer-assisted telephone interview. We collected data on personal health history, first degree family history of cancer, sociodemographic factors, alcohol use, detailed reproductive history, anthropometric measures, and lifecourse exposures to tobacco smoke.

In this study we used data from the adult interviews and mammographic density data. We used data on race/ethnicity, family history of breast cancer, menopausal status, alcohol use at age 20-29 (yes/no), body mass index (kg/m^2; BMI) during 30s, age at menarche (reported in increments of 0.5 years), and parity. In parous women we assessed age at first birth, age at last birth, and breastfeeding (ever/never). We collected mammographic density information during the adult interview, and asked participants if they had a mammogram in the two years prior to the interview or if they were planning on having one in the following 12 months. We collected benign breast disease (BBD) diagnosis through self-report on the adult interview. We asked women, “Has a health care provider ever told you that you have fibrocystic breast disease? Sometimes this is also called benign breast disease or multiple cysts in breast”. We then asked women who answered yes at what age they first saw a doctor about their BBD. For our analysis, we excluded 13 women who lacked BBD information. Mean age of BBD diagnosis in our population was 32 years, before the age of screening mammography; therefore it is unlikely that these BBD diagnoses were made through screening mammography. Our prevalence of women with a history of BBD diagnosis was 17.6%, this prevalence is similar to other cohort studies, such as the Women’s Health Study and the California Teachers Study [17, 18].

For those women with mammographic data we collected signed medical release authorization forms allowing us to borrow their mammograms for density assessment. We collected and measured 700 women with film mammograms using Cumulus, a computer-assisted thresholding program [19]. We calculated absolute breast area and dense area by converting the measure from pixels to cm^2. We then calculated percent mammographic density by dividing dense area by breast area and multiplying by 100. We calculated non-dense area as total breast area minus dense breast area, to get non-dense area in cm^2. Researchers at Columbia University read the films in batches of 50 films with repeated readings for 10% of films from the same batch and repeated another 10% of films in every batch to assess batch-to-batch variability [16]. We read the left cranio-caudal (CC) film except in cases where the left was unavailable; then we read the right. We found an overall within-batch correlation coefficient of 0.96 for percent density and an intraclass correlation coefficient of 0.95 for between-batch reliability [16].

2.3.1 Statistical analysis

Of the 700 women with film mammograms, we had repeated measures on 428 who had at least one other mammogram measured. In the 700 women with film mammograms and 1121 women with BBD data, we have 691 women with both mammogram measurements and BBD data. In this analysis, we wanted to assess the effects of BBD on mammographic density, using mammographic density as the outcome and BBD as the exposure. The majority of women were diagnosed with BBD prior to their film mammogram, however we excluded 10 women who did not have a single mammographic measurement after their BBD diagnosis. Thus, for this analysis, we have 681 women: 124 with a history of BBD, and 557 with no history of BBD.

The average age of BBD diagnosis was 32 years, therefore we used adult risk factors from when the women were in their 30s as well as reproductive factors. We compared these factors between those with a history of BBD to those with no BBD. Next, we examined histograms of first mammographic measures (percent density, dense area, and non-dense area) by BBD status. Using generalized estimating equation (GEE) models to account for correlation between sibling sets, we assessed the association between history of BBD and mammographic density. We inspected the association between age at BBD diagnosis (age when they first saw a doctor) and time between BBD diagnosis and first mammogram for differences by age and time. Given

that we only have age at BBD and time since BBD data on women with BBD we used centering to incorporate the women without BBD into the analysis. To center, we calculated the average age at BBD and used that value for all women without BBD. We then subtracted the average age at BBD from all ages at BBD and created a dummy variable for no BBD; we used the same method for time since BBD. We then estimated four models; model 1 was BBD and mammographic density adjusting for age at mammogram. The subsequent models we adjusted for potential confounders (defined as those risk factors that altered the association between BBD and mammographic density by more than 10%). We then added these factors to the models in stages; model 2 included age at mammogram, race, and BMI during 30s, model 3 included those factors with the addition of age at menarche, and model 4 included those factors in model 3 with the addition of alcohol use from age 20-29. We assessed all our mammographic measurements at first mammogram, last mammogram, and change in measurements from first to last mammogram. In addition, we assessed the influence of parity, specifically timing of parity and BBD diagnosis on mammographic density. We categorized women with BBD into five groups; nulliparous no BBD, parous no BBD, nulliparous BBD, women with BBD diagnosed prior to age at first birth, and women diagnosed with BBD after age at first birth. We performed analyses using SAS version 9.2.

2.4 Results

Table 2.1 shows the demographic characteristics of our population by history of BBD. With a median age of 32 years, BBD diagnosis ages ranged from 12 years to 44 years. The median time between BBD diagnosis and a woman's first mammogram was 9.1 years. The median age at first mammogram was similar between the women with BBD and the women without BBD; they also had similar time between first and last mammograms. While the women with BBD had lower mean changes in mammographic density measures, they were not significantly different than the women without BBD. We saw significant differences in BMI during 30s between women with BBD and women without BBD; women with BBD tended to have lower average BMI than women with BBD (23.7 vs. 25.0, p=0.02). In addition, in women with BBD we found higher percentage of nulliparous women than nulliparous women with no BBD (17.7% vs. 8.8%, p=0.01).

Next, we examined histograms of mammographic density at first mammogram by BBD status. Both distributions were normal, with most women falling into the 30-40% density range for women without BBD and 35-45% for women with BBD (**Figure 2.1**). The BBD group had a slightly higher percent of women with mammographic density greater than 40% as compared to the group with no BBD. Dense area was similar in women with and without BBD. Women with BBD had slightly higher frequency higher dense area (**Figure 2.2**). Women with BBD also had a higher frequency of lower non-dense area than women without a history of BBD (**Figure 2.3**).

Our initial age-adjusted model (**Table 2.2**) showed that women with BBD on average had 5.67% higher mammographic density at their first mammogram compared to those without BBD (β: 5.67, p-value = 0.002). The higher percent mammographic density persisted over time, women with BBD on average had 5.95% higher mammographic density on their last mammogram than women without BBD (β: 5.95, p-value=0.01). We saw no differences in age-adjusted dense area between women with and without BBD. However, we did see a 15.80 cm^2 lower non-dense area in women with BBD at first mammogram as compared to women without BBD at first mammogram (β: -15.80, p-value=0.01). Women with BBD continued to have lower non-dense area at last mammogram as compared to women without BBD (β: -17.46, p-value=0.05). Upon adjustment for other factors these associations attenuated. Model 2 supports the independent effects of BBD on percent density even after adjusting for age at mammogram, race, and BMI during 30s. The additional adjustment of age at menarche (Model 3) did not substantially change these results. After adjustment for alcohol use in age 20-29, the only association that remained significant was between BBD and percent density at first mammogram. The final model showed that women with BBD on average had 3.54% higher percent density on their first mammogram than women without BBD (β: 3.54, p-value=0.04).

We assessed models using centered age at BBD diagnosis and time between BBD and first mammogram and saw no significant associations between either percent density or dense area (**Table 2.3 and 2.4**). However, we did see a 1.51 cm^2 higher non-dense area with each year increase in age at BBD diagnosis in the first mammogram (β: 1.51, p-value=0.02; **Table 2.3**). This trend increased at the last mammogram to a 2.21 cm^2 higher non-dense area with each year increase of age at BBD diagnosis (β: 2.21, p-value=0.01). Upon adjustment the association with non-dense area on first mammogram was

no longer significant, but the non-dense area on last mammogram remained similar (β: 1.98, p-value=0.02). We found a significant association between dense area on last mammogram and age at BBD in multivariable models, but the increase in dense area was small (β: 0.85, p-value=0.04). We saw the reverse trend with time between BBD diagnosis and first mammogram, with a 1.51 cm^2 decrease in non-dense area for every additional year between BBD diagnosis and mammogram (β: -1.51, p-value=0.03; **Table 2.4**). For the last mammogram results suggested a similar, but non-significant 1.93 cm^2 decrease in non-dense area for every additional year between BBD diagnosis and mammogram (β: -1.93, p-value=0.06). Dense area on last mammogram showed a 0.69 cm^2 decrease for every additional year between BBD and first mammogram (β: -0.69, p-value=0.04). Upon adjustment only the associations with dense and non-dense area remained for the last mammogram, dense area had a 0.93 cm^2 decrease and non-dense area had a 1.86 cm^2 decrease for each additional year of follow-up between BBD and first mammogram (β: -0.93, p-value=0.03 and β: -1.86, p-value=0.04, respectively).

Finally, we wanted to assess the association between mammographic density measures and how parity influences the relationship with BBD. We created a variable categorizing women by BBD and parity; for parous women with BBD we grouped them based on whether their BBD was diagnosed prior to or after age at first mammogram. In univariate analysis we saw associations with percent density and dense area, specifically in women with BBD diagnosed prior to pregnancy. After adjusting for other risk factors, we found an 8.64% higher density on last mammogram in women diagnosed with BBD prior to pregnancy as compared to nulliparous women without BBD (β: 8.64, p-value=0.04; **Table 2.5**). While results showed an attenuated, insignificant association with non-dense area on last mammogram, we did find that women with BBD prior to pregnancy had an 8.44 cm^2 higher non-dense area as compared to nulliparous women without BBD (β: 8.44, p-value=0.04).

2.5 Discussion

Our results associated BBD with higher percent density, whereas they associated dense area and non-dense area with age at BBD diagnosis and time between BBD and first mammogram. We noted an association between BBD/parity and percent density/change in non-dense area. Our data support an association between histologic changes and mammographic percent density, which appears consistent with previous studies that showed an association between these two factors [8, 9]. Previous studies have

shown a positive association between BBD and mammographic density [8, 9]. However, in these studies researchers measured mammographic density prior to BBD diagnosis. In addition, these studies used mammograms collected during the 1980s and estimates of density were subjectively measured by visual inspection [8, 9], whereas out results used computer-assisted methods of density measurement.

Age and time stand out as key factors that affect mammographic measures [1, 12-15]. Although we did not find an association between age at BBD diagnosis and percent density, we did find an association between age at BBD diagnosis and dense area/non-dense area. Specifically, the older a woman was at diagnosis of BBD the higher non-dense area she had on her later mammogram. This aligns with previous studies that associate younger age at diagnosis with BBD increased risk of breast cancer [20-22]. Our results also associate dense/non-dense area with time between BBD diagnosis and first mammogram. The longer a woman's follow-up time there was an association with decreased dense and non-dense area. Cohort studies have examined the association between time since BBD diagnosis and breast cancer and found that the longer the time between the two, the greater the risk of breast cancer [22, 23]. If women with BBD experience decreases in their non-dense area for every year of follow-up this could affect their subsequent breast cancer risk.

Nulliparity and older age at first birth are known breast cancer risk factors [24]. Studies associate parity with lower mammographic density (reviewed in [2, 25]). Parity was not a confounder of the association between BBD and mammographic density. However, we saw that women with BBD were more often nulliparous than women without BBD in our population. We also wanted to look at timing of pregnancy in relation to BBD diagnosis and changes in mammographic measures. Interestingly, we saw associations between percent density and BBD diagnosed prior to pregnancy. Women diagnosed with BBD prior to first pregnancy had higher percent density than nulliparous women without BBD. It appears that the typically protective effect of parity is absent in women diagnosed with BBD prior to their first pregnancy. Likewise, women with BBD prior to pregnancy have a greater change in non-dense area compared to nulliparous women without BBD.

The relationship between histological and mammographic measures of the breast is not a new hypothesis; it has been suggested that variations in these tissues correspond to variations in mammographic measures [2, 25]. Previous studies have linked mammographic density with proliferation

and appearance of epithelium or stroma (reviewed in [2, 25]). A biological hypothesis exists positing that genetic and environmental factors affect the proliferative activity and quantity of stromal and epithelial tissue in the breast and that mammographic measures reflect differences [25]. The dense are of the mammogram shows stromal and epithelial tissue, whereas non-dense area shows the fat. Our study has shown a link between BBD with differences in dense and non-dense area. Mammographically dense tissue may reflect the proliferation of the breast epithelium and stroma in response to a number of factors [2]. Our data supports this, but also shows that fatty areas of the breast may also correspond to breast cancer risk, especially in women with prior BBD.

Our ability to use computer-assisted mammographic density measures in women with BBD proved a key strength of this study. Furthermore, BBD diagnoses were all measured prior to first mammogram. In addition, our longitudinal data allowed us to assess change in mammographic density over time, and to look at associations between BBD and density at different points in time. There are, however, a number of restrictions to this analysis. First, the BBD diagnosis was based on self-reported data. Self-reported data is often unreliable as it is prey to recall bias; for example a woman could have gotten a breast biopsy, but the result might not necessarily fit the Dupont and Page Criteria of BBD. Second, self-reported BBD does not account for the subtype of BBD. BBD is a heterogenous disease; by lumping all women into one group, (*i.e.* BBD,) we potentially mask stronger effects in the more severe cases of BBD. Future research should replicate this study in another BBD population with varying degrees of BBD severity.

In conclusion, our results suggest a link between BBD and higher percent mammographic density. It also appears that age at BBD and timing of BBD and pregnancy influence mammographic measures. The clinical care of women depends on understanding these relationships. Given their higher risk of breast cancer and increased density, physicians should follow these women up with breast ultrasound, MRI, or tomosynthesis (3D mammograms) as adjuncts to screening mammography as opposed to mammograms alone in these high-risk women.

Figure 2.1. Histogram of mammographic percent density at first mammogram by BBD status

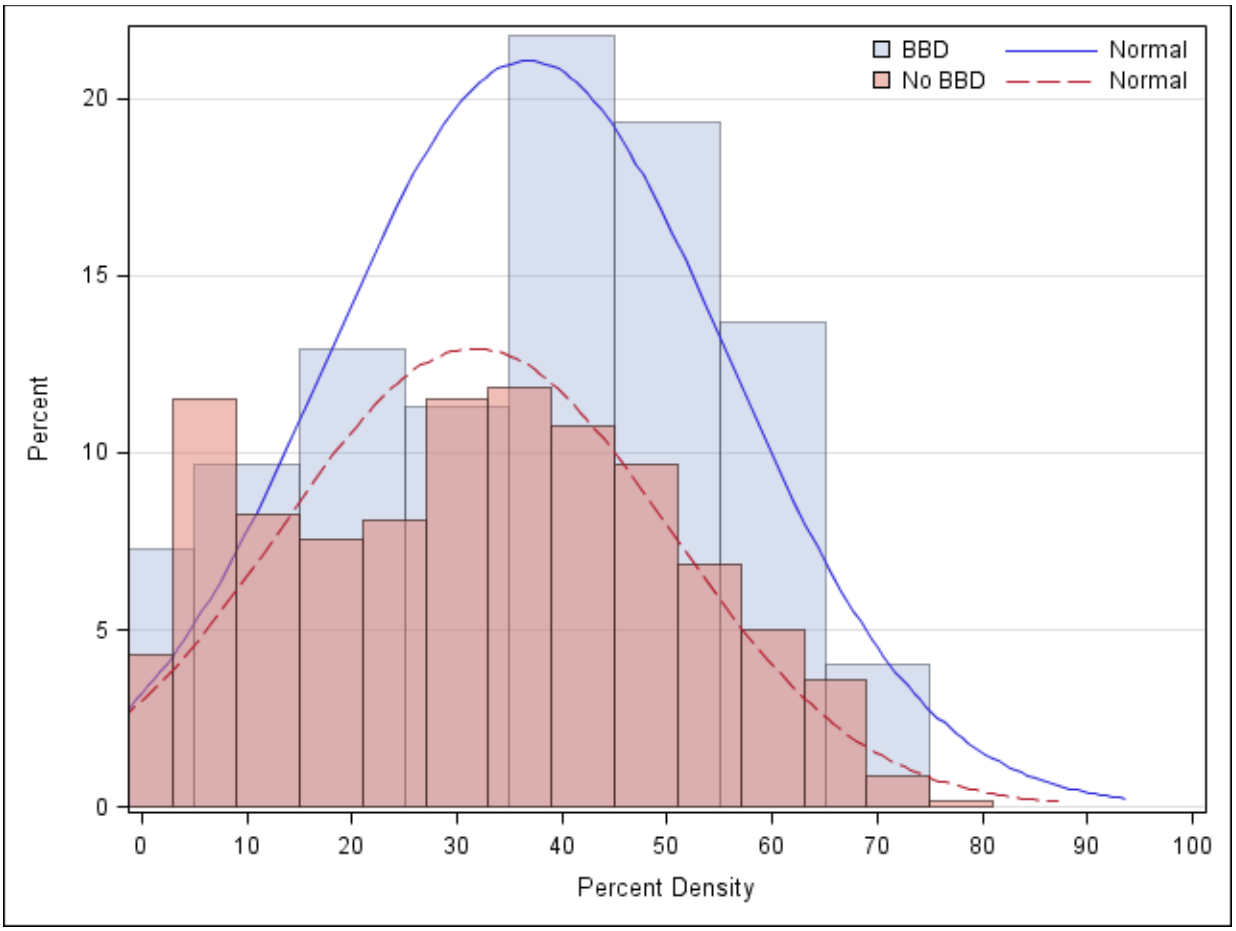

Figure 2.2. Histogram of mammographic dense area at first mammogram by BBD status

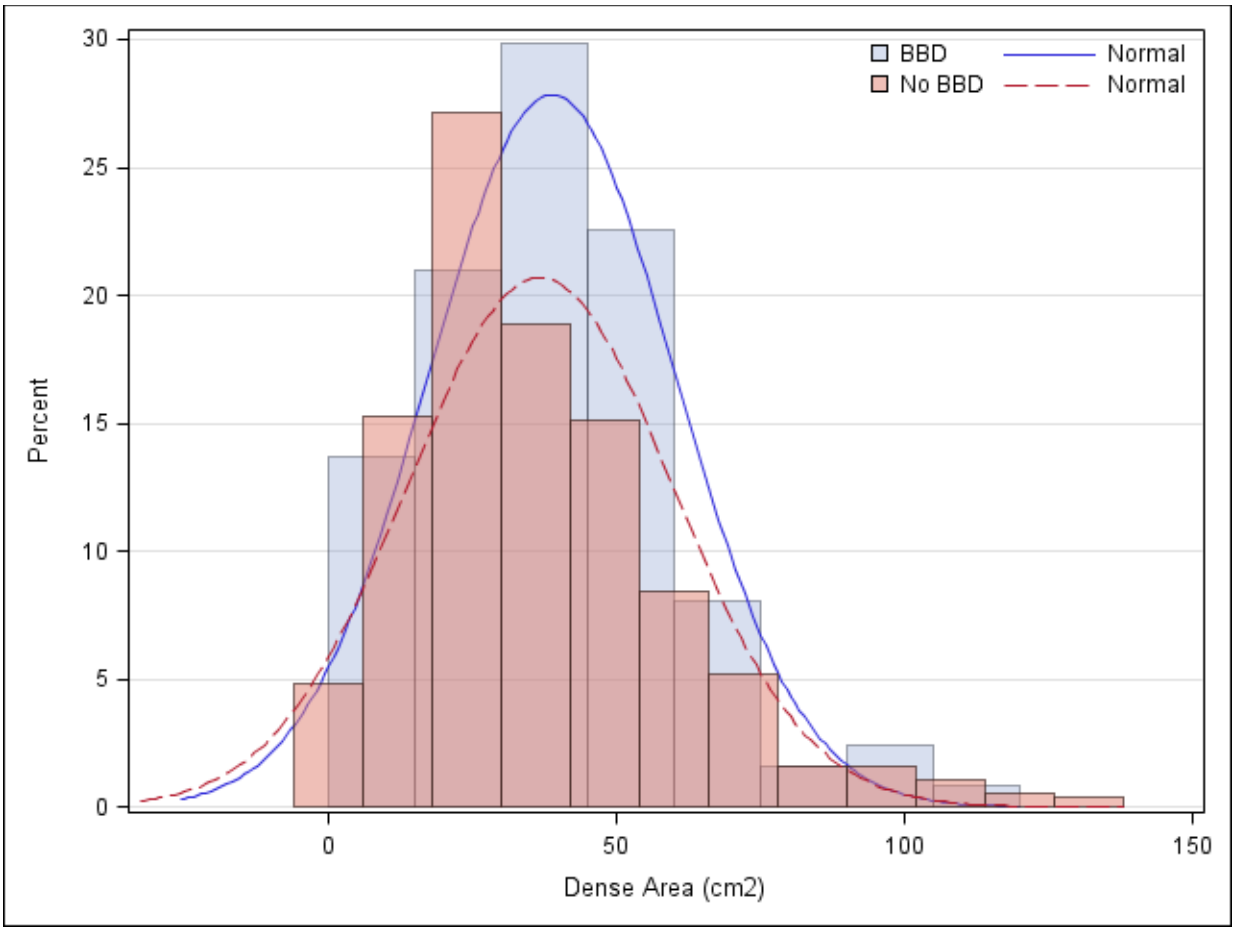

Figure 2.3. Histogram of mammographic non-dense area at first mammogram by BBD status

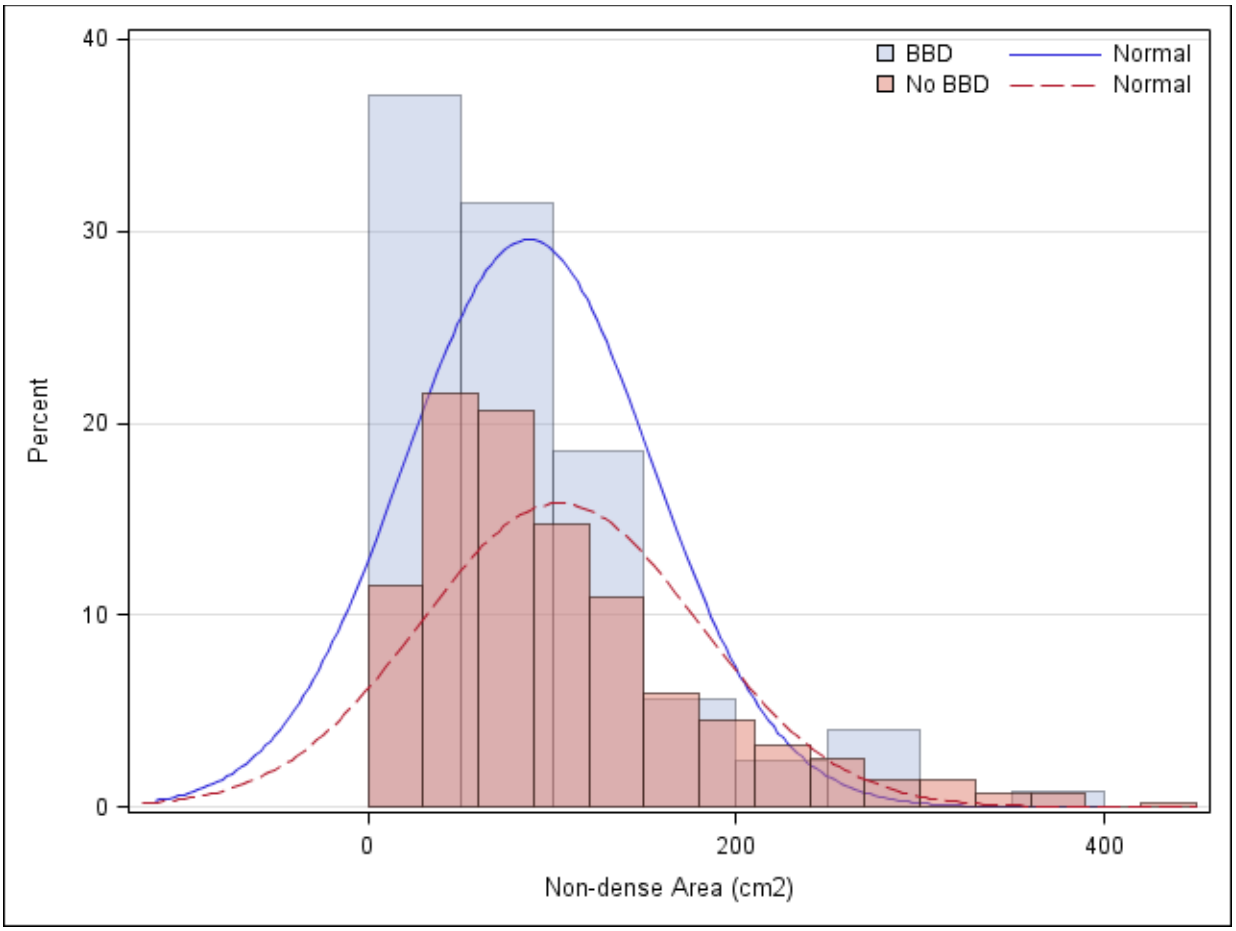

Table 2.1. Distribution of demographic and density characteristics in women with a history of benign breast disease and no history of benign breast disease

Characteristic	BBD (n=124) N (%)	No BBD (n=557) N (%)	p-value
Median age BBD diagnosis	32.0 years (range 12.0 - 44.0)	N/A	
Median time between BBD diagnosis and first mammogram	9.1 (range 0.1 - 27.6)	N/A	
Median age at first mammogram	41.3 years (range 30.1 - 45.9)	40.8 years (range 24.7 - 47.6)	0.33
Median time between mammograms (years; first to last mammogram)	2.9 years (range 0.0 - 16.6)	3.6 years (range 0.2 - 19.8)	0.31
Mean change in % density (first to last mammogram)	0.8 (range -20.4 - 22.5)	1.7 (range -27.6 - 31.6)	0.84
Mean change in dense area cm^2 (first to last mammogram)	0.0 (range -22.3 - 22.5)	2.3 (range -31.7 - 48.8)	0.65
Mean change in non-dense area cm^2 (first to last mammogram)	-2.7 (range -53.4 - 24.8)	-3.0 (range -123.9 - 150.8)	0.25
Race/Ethnicity			0.17
Non-Hispanic White	94 (75.8%)	435 (78.4%)	
Non-Hispanic African American	12 (9.7%)	72 (13.0%)	
Hispanic	12 (9.7%)	28 (5.1%)	
Other	6 (4.8%)	20 (3.6%)	
Family history of breast cancer			0.92
Yes	16 (12.9%)	70 (12.6%)	
No	108 (87.1%)	487 (87.4%)	
Menopausal Status			0.93
Premenopausal	86 (79.5%)	379 (69.0%)	
Perimenopausal	21 (17.2%)	96 (17.5%)	
Postmenopausal	15 (12.3%)	74 (13.5%)	
Alcohol Use age 20-29			0.35
Yes	80 (79.2%)	346 (83.2%)	
No	21 (20.8%)	70 (16.8%)	
BMI in 30s (mean±std)	23.7±5.5	25.0±5.6	0.02
Age Menarche (mean±std)	12.9±1.7	12.7±1.6	0.08
Parity			0.01
Nulliparous	18 (17.7%)	43 (8.8%)	
Parous	84 (82.4%)	446 (91.2%)	
Among parous women only:			
Age at first birth (mean±std)	26.5±5.4	27.6±5.7	0.09
Age at last birth (mean±std)	30.7±5.8	31.9±5.5	0.09
Breastfeeding			0.82
Never	20 (23.8%)	101 (22.7%)	
Ever	64 (76.2%)	344 (77.3%)	

Table 2.2. Association between mammographic breast density and change in breast density and BBD risk

	Model 1			Model 2			Model 3			Model 4		
	Age-adjusted model			**Adjusted for Age, Race, BMI 30s**			**Adjusted for Age, Race, BMI 30s, Age Menarche**			**Adjusted for Age, Race, BMI 30s, Age Menarche, Alcohol Use 20-29**		
Variables	**Estimate**	**Standard Error**	**p-value**	**Estimate**	**Standard Error**	**p-value**	**Estimate**	**Standard Error**	**p-value**	**Estimate**	**Standard Error**	**p-value**
Percent Density, First Mammogram BBD	5.67	1.80	0.002	3.65	1.45	0.01	3.64	1.46	0.01	3.54	1.71	0.04
Percent density, Last Mammogram BBD	5.95	2.39	0.01	4.05	1.95	0.04	4.05	1.96	0.04	2.74	2.32	0.24
Change in percent density BBD	-0.13	0.94	0.89	-0.22	0.96	0.82	-0.23	0.97	0.81	-0.40	1.04	0.70
Dense area, First Mammogram BBD	3.69	2.18	0.09	3.60	2.08	0.08	3.57	2.08	0.09	2.97	2.35	0.21
Dense area, Last Mammogram BBD	3.65	2.77	0.19	4.88	3.03	0.11	5.26	3.18	0.10	3.56	3.13	0.25
Change in dense area BBD	-0.59	1.38	0.67	-0.39	1.43	0.78	-0.49	1.43	0.73	-1.37	1.62	0.40
Non-dense area, First Mammogram BBD	-15.80	6.46	0.01	-5.22	4.92	0.29	-4.83	4.95	0.33	-3.73	5.41	0.49
Non-dense area, Last Mammogram BBD	-17.46	8.86	0.05	-4.55	7.12	0.52	-3.80	7.25	0.60	3.19	7.65	0.68
Change in non-dense area BBD	-2.81	2.16	0.19	-2.53	2.17	0.24	-2.75	2.23	0.22	-3.76	2.46	0.13

Table 2.3. Association between mammographic breast density and change in breast density and BBD risk using centered age at BBD

	Model 1			Model 2		
	Age at BBD centered model			**Adjusted for Age, Race, BMI 30s, Age at Menarche, Alcohol Use 20-29**		
Variables	**Estimate**	**Standard Error**	**p-value**	**Estimate**	**Standard Error**	**p-value**
Percent Density, First Mammogram						
no BBD	-5.66	1.79	0.002	-3.55	1.71	0.04
Age at BBD	-0.26	0.20	0.21	0.003	0.20	0.99
Percent density, Last Mammogram						
no BBD	-5.89	2.40	0.01	-2.93	2.35	0.21
Age at BBD	-0.19	0.30	0.53	0.14	0.29	0.63
Change in percent density						
no BBD	0.22	0.95	0.81	0.50	1.05	0.63
Age at BBD	-0.20	0.12	0.12	-0.12	0.12	0.29
Dense area, First Mammogram						
no BBD	-3.70	2.19	0.09	-3.03	2.34	0.20
Age at BBD	0.004	0.34	0.99	0.16	0.35	0.65
Dense area, Last Mammogram						
no BBD	-3.76	2.77	0.17	-4.43	3.18	0.16
Age at BBD	0.58	0.32	0.07	0.85	0.41	0.04
Change in dense area						
no BBD	0.68	1.38	0.62	1.60	1.65	0.33
Age at BBD	-0.26	0.19	0.17	-0.26	0.21	0.21
Non-dense area, First Mammogram						
no BBD	16.01	6.34	0.01	3.44	5.43	0.53
Age at BBD	1.51	0.63	0.02	0.77	5.43	0.17
Non-dense area, Last Mammogram						
no BBD	16.96	8.71	0.05	-5.13	7.76	0.51
Age at BBD	2.21	0.86	0.01	1.98	0.82	0.02
Change in non-dense area						
no BBD	2.76	2.19	0.21	4.31	2.47	0.08
Age at BBD	-0.26	0.18	0.16	-0.60	0.27	0.03

Table 2.4. Association between mammographic breast density and change in breast density and BBD risk using time between BBD and first mammogram centered

	Model 1			Model 2		
	Time Between BBD centered model			**Adjusted for Age, Race, BMI 30s, Age at Menarche, Alcohol Use 20-29**		
Variables	**Estimate**	**Standard Error**	**p-value**	**Estimate**	**Standard Error**	**p-value**
Percent Density, First Mammogram						
no BBD	-5.64	1.79	0.002	-3.55	1.71	0.04
Time Between BBD and First Mammogram	0.18	0.23	0.44	-0.02	0.23	0.92
Percent density, Last Mammogram						
no BBD	-5.97	2.42	0.01	-2.79	2.31	0.23
Time Between BBD and First Mammogram	0.08	0.37	0.84	-0.23	0.34	0.49
Change in percent density						
no BBD	0.14	0.97	0.88	0.38	1.04	0.71
Time Between BBD and First Mammogram	0.05	0.12	0.65	0.07	0.12	0.59
Dense area, First Mammogram						
no BBD	-3.68	2.19	0.09	-3.03	2.34	0.20
Time Between BBD and First Mammogram	-0.14	0.36	0.70	-0.23	0.36	0.53
Dense area, Last Mammogram						
no BBD	-3.14	2.66	0.24	-3.54	2.99	0.24
Time Between BBD and First Mammogram	-0.69	0.34	0.04	-0.93	0.43	0.03
Change in dense area						
no BBD	0.56	1.40	0.69	1.34	1.61	0.41
Time Between BBD and First Mammogram	0.10	0.16	0.53	0.15	0.19	0.45
Non-dense area, First Mammogram						
no BBD	15.96	6.34	0.01	3.51	5.42	0.52
Time Between BBD and First Mammogram	-1.51	0.69	0.03	-0.78	0.60	0.19
Non-dense area, Last Mammogram						
no BBD	18.73	8.55	0.03	-3.06	7.43	0.68
Time Between BBD and First Mammogram	-1.93	1.01	0.06	-1.86	0.88	0.04
Change in non-dense area						
no BBD	2.44	2.13	0.25	3.68	2.39	0.12
Time Between BBD and First Mammogram	0.38	0.23	0.09	0.52	0.33	0.11

Table 2.5. Association between mammographic breast density and change in breast density and BBD by pregnancy

		Model 1			Model 2		
		Parity model			Adjusted for Age, Race, BMI 30s, Age at Menarche, Alcohol Use 20-29		
Variables	**N**	**Estimate**	**Standard Error**	**p-value**	**Estimate**	**Standard Error**	**p-value**
Percent Density, First Mammogram							
No BBD Nulliparous	43	1.0 (ref)			1.0 (ref)		
No BBD Parous	446	-3.35	3.09	0.28	-2.50	2.69	0.35
BBD Nulliparous	18	9.73	4.53	0.03	5.10	4.55	0.26
BBD prior to pregnancy	26	9.78	4.65	0.04	5.09	3.84	0.19
BBD after pregnancy	58	-2.50	3.83	0.51	-2.31	3.40	0.50
Percent density, Last Mammogram							
No BBD Nulliparous	30	1.0 (ref)			1.0 (ref)		
No BBD Parous	277	-3.24	2.93	0.27	-2.06	2.70	0.45
BBD Nulliparous	8	0.59	4.59	0.90	-4.85	5.49	0.38
BBD prior to pregnancy	21	13.47	4.66	0.004	8.64	4.18	0.04
BBD after pregnancy	41	-1.47	4.35	0.74	-1.84	4.03	0.65
Change in percent density							
No BBD Nulliparous	30	1.0 (ref)			1.0 (ref)		
No BBD Parous	277	-2.73	1.63	0.09	-2.90	1.80	0.11
BBD Nulliparous	8	-1.56	1.91	0.42	-1.25	2.14	0.56
BBD prior to pregnancy	21	-2.56	2.63	0.33	-4.04	2.52	0.11
BBD after pregnancy	35	-2.57	1.84	0.16	-1.97	2.11	0.35
Dense area, First Mammogram							
No BBD Nulliparous	43	1.0 (ref)			1.0 (ref)		
No BBD Parous	446	-1.78	4.35	0.68	-1.97	3.51	0.58
BBD Nulliparous	18	18.75	9.21	0.04	12.39	6.97	0.08
BBD prior to pregnancy	26	0.56	5.28	0.92	-0.76	4.84	0.87
BBD after pregnancy	58	-2.55	4.95	0.61	-1.24	4.46	0.78
Dense area, Last Mammogram							
No BBD Nulliparous	30	1.0 (ref)			1.0 (ref)		
No BBD Parous	277	-7.55	6.61	0.25	-6.59	4.16	0.11
BBD Nulliparous	8	0.87	8.09	0.91	-1.43	7.44	0.85
BBD prior to pregnancy	21	-2.51	6.96	0.72	-3.54	5.32	0.51
BBD after pregnancy	41	0.73	9.30	0.94	-1.74	6.26	0.78

Change in dense area							
No BBD Nulliparous	30	1.0 (ref)			1.0 (ref)		
No BBD Parous	277	-0.96	2.25	0.67	-1.52	2.50	0.54
BBD Nulliparous	8	-0.76	2.62	0.77	-1.11	3.06	0.72
BBD prior to pregnancy	21	-1.13	3.55	0.75	-2.42	3.50	0.49
BBD after pregnancy	35	-1.64	2.79	0.56	-2.35	3.25	0.47
Non-dense area, First Mammogram							
No BBD Nulliparous	43	1.0 (ref)			1.0 (ref)		
No BBD Parous	446	4.49	13.45	0.74	1.50	9.31	0.87
BBD Nulliparous	18	-28.29	19.19	0.14	-0.08	15.81	1.00
BBD prior to pregnancy	26	-31.03	17.09	0.07	-12.34	11.16	0.27
BBD after pregnancy	58	-3.43	15.55	0.83	5.24	11.80	0.66
Non-dense area, Last Mammogram							
No BBD Nulliparous	30	1.0 (ref)			1.0 (ref)		
No BBD Parous	277	-0.86	14.99	0.95	-3.04	10.85	0.78
BBD Nulliparous	8	-17.00	19.68	0.39	6.41	20.62	0.76
BBD prior to pregnancy	21	-52.45	17.07	0.002	-22.89	12.10	0.06
BBD after pregnancy	41	-3.82	19.58	0.85	16.42	16.06	0.31
Change in non-dense area							
No BBD Nulliparous	30	1.0 (ref)			1.0 (ref)		
No BBD Parous	277	8.52	4.99	0.09	5.95	3.68	0.11
BBD Nulliparous	8	6.19	6.23	0.32	2.91	5.93	0.62
BBD prior to pregnancy	21	8.92	5.00	0.07	8.44	4.08	0.04
BBD after pregnancy	41	3.65	5.52	0.51	-2.43	4.96	0.62

2.6 References

1. Boyd NF, Byng JW, Jong RA*, et al.* Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst 1995;87(9):670-5.

2. Boyd NF, Lockwood GA, Byng JW*, et al.* Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers Prev 1998;7(12):1133-44.

3. Byrne C, Schairer C, Wolfe J*, et al.* Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 1995;87(21):1622-9.

4. Bodian CA, Perzin KH, Lattes R*, et al.* Prognostic significance of benign proliferative breast disease. Cancer 1993;71(12):3896-907.

5. Ris HB, Niederer U, Stirnemann H*, et al.* Long-term follow-up of patients with biopsy-proven benign breast disease. Annals of Surgery 1988;207(4):404-9.

6. Bartow SA, Pathak DR, Mettler FA. Radiographic microcalcification and parenchymal patterns as indicators of histologic "high-risk" benign breast disease. Cancer 1990;66(8):1721-5.

7. Bright RA, Morrison AS, Brisson J*, et al.* Histologic and mammographic specificity of risk factors for benign breast disease. Cancer 1989;64(3):653-7.

8. Boyd NF, Jensen HM, Cooke G*, et al.* Relationship between mammographic and histological risk factors for breast cancer. J Natl Cancer Inst 1992;84(15):1170-9.

9. Boyd NF, Jensen HM, Cooke G*, et al.* Mammographic densities and the prevalence and incidence of histological types of benign breast disease. Reference Pathologists of the Canadian National Breast Screening Study. Eur J Cancer Prev 2000;9(1):15-24.

10. Byrne C, Schairer C, Brinton LA*, et al.* Effects of mammographic density and benign breast disease on breast cancer risk (United States). Cancer Causes Control 2001;12(2):103-10.

11. Tice JA, O'Meara ES, Weaver DL*, et al.* Benign Breast Disease, Mammographic Breast Density, and the Risk of Breast Cancer. J Natl Cancer Inst 2013;105(14):1043-9.

12. Oza AM, Boyd NF. Mammographic parenchymal patterns: a marker of breast cancer risk. Epidemiologic reviews 1993;15(1):196-208.

13. Bartow SA, Pathak DR, Mettler FA*, et al.* Breast mammographic pattern: a concatenation of confounding and breast cancer risk factors. American Journal of Epidemiology 1995;142(8):813-9.

14. Boyd N, Martin L, Stone J*, et al.* A longitudinal study of the effects of menopause on mammographic features. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2002;11(10 Pt 1):1048-53.

15. Maskarinec G, Pagano I, Lurie G*, et al.* A longitudinal investigation of mammographic density: the multiethnic cohort. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2006;15(4):732-9.

16. Terry MB, Schaefer CA, Flom JD*, et al.* Prenatal smoke exposure and mammographic density in mid-life. Journal of Developmental Origins of Health and Disease 2011;2(6):340-52.

17. Horn-Ross PL, Canchola AJ, West DW*, et al.* Patterns of alcohol consumption and breast cancer risk in the California Teachers Study cohort. Cancer Epidemiology, Biomarkers & Prevention 2004;13(3):405-11.

18. Ishitani K, Lin J, Manson JE*, et al.* Caffeine consumption and the risk of breast cancer in a large prospective cohort of women. Archives of Internal Medicine 2008;168(18):2022-31.

19. Byng JW, Boyd NF, Fishell E*, et al.* The quantitative analysis of mammographic densities. Physics in medicine and biology 1994;39(10):1629-38.

20. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312(3):146-51.

21. Hartmann LC, Sellers TA, Frost MH*, et al.* Benign breast disease and the risk of breast cancer. New England Journal of Medicine 2005;353(3):229-237.

22. Kabat GC, Jones JG, Olson N*, et al.* Risk factors for breast cancer in women biopsied for benign breast disease: a nested case-control study. Cancer Epidemiol 2010;34(1):34-9.

23. Collins LC, Baer HJ, Tamimi RM*, et al.* Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia: results from the Nurses' Health Study. Cancer 2007;109(2):180-7.

24. Harris JR. *Diseases of the breast*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2010.

25. Boyd NF, Rommens JM, Vogt K*, et al.* Mammographic breast density as an intermediate phenotype for breast cancer. The Lancet. Oncology 2005;6(10):798-808.

Chapter 3:

Modification by reproductive, hormonal, and lifestyle factors of breast cancer risk in a prospective cohort of women with benign breast disease

3.1 Abstract

Introduction: Although family history and age are consistently associated with risk of breast cancer after a diagnosis of benign breast disease (BBD), less is known about other risk factors, particularly modifiable ones. We investigated the associations between reproductive factors, lifestyle factors and BBD and risk of invasive breast cancer.

Methods: We examined the association of BBD and reproductive, hormonal, and other lifestyle factors with risk of breast cancer using information from 1,240 women with BBD and 1,322 women without BBD enrolled in the Women At Risk (WAR) registry from 1991 to 2011 at Columbia University Medical Center. Hazard ratios for invasive breast cancer were estimated using Cox regression, adjusting for age, race, first-degree family history, age at first birth, number of live births, age at last birth, and current alcohol consumption.

Results: Over 22,078 person-years of observation and an average follow-up of 8.62 years, there were 121 incident breast cancers: 74 in women with BBD and 47 in women without BBD. Women with BBD had 2.68 higher risk of BC compared to women without BBD (HR: 2.68, 95% CI: 1.86-3.87). In nulliparous women, those with BBD had an almost 5-fold higher risk of breast cancer than women without BBD (nulliparous, BBD vs. nulliparous, no BBD: HR: 4.87, 95% CI: 2.41-9.86). There was multiplicative interaction for the association between BBD and parity (Ratio of HR: 0.37, 95% CI: 0.16-0.86). In women with BBD, breast cancer risk increased with increasing frequency of alcohol consumption, whereas in women without BBD there was a suggestion of an inverse association with breast cancer risk, regardless of frequency of consumption (Alcohol use, Yes vs. No, BBD: HR: 2.11, 95% CI: 1.25-3.57, no BBD: HR: 0.56, 95% CI: 0.31-1.02). We found both multiplicative and additive interaction between alcohol use and BBD.

Conclusions: We observed differences in selected established breast cancer risk factors (parity and alcohol consumption) by whether women were also diagnosed with BBD. However, associations between age at menarche, oral contraceptive use, and smoking status were similar regardless of BBD status. If replicated in other larger BBD cohorts, these data suggest that it may be important to counsel women with BBD on reducing their alcohol intake.

3.2 Introduction

Breast biopsies are common and typically result in benign histologic diagnoses [1]. Benign breast disease (BBD) is an important risk factor for subsequent development of breast cancer [2-4]. Epidemiologic studies show an association between reproductive, hormonal, and nutritional and lifestyle factors and breast cancer risk (reviewed in [5]). However, epidemiologic studies of these same factors show inconsistent or null results with BBD risk (reviewed in [6]). If risk factors for BBD are not similar to risk factors for breast cancer, BBD may not be a mediator between these exposures and breast cancer. Alternatively, they may be joint exposures that work together to increase breast cancer risk. Indeed, BBD could be a result of genetic factors or accelerated tissue aging as a result of earlier life factors. A number of studies within the Nurses' Health Study have shown an association between adolescent factors and BBD [7-12].

Previous cohort studies in women with BBD have been derived from clinic [13-17], screening [18-21], or existing cohorts [22-26]. None of these studies have been conducted in a high-risk population enriched for family history of breast cancer. First-degree family history has been associated with increased breast cancer risk among women with BBD [2-4, 27-30]. Family history is a major breast cancer risk factor that has implications for both screening and prevention. How family history is accounted for in women counseled with BBD is important to providing comprehensive care.

Time is important to subsequent risk of breast cancer – both time of BBD diagnosis and risk factor collection. With the exception of the screening based cohorts [18-21], previous studies collected risk factor information on women with prevalent BBD. Risk factors may be different in women with prevalent versus incident BBD, and the timing of BBD in relation to risk factor collection should be accounted for. Accounting for different timing of BBD diagnosis in relation to BBD diagnosis could help explain discrepancies between breast cancer risk and time since BBD biopsy. A screening-based cohort found that risk of breast cancer was greatest within the first 15 years since BBD diagnosis [18], whereas an analysis in an existing cohort found that risk was slightly higher more than 10 years after BBD diagnosis [31]. Although screening cohorts were assessing risk factor information in incident BBD, these cohorts were made up of an average risk population with approximately 10-16% of women having a family history of breast cancer [18-21].

Family history and age are consistently associated with risk of breast cancer after a diagnosis of BBD; less is known about other established breast cancer risk factors [2-4]. Specifically, few cohort studies have examined effect modification of breast cancer risk between BBD and reproductive [4, 15, 18, 23, 31, 32], hormonal [22, 32-37], nutritional and lifestyle factors [24-26, 38, 39]. These cohorts examined multiplicative interactions between age at first birth [15], menopause [2, 4, 23, 30-32] , exogenous estrogens [32, 34, 35, 37], and alcohol use [24, 25, 38]. None of these cohort studies examined multiplicative interaction with age at menarche, breastfeeding, obesity, physical activity, smoking, or other breast cancer risk factors. Many of these factors are important as they are potentially modifiable risk factors, i.e. obesity, physical activity, and smoking. Prevention is a key component to clinical counseling of high-risk women. If these factors can help reduce risk of breast cancer, women need to be encouraged to make these lifestyle changes. Therefore, additional cohort studies are needed to examine both multiplicative and additive interaction between established breast cancer risk factors and BBD.

We followed a cohort of high-risk women to investigate the development of invasive breast cancer and examined differences in incidence in women with and without BBD. We investigated effect modification between reproductive, hormonal, nutritional and lifestyle factors and BBD and risk of invasive breast cancer.

3.3 Methods

The Women At Risk (WAR) registry at Columbia University Medical Center (CUMC) is a prospectively-followed cohort of women at high risk from breast cancer. This study has been previously described [40-42]. Initiated in 1991, the WAR registry continued to enroll patients until July 2011. Eligible participants met one or more of the following criteria: 1) one or more first-degree relatives (mother, daughter, or sister) with premenopausal breast cancer, 2) two or more first-degree relatives with breast cancer, and/or 3) history of biopsy-proven lobular carcinoma *in situ*, atypical ductal hyperplasia (ADH), or atypical lobular hyperplasia (ALH). 39% of women included only had a strong family history of breast cancer and no biopsy proven diseases. A detailed questionnaire administered at baseline provided information on demographics and breast cancer risk factors. We obtained clinical follow-up on patient outcomes by medical chart review and tracking breast cancer outcomes through linkage with New York-Presbyterian Tumor Registry.

In total, the WAR registry includes 2,674 women. We excluded from our analyses women within WAR with LCIS (N=111) prior to WAR enrollment. In addition, we excluded women whose breast cancer diagnosis was less than 6 months after enrollment (N=3).

We determined BBD diagnosis through chart review of biopsy and/or surgical specimens. BBD was broken into the three main categories as defined by Dupont and Page [27]: atypical hyperplasia (AH), proliferative disease without atypia (PDWA), and nonproliferative disease (NP). If a patient had multiple different types of BBD listed in her chart, we selected the most progressive diagnosis for that woman. For example, if a woman had a core biopsy that listed fibrocystic disease, but also had a focus of atypical ductal hyperplasia, that woman was defined as having atypical hyperplasia. We examined the association of BBD and reproductive, hormonal, and other lifestyle factors with risk of subsequent breast cancer using 1,240 women with BBD and 1,320 women without BBD. Women with prevalent BBD are women diagnosed with BBD prior to enrollment in WAR (N=396), and incident BBD are women diagnosed with BBD during WAR follow-up (N=844).

For some of our epidemiologic risk factors we had missing at random (MAR) data on women in WAR. MAR is when missing data does not depend on the value of another variable. For this analysis, we determined whether or not variables were MAR based on if they are associated with BBD (Appendix A, Table A1). If any of the variables with missing data are related to BBD, our main exposure of interest, then the data would not be considered MAR. The only variable that showed an association with BBD was ever smoker. However, the MAR assumption is not testable [43]. To determine if our imputation approach was acceptable, we assessed the association between breast cancer risk and each of the variables with >5% missing data and found that the beta estimates remained unchanged (Appendix A, Table A2). The only exception was “ever smoker”, which showed an attenuation of the association with breast cancer risk. We used the sequential regression imputation method for multiple imputation, using Imputation and Variance Estimation Software (IVEware) 0.2, developed by researchers at University of Michigan [44]. We imputed those variables with >5% missing data, menopausal status, age at menarche, BMI, oral contraceptive use and duration, alcohol use and frequency of consumption, smoking status and duration of smoking. We then exported the imputed data and analyzed in SAS version 9.3 (Cary, NC) for all analyses.

We estimated hazard ratios for invasive breast cancer using Cox regression [45]. A log-negative log graph showed our models met the assumption of proportionality. We modeled BBD as a time varying covariate, to account for the fact that women may change in value over the course of follow-up [45, 46]. To account for multiple dates of diagnosis and determine the most appropriate follow-up for all women we based follow-up time on a number of different criteria. We used the counting process method, which provides a record of observation for each interval of time during which all covariates remain constant [46]. For women without BBD there is only one record. Prevalent BBD, women diagnosed with BBD prior to enrollment in WAR, also only have one record and enter into the model with a BBD diagnosis. Women diagnosed with incident BBD require two records: one to account for their interval between enrollment and BBD diagnosis, and the second the interval between BBD diagnosis and either breast cancer diagnosis, mastectomy, death, or date of last follow-up (July 1, 2013). We conducted a sensitivity analysis to see how our estimates varied based on not modeling BBD as a time-varying covariate, we found that by not modeling BBD this way the associations with breast cancer risk were similar for many variables, but slightly attenuated for a number of factors (Appendix A, Table A3). We would expect that the results would differ more modeling BBD these two different ways, however, seeing no change in the associations may be due to the fact that many of these other factors are fixed (i.e. reproductive factors that have already occurred) and that there is no change in their association over time. Follow-up on women without BBD was from time of enrollment to breast cancer diagnosis, mastectomy, death, or date of last follow-up (July 1, 2013). Women with ductal carcinoma *in situ* (DCIS) were censored at their date of diagnosis of DCIS and not included in the definition of a breast cancer case. There were only 30 (1.2%) women diagnosed with DCIS on follow-up, 21 (1.7%) were women with a history of BBD and 9 (0.7%) were women with no history of BBD.

Interactions between BBD and reproductive, hormonal, nutritional and lifestyle factors were entered into a model to assess the association with BBD on risk of invasive breast cancer. We used a macro developed by Rod *et al.* to estimate additive and multiplicative interactions in a Cox proportional hazards model [47]. We excluded nulliparous women from interactions with age at first birth, number of live births, and age at last live birth. We examined established breast cancer risk factors as potential confounders in our analyses (including age at mammogram, race/ethnicity, BMI, menopausal status, age

at menarche, parity, number of live births, breast feeding, oral contraceptive use, current alcohol use, ever smoker, and first degree family history of breast cancer). Alcohol consumption was categorized as frequency, less than once per month, 1-3 times per month, once a week, 2-3 times per week, daily, 2-3 times per day. In the women with prevalent BBD these factors are measured after their diagnosis with BBD, whereas in women with incident BBD these are all measured prior to BBD diagnosis. Including BBD as a time-varying covariate will account for this, as all prevalent BBD enter the model as already being diagnosed with BBD, whereas the incident BBD are modeled as BBD once they are diagnosed with BBD. Models included adjustment for covariates that changed the association between BBD and invasive breast cancer by more than 10%. Adjusted models included age, race, first-degree family history of breast cancer, age at first birth, number of live births, age at last birth, and current alcohol consumption.

3.4 Results

Table 3.1 shows the number of women with breast cancer and person years of follow-up for reproductive and lifestyle factors known to be associated with breast cancer risk. In this table, we also show the unadjusted associations between these factors and breast cancer risk. As expected, having a history of BBD is associated with an almost 3-fold higher risk of breast cancer (HR: 2.75, 95% CI: 1.90-3.98). We see a higher overall breast cancer risk in postmenopausal women, women with an earlier age at menarche, and women who consumed alcohol on a daily basis. However, overall, we did not observe an effect of parity (HR: 0.84, 95% CI: 0.58-1.26) and saw a reduced risk with oral contraceptive use (yes/no) (HR: 0.67, 95% CI: 0.46-0.97). This inverse association was strongest among those women who had used oral contraceptives for 2 years or less. We also found a reduced breast cancer risk in women with a first-degree family history as compared to women with no first-degree family history (HR: 0.54, 95% CI: 0.36-0.81). Fifty-one percent of the women with BBD had no first-degree family history; in addition, 66% of the women with no family history had BBD, whereas only 38% of the women with one first-degree family history had BBD.

We examined hormonal, reproductive, nutritional and lifestyle factors to assess if there was effect modification between these factors and BBD on the risk of invasive breast cancer. We found that parity, age at first birth, number of births, and age at last birth had significant multiplicative interaction with BBD

(**Table 3.2**). Using a common referent group of no BBD and nulliparous women, we found that nulliparous women with BBD had a 5-fold higher risk of breast cancer, adjusting for age, race, family history of breast cancer, current alcohol use, age at first birth, number of live births, and age at last live birth (RR: 5.33, 95% CI: 2.57-11.05). Parous women with no BBD had a 50% higher risk of breast cancer than nulliparous women with no BBD, adjusting for age, race, family history of breast cancer, current alcohol use, age at first birth, number of live births, and age at last live birth (RR:1.50, 95% CI: 0.64-3.52). Parous women with BBD had 3-fold higher risk of breast cancer compared to nulliparous women with no BBD in the adjusted model (RR: 2.93, 95% CI: 1.27-6.76). We found a negative multiplicative interaction between parity and BBD when using the referent group of nulliparous women with no BBD (RR: 0.37, 95% CI: 0.16-0.86; **Table 3.2**), however, we saw no additive interaction. Due to the strong effect between nulliparous women with and without BBD, we examined the remaining reproductive factors excluding nulliparous women to see if effect modification persisted in only parous women. Age at first birth showed a trend of increasing risk of breast cancer with increasing age at first birth (**Table 3.2**). We found an increased risk of breast cancer for women with no BBD and two or more live births, as compared to women with no BBD and only one live birth (RR: 2.36, 95% CI: 0.99-5.60). However, we found no multiplicative or additive interaction between BBD and number of live births. For all women with BBD, regardless of number of live births, their risk of breast cancer was 3-4 fold higher than women with no BBD and only one live birth. Interval between age at menarche and age at first birth showed increasing breast cancer risk with increasing interval regardless of BBD status. Neither interval between age at menarche and age at first birth nor age at last live birth showed a multiplicative or additive interaction with BBD.

Current alcohol use and frequency of consumption were the only lifestyle factors we examined that had a significant multiplicative and additive interaction with BBD (**Table 3.2**). Within women without BBD, current alcohol users had a 40% decreased risk of breast cancer as compared to women with no current alcohol use (RR: 0.60, 95% CI: 0.33-1.09). We found a 38% increased risk of breast cancer in women with BBD who are not current alcohol users compared to women with no BBD and no current alcohol use (RR: 1.38, 95% CI: 0.73-2.61), whereas women with both BBD and current alcohol use had a significant 2-fold higher risk of breast cancer as compared to women with no BBD and no current alcohol

use (RR: 2.27, 95% CI: 1.33-3.87). There was a significant synergistic multiplicative and additive interaction between BBD and current alcohol use (RR: 2.73, 95% CI: 1.24-6.01 and Relative Excess Risk Index (RERI): 1.29, 95% CI: 0.36-2.22). Examining alcohol use by consumption, we found regardless of amount of consumption, women with no BBD who consumed alcohol still had a decreased risk of breast cancer as compared to women with no BBD and who do not consume alcohol. Risk of breast cancer increased approximately 2-fold in women with BBD for <1-3 times per month, 1-3 times per week, and daily or 2-3 times per day as compared to non-drinkers without BBD (RR: 2.40, 95% CI: 1.29-4.46; RR: 1.99, 95% CI: 1.05-3.78; RR 2.63, 95% CI: 1.23-5.61, respectively).

We were concerned with the potential collider bias due to the inclusion criteria for the cohort of having a strong family history, meaning potentially our reference group of no BBD was made up of a large proportion of women with family history and therefore may bias our associations. Collider bias is a type of selection bias where conditioning on a common effect of exposure and outcome may bias estimates [48]. To assess this we examined our interaction results for no BBD and BBD in women with a family history of breast cancer. Overall, we found very similar associations in women with a family history of breast cancer as we saw for the entire cohort (Appendix A, Table A4). Although slightly attenuated, we still see an increased risk of breast cancer in nulliparous women with a history of BBD as compared to nulliparous women without BBD. For alcohol consumption we still see a slightly higher risk in women with BBD who consume alcohol compared to women without BBD who do not consume alcohol. However, there is little difference in the effect estimates in women with BBD who consume and do not consume alcohol.

3.5 Discussion

Epidemiologic studies have shown approximately a 2-fold increased risk of breast cancer in women with BBD as compared to population controls [3, 13, 14]. Many cohort studies though have not used internal normal controls as a comparison group [3, 13-15, 19, 30]. We found an almost 3-fold increased risk of breast cancer in women with BBD as compared to women without BBD in a high-risk population. In addition, only a few cohort studies have examined joint effects of BBD and reproductive [4, 15, 18, 23, 31, 32], hormonal [22, 32-37], nutritional and lifestyle factors [24-26, 38, 39] on breast cancer risk. In this study, we found women with BBD and who are nulliparous have a 5-fold increased risk of invasive breast cancer after controlling for other factors. Women with BBD and who consumed alcohol

were at a significantly increased risk of breast cancer as compared to women without BBD and who did not consume alcohol. The BBD and alcohol association was also strongest in those women that consumed alcohol daily. Interactions, either additive or multiplicative, between BBD and race, menopausal status, body mass index (BMI), age at menarche, oral contraceptive use, smoking, and family history of breast cancer were statistically non-significant.

Previous research suggests that the differentiation of breast tissue at time of exposure to a carcinogen is important and poorly differentiated tissue is more likely to develop into invasive breast cancer [49]. Therefore, increased risk in women with BBD may be due to their tissue being less well differentiated at time of exposure as compared to women without BBD. Differentiation may be an important factor as to why we are seeing joint effects with nulliparity and alcohol consumption.

Regardless of parity status, BBD increases breast cancer risk. However, in women with both BBD and nulliparity this risk is almost 5-fold higher as compared to women without BBD and who are nulliparous; in parous women the increase is 3-fold with BBD. This combination of BBD, (that increases susceptibility, and nulliparity, that has different hormonal milieu,) creates an environment in the breast for carcinogenesis. Epithelial cells in BBD may not have reached their malignant potential – however, progression may depend on hormonal promotion [50]. Hormones may be influencing malignancy of BBD tissue in two ways: either through progesterone or prolactin. Women with BBD have low production of progesterone during the luteal phase of their menstrual cycle [50]. In addition, an increased risk of BBD, specifically in proliferative lesions, was associated with increased levels of estradiol [51]. Previous studies have shown that hyperplastic changes occur with high levels of estradiol and deficient progesterone secretion [50]. Furthermore, parous and nulliparous women have differing levels of estradiol [52].

A more likely mechanism driving the increased risk in nulliparous women with BBD may be through the effects of prolactin on the breast tissue. Prolactin is locally produced in breast tissue [53] and increases cell proliferation, inhibition of apoptosis, and motility [54]. Prolactin has a positive association with breast cancer risk in postmenopausal women [55-58]. The protective effect of parity may be mediated in part by lower prolactin levels in parous women [59-62]. Elevated levels of prolactin have been found in women with BBD [63-66], whereas other studies found normal levels [60, 61, 67]. However,

all the studies that found no difference in prolactin between women with and without BBD were self-reported studies. An important factor in the pathogenesis could be higher expression of prolactin receptor in cells of BBD compared with normal cells [68]. BBD associated with increased epithelial proportion [69] and the prolactin receptor is concentrated more heavily in epithelial (compared to stromal) tissue [68]. Only one study assessed BBD and parity simultaneously and found higher prolactin levels in nulliparous women with fibroadenoma (compared to parous women with fibroadenoma) [70]. Large prospective studies with pathologically-confirmed BBD are needed to investigate this potential mechanism.

We found both additive and multiplicative interaction on breast cancer risk between BBD and alcohol consumption. This is of note as additive interactions are thought to be more important in addressing public health relevance [48]. In addition, alcohol consumption is a modifiable risk factor whereas parity is typically considered a non-modifiable risk factor. Advising women with a diagnosis of BBD to avoid alcoholic beverages may reduce invasive breast cancer incidence. Alcohol consumption has consistently been associated with increased breast cancer risk [71-73]. The association between alcohol consumption and BBD has been less consistent. Recent alcohol consumption has no association with BBD in some studies [38, 74-76] and others a decreased risk of BBD [77]. A large-pooled study, in average risk women, found no interaction between BBD and alcohol consumption on breast cancer risk [78]. However, similar to our findings, a more recent study found greatest risk of breast cancer in recent heavy alcohol consumption and women who have a history of BBD [25].

There are a number of proposed mechanisms through which alcohol may influence breast cancer risk; the most common is alcohol increasing estrogen levels [79-81]. Estrogen is related to breast carcinogenesis through its actions on binding to estrogen receptor alpha leading to an increase in cell proliferation [82]. This corresponds with the theory of alcohol as a breast tumor promoter. Alcohol could be acting on the BBD tissue that is less well differentiated by increasing the growth rate of cells. Recent alcohol use may be conferring a greater risk in women with BBD by reducing the latency between time of exposure to the carcinogen and invasive breast cancer.

Our study limitations are the relatively imprecise measurement of alcohol consumption and changes in parity over time. We only have consumption based on number of times of drinks per day, week, or month. We do not have any detailed information on number of drinks or amount of alcohol

consumed in each sitting. In addition, while the entire study population showed an increased risk of breast cancer in the highest consumption group, in women without BBD we saw decreased risks for all levels of consumption compared to non-drinkers. This finding is unexpected and it is unclear why these women would have a reduced risk of breast cancer. While we were able to model BBD as a time-varying covariate, other variables that may change over time (specifically parity) were based on baseline responses. In addition, follow-up of this cohort was passive follow-up and the diagnoses of breast cancer and/or other events were based on death and/or tumor registry records. Of note, if we do not model BBD as a time-varying covariate, our associations with breast cancer risk attenuate slightly, indicating that timing of BBD diagnosis is an important confounder in these associations. If parity changed over time our estimate among nulliparous women may be biased if in fact these women had children after baseline but before breast cancer diagnosis. However, we are examining the joint effects of these two factors and it is not important which came before the other as we are not examining mediation. What is important is that the changes in the tissue, potentially due to prolactin, are stronger with women who have both these risk factors.

In conclusion, we found that diagnosis of BBD with parity and BBD with alcohol consumption modify breast cancer risk. Our study examines both additive and multiplicative interaction for various reproductive and lifestyle factors. It is important to consider additive interactions, especially when trying to address public health interventions. Additive interaction implies that prevention would differ based on target population. In this study, we see that women with BBD are an important subgroup to target for prevention of breast cancer through reduction of alcohol consumption. While parity is a non-modifiable risk factor, women diagnosed with BBD who currently consume alcohol should be counseled on their drinking behaviors. Interventions to reduce alcohol consumption may help reduce risk of breast cancer in women with BBD.

Table 3.1. Univariable relative risk of invasive breast cancer by reproductive factors, lifestyle factors and BBD, WAR 1991-2013

	No. of Women (n=2560), No. (%)	No. of women with breast cancer (n=119)	No. of person-years of follow-up	HR (95% CI)
Benign Breast Disease				
Yes	1240 (48.4%)	74	9895.79	2.75 (1.90-3.98)
No	1320 (51.6%)	45	12182.67	1.00
Histology				
No BBD	1320 (51.6%0	45	12182.67	1.00
Nonproliferative disease	400 (15.6%)	25	3450.75	1.96 (1.20-3.20)
Proliferative disease without atypia	309 (12.1%)	16	2393.37	1.82 (1.03-3.22)
Atypical Hyperplasia	531 (20.7%)	33	4051.66	2.33 (1.49-3.67)
Age				
≤35 years	357 (14.0%)	10	3258.56	1.00
36-45 years	836 (32.7%)	34	7463.38	1.49 (0.74-3.01)
46-55 years	801 (31.3%)	36	6948.19	1.73 (0.86-3.49)
>55 years	564 (22.1%)	39	4372.87	2.95 (1.47-5.90)
Race/Ethnicity				
Caucasian	1907 (74.5%)	98	17012.46	1.00
Hispanic	243 (9.5%)	7	1840.46	0.65 (0.30-1.40)
African American	98 (3.8%)	4	777.86	0.91 (0.34-2.49)
Asian	84 (3.3%)	2	537.67	0.70 (0.17-2.82)
Other	228 (8.9%)	8	1910.01	0.73 (0.36-1.50)
Menopausal Status				
Premenopausal	1416 (55.3%)	56	12725.27	1.00
Postmenopausal	1144 (44.7%)	63	9353.19	1.53 (1.07-2.20)
BMI				
<25 kg/m^2	1640 (64.1%)	68	14323.21	1.00
≥25 kg/m^2	920 (35.9%)	51	7755.25	1.37 (0.95-1.97)
Age at Menarche				
≤11 years	490 (19.1%)	26	4220.72	1.19 (0.77-1.85)
≥12 years	2070 (80.9%)	93	17857.74	1.00
Parity				
Nulliparous	737 (28.8%)	39	6390.8	1.00
Parous	1823 (71.2%)	80	15687.66	0.84 (0.58-1.24)
Age at First Birth				
<30 years	1243 (48.6%)	54	10788.6	0.84 (0.55-1.26)
≥30 years	580 (22.7%)	26	4899.06	0.86 (0.52-1.41)
No Births	737 (28.8%)	39	6390.8	1.00
Number of Births				
1 birth	597 (23.3%)	19	5175.58	0.59 (0.34-1.01)
≥2 births	1226 (47.9%)	61	10512.08	0.98 (0.65-1.47)
No Births	737 (28.8%)	39	6390.8	1.00
Age at Last Live Birth				
<35 years	1305 (51.0%)	60	11249.95	0.89 (0.59-1.33)
≥35 years	518 (20.2%)	20	4437.71	0.74 (0.43-1.27)
No Births	737 (28.8%)	39	6390.8	1.00
Interval between Age at Menarche and Age at First Birth				
<15 years	958 (37.4%)	42	8249.06	0.85 (0.55-1.32)
≥15 years	865 (33.8%)	38	7438.6	0.83 (0.53-1.30)
No Births	737 (28.8%)	39	6390.8	1.00
Breastfeeding (among parous)				
Yes	980 (53.8%)	45	8407.08	1.08 (0.69-1.68)
No	843 (26.2%)	35	7280.58	1.00
Duration of Breastfeeding (among parous)				
<2 years	723 (39.7%)	35	6163.96	1.14 (0.71-1.82)
≥2 years	257 (14.1%)	10	2243.12	0.92 (0.46-1.87)
None	843 (46.2%)	35	7280.58	1.00
Oral Contraceptive Use				
Yes	1273 (49.7%)	47	10828.88	0.67 (0.46-0.97)
No	1287 (50.3%)	72	11249.58	1.00
Duration of Use				
<2 years	625 (24.4%)	19	5738.1	0.51 (0.31-0.84)
≥2 years	648 (25.3%)	28	5090.78	0.86 (0.55-1.33)
None	1287 (50.3%)	72	11249.58	1.00
Current Alcohol Use				
Yes	1677 (65.5%)	79	14387.19	1.06 (0.73-1.56)

No	883 (34.5%)	40	7691.27	1.00
Frequency of Consumption				
<1 - 3 times per month	703 (27.5%)	33	6137.8	1.05 (0.66-1.66)
1-3 times per week	710 (27.7%)	31	6100.78	0.98 (0.61-1.56)
Daily to 2-3 times per day	264 (10.3%)	15	2148.61	1.36 (0.75-2.46)
None	883 (34.5%)	40	7691.27	1.00
Ever Smoker				
Yes	1164 (45.5%)	53	9914.60	1.00 (0.70-1.43)
No	1396 (54.5%)	66	12163.85	1.00
Duration of Smoking (among Yes)				
<5 years	430 (16.8%)	19	3629.53	0.98 (0.59-1.63)
6-10 years	190 (7.4%)	14	1608.82	1.61 (0.90-2.86)
>10 years	544 (21.3%)	20	4676.26	0.80 (0.49-1.32)
None	1396 (54.5%)	66	12163.85	1.00
First Degree Family History of Breast Cancer				
No First Degree Family History	905 (36.6%)	49	7182.19	1.00
1 First Degree Family Member	1267 (51.3%)	47	11982.1	0.54 (0.36-0.81)
>1 First Degree Family Member	299 (12.1%)	21	2401.78	1.29 (0.77-2.15)

Table 3.2. Effect modification of breast cancer risk between BBD and reproductive, hormonal, and lifestyle factors

	Benign Breast Disease, No (n = 1320)			Benign Breast Disease, Yes (n = 1240)					
	No. of person-years of follow-up	No. of women with breast cancer (n=119)	Multivariable adjusted HR (95% CI)	No. of person-years of follow-up	No. of women with breast cancer (n=119)	Multivariable adjusted HR (95% CI)	HR (95% CI) for BBD within strata of Risk Factor	Effect Modification on Multiplicative Scale Ratio of HR (95% CI)	Effect Modification on Additive Scale RERI (95% CI)
Age									
≤35 years	2126.83	4	1.0	1131.73	6	3.26 (0.87-12.25)	3.26 (0.87-12.25)		
36-45 years	3827.83	12	1.60 (0.51-5.01)	3635.55	22	4.78 (1.61-14.20)	2.99 (1.46-6.12)	0.92 (0.09-1.89)	0.15 (-3.76-4.06)
46-55 years	3635	13	2.06 (0.66-6.46)	3313.19	23	5.06 (1.69-15.16)	2.46 (1.24-4.89)	0.75 (0.17-3.34)	-0.15 (-4.18-3.89)
>55 years	2557.55	16	3.74 (1.21-11.52)	1815.32	23	9.29 (3.07-28.13)	2.49 (1.30-4.76)	0.76 (0.18-3.31)	2.22 (-2.98-7.42)
Menopausal Status									
Premenopausal	7183.70	21	1.0	5541.57	35	2.74 (1.57-4.78)	2.72 (1.56-4.75)		
Postmenopausal	4998.97	24	1.07 (0.54-2.12)	4354.21	39	2.81 (1.49-5.30)	2.62 (1.56-4.41)	0.96 (-0.79-0.71)	0.01 (-1.50-1.52)
BMI									
<25 kg/m^2	7776.29	28	1.0	6546.92	40	2.16 (1.32-3.55)	2.16 (1.32-3.55)		
≥25 kg/m^2	4406.38	17	1.02 (0.55-1.88)	3348.87	34	3.77 (2.23-6.37)	3.71 (2.05-6.74)	1.51 (0.80-3.70)	1.60 (0.006-3.18)
Age at Menarche									
≤11 years	2328.39	9	1.03	1892.	17	3.34 (1.83-	3.23 (1.41-	1.27	0.77 (-

			(0.49-2.16)	33		6.09)	7.41)	(0.50-3.21)	1.15-2.68)
≥12 years	9854.28	36	1.0	8003.46	57	2.54 (1.65-3.90)	2.54 (1.65-3.90)		
Parity									
Nulliparous	3769.2	10	1.00	2621.6	29	5.33 (2.57-11.05)	5.33 (2.57-11.05)		
Parous	8413.47	35	1.50 (0.64-3.52)	7274.18	45	2.93 (1.27-6.76)	1.95 (1.24-3.08)	0.37 (0.16-0.86)	-2.9 (-6.26-0.45)
Age at First Birth (among parous women)									
<30 years	5741.05	24	1.00	5047.54	30	1.82 (1.04-3.16)	1.82 (1.04-3.16)		
≥30 years	2672.42	11	1.52 (0.68-3.39)	2226.64	15	3.58 (1.64-7.84)	2.35 (1.06-5.21)	1.29 (0.50-3.38)	1.24 (-1.13-3.62)
Number of Births (among parous women)									
1 birth	3083.9	7	1.00	2091.68	12	3.03 (1.16-7.94)	3.03 (1.16-7.94)		
≥2 births	5329.57	28	2.36 (0.99-5.60)	5182.51	33	4.11 (1.74-9.76)	1.74 (1.04-2.93)	0.57 (0.19-1.70)	-0.28 (-2.96-2.40)
Age at Last Live Birth (among parous women)									
<35 years	6162.39	27	1.00	5087.56	33	2.00 (1.18-3.39)	2.00 (1.18-3.39)		
≥35 years	2251.08	8	0.65 (0.28-1.52)	2186.63	12	1.23 (0.58-2.61)	1.89 (0.76-4.71)	0.94 (0.33-2.68)	-0.42 (-1.67-0.82)
Interval between Age at Menarche and Age at First Birth (among parous women)									
<15 years	4447.64	17	1.00	3801.42	25	2.23 (1.18-4.21)	2.23 (1.18-4.21)		
≥15 years	3965.83	18	1.43 (0.72-2.85)	3472.77	20	2.31 (1.18-4.56)	1.62 (0.84-3.10)	0.73 (0.29-1.79)	-0.35 (-2.02-1.33)
Breastfeeding (among parous)									
Yes	4357.08	20	1.62	4050	25	2.81 (1.44-	1.73 (0.94-	0.77	-0.05 (-

			(0.81-3.26)			5.49)	3.19)	(0.31-1.91)	1.80-1.70)
No	4056.39	15	1.0	3224.19	20	2.24 (1.13-4.430	2.24 (1.13-4.43)		
Duration of Breastfeeding (among parous)									
<2 years	3188.97	16	1.72 (0.83-3.56)	2974.99	19	3.02 (1.48-6.16)	1.76 (0.88-3.50)	0.79 (0.30-2.05)	0.07 (-1.91-2.05)
≥2 years	1168.11	4	1.34 (0.43-4.17)	1075.01	6	2.31 (0.88-6.11)	1.73 (0.48-6.24)	0.77 (0.18-3.29)	-0.26 (-2.83-2.31)
None	4056.39	15	1.0	3224.19	20	2.24 (1.13-4.43)	2.24 (1.13-4.43)		
Oral Contraceptive Use									
Yes	5943.48	20	0.88 (0.48-1.59)	4885.4	27	1.96 (1.12-3.42)	2.24 (1.24-4.03)	0.74 (0.35-1.59)	-0.94 (-2.38-0.51)
No	6239.19	25	1.0	5010.38	47	3.02 (1.83-4.97)	3.02 (1.83-4.97)		
Duration of Use									
<2 years	3146.74	6	0.51 (0.21-1.26)	2591.36	13	1.73 (0.87-3.44)	3.38 (1.28-9.95)	1.12 (0.38-3.33)	-0.79 (-2.32-0.75)
≥2 years	2796.74	14	1.27 (0.65-2.47)	2294.04	14	2.23 (1.15-4.33)	1.76 (0.83-3.73)	0.59 (0.24-1.43)	-1.04 (-2.85-0.76)
None	6239.19	25	1.0	5010.38	47	3.01 (1.83-4.95)	3.01 (1.83-4.95)		
Current Alcohol Use									
Yes	8199.61	25	0.60 (0.33-1.09)	6187.58	54	2.27 (1.33-3.87)	3.77 (2.32-6.11)	2.73 (1.24-6.01)	1.29 (0.36-2.22)
No	3983.06	20	1.00	3708.21	20	1.38 (0.73-2.61)	1.38 (0.73-2.61)		
Frequency of Consumption									
<1 - 3 times per month	3641.91	10	0.52 (0.24-1.12)	2495.89	23	2.40 (1.29-4.46)	4.60 (2.16-9.78)	3.34 (1.25-8.92)	1.50 (0.24-2.76)
1-3 times per week	3446.16	11	0.70	2654.	20	1.99 (1.05-	2.85 (1.35-	2.07	0.92 (-

			(0.33-1.48)	61		3.78)	6.01)	(0.79-5.46)	0.24-2.08)
Daily to 2-3 times per day	1111.54	4	0.61 (0.21-1.79)	1037.08	11	2.63 (1.23-5.61)	4.34 (1.37-13.71)	3.15 (0.85-11.70)	1.65 (-0.18-3.48)
None	3983.06	20	1.00	3708.21	20	1.38 (0.73-2.60)	1.38 (0.73-2.60)		
Ever Smoker									
Yes	5684.32	21	0.92 (0.51-1.67)	4230.28	32	2.49 (1.44-4.31)	2.63 (1.57-4.40)	1.03 (0.49-2.18)	-0.06 (-1.40-1.28)
No	6498.35	24	1.00	5665.51	42	2.63 (1.57-4.40)	2.70 (1.55-4.73)		
Duration of Smoking									
<5 years	1951.36	4	0.49 (0.17-1.42)	1678.16	15	3.17 (1.62-6.20)	6.48 (2.12-19.77)	2.46 (0.73-8.32)	1.05 (-0.85-2.95)
6-10 years	937.73	8	2.38 (1.06-5.36)	671.08	6	3.19 (1.29-7.93)	1.34 (0.46-3.95)	0.51 (0.16-1.67)	-0.82 (-4.09-2.46)
>10 years	2795.23	9	0.79 (0.37-1.72)	1881.03	11	1.73 (0.83-3.61)	2.19 (0.90-5.33)	0.83 (0.30-2.32)	-0.69 (-2.28-0.90)
None	6498.35	24	1.00	5665.51	42	2.63 (1.57-4.41)	2.63 (1.57-4.41)		
First Degree Family History of Breast Cancer									
No First Degree Family History	2787.86	10	1.00	4394.33	39	3.77 (1.88-7.58)	3.77 (1.88-7.58)		
1 First Degree Family Member	7707.28	25	1.11 (0.53-3.33)	4274.82	22	2.26 (1.06-4.83)	2.04 (1.15-3.65)	0.54 (0.22-1.34)	-1.62 (-3.89-0.66)
>1 First Degree Family Member	1534.98	10	2.07 (0.86-5.01)	866.80	11	5.58 (2.35-13.23)	2.69 (1.14-6.36)	0.71 (0.24-2.16)	0.73 (-3.03-4.49)

*adjusted for: age, race, family history of breast cancer, for reproductive variables: also adjusted for current alcohol use, age at first birth, number of live births and age last birth; for alcohol use: also adjusted for age at first birth, number of live births and age at last birth.

3.6 References:

1. Silverstein M. Where's the outrage? J Am Coll Surg 2009;208(1):78-9.

2. Dupont WD, Parl FF, Hartmann WH*, et al.* Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. Cancer 1993;71(4):1258-65.

3. Hartmann LC, Sellers TA, Frost MH*, et al.* Benign breast disease and the risk of breast cancer. New England Journal of Medicine 2005;353(3):229-237.

4. London SJ, Connolly JL, Schnitt SJ*, et al.* A prospective study of benign breast disease and the risk of breast cancer.[Erratum appears in JAMA 1992 Apr 1;267(13):1780]. JAMA 1992;267(7):941-4.

5. Harris JR. *Diseases of the breast*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2010.

6. Silvera SA, Rohan TE. Benign proliferative epithelial disorders of the breast: a review of the epidemiologic evidence. Breast Cancer Res Treat 2008;110(3):397-409.

7. Baer HJ, Schnitt SJ, Connolly JL*, et al.* Adolescent diet and incidence of proliferative benign breast disease. Cancer Epidemiol Biomarkers Prev 2003;12(11 Pt 1):1159-67.

8. Baer HJ, Schnitt SJ, Connolly JL*, et al.* Early life factors and incidence of proliferative benign breast disease. Cancer Epidemiol Biomarkers Prev 2005;14(12):2889-97.

9. Berkey CS, Tamimi RM, Willett WC*, et al.* Adolescent physical activity and inactivity: a prospective study of risk of benign breast disease in young women. Breast Cancer Res Treat 2014;146(3):611-8.

10. Berkey CS, Willett WC, Frazier AL*, et al.* Prospective study of growth and development in older girls and risk of benign breast disease in young women. Cancer 2011;117(8):1612-20.

11. Berkey CS, Willett WC, Frazier AL*, et al.* Prospective study of adolescent alcohol consumption and risk of benign breast disease in young women. Pediatrics 2010;125(5):e1081-7.

12. Su X, Colditz GA, Collins LC*, et al.* Adolescent intakes of vitamin D and calcium and incidence of proliferative benign breast disease. Breast Cancer Res Treat 2012;134(2):783-91.

13. Bodian CA, Perzin KH, Lattes R*, et al.* Prognostic significance of benign proliferative breast disease. Cancer 1993;71(12):3896-907.

14. Hutchinson WB, Thomas DB, Hamlin WB*, et al.* Risk of breast cancer in women with benign breast disease. Journal of the National Cancer Institute 1980;65(1):13-20.

15. Dupont WD, Page DL. Breast cancer risk associated with proliferative disease, age at first birth, and a family history of breast cancer. Am J Epidemiol 1987;125(5):769-79.

16. Berg JC, Visscher DW, Vierkant RA*, et al.* Breast cancer risk in women with radial scars in benign breast biopsies. Breast Cancer Research & Treatment 2008;108(2):167-74.

17. Worsham MJ, Abrams J, Raju U*, et al.* Breast cancer incidence in a cohort of women with benign breast disease from a multiethnic, primary health care population. Breast J 2007;13(2):115-21.

18. Kabat GC, Jones JG, Olson N*, et al.* A multi-center prospective cohort study of benign breast disease and risk of subsequent breast cancer. Cancer Causes Control 2010;21(6):821-8.

19. Carter CL, Corle DK, Micozzi MS*, et al.* A prospective study of the development of breast cancer in 16,692 women with benign breast disease. Am J Epidemiol 1988;128(3):467-77.

20. Ashbeck EL, Rosenberg RD, Stauber PM*, et al.* Benign breast biopsy diagnosis and subsequent risk of breast cancer. Cancer Epidemiology, Biomarkers & Prevention 2007;16(3):467-72.

21. Tice JA, O'Meara ES, Weaver DL*, et al.* Benign Breast Disease, Mammographic Breast Density, and the Risk of Breast Cancer. J Natl Cancer Inst 2013;105(14):1043-9.

22. Mills PK, Beeson WL, Phillips RL*, et al.* Prospective study of exogenous hormone use and breast cancer in Seventh-day Adventists. Cancer 1989;64(3):591-7.

23. Marshall LM, Hunter DJ, Connolly JL*, et al.* Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. Cancer Epidemiol Biomarkers Prev 1997;6(5):297-301.

24. van den Brandt PA, Goldbohm RA, van 't Veer P. Alcohol and breast cancer: results from The Netherlands Cohort Study. American Journal of Epidemiology 1995;141(10):907-15.

25. Horn-Ross PL, Canchola AJ, West DW*, et al.* Patterns of alcohol consumption and breast cancer risk in the California Teachers Study cohort. Cancer Epidemiology, Biomarkers & Prevention 2004;13(3):405-11.

26. Gierach GL, Freedman ND, Andaya A*, et al.* Coffee intake and breast cancer risk in the NIH-AARP diet and health study cohort. International Journal of Cancer 2012;131(2):452-60.

27. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312(3):146-51.

28. Page DL, Dupont WD, Rogers LW*, et al.* Atypical hyperplastic lesions of the female breast. A long-term follow-up study. Cancer 1985;55(11):2698-708.

29. Collins LC, Baer HJ, Tamimi RM*, et al.* The influence of family history on breast cancer risk in women with biopsy-confirmed benign breast disease: results from the Nurses' Health Study. Cancer 2006;107(6):1240-7.

30. Kabat GC, Jones JG, Olson N*, et al.* Risk factors for breast cancer in women biopsied for benign breast disease: a nested case-control study. Cancer Epidemiol 2010;34(1):34-9.

31. Collins LC, Baer HJ, Tamimi RM*, et al.* Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia: results from the Nurses' Health Study. Cancer 2007;109(2):180-7.

32. Byrne C, Connolly JL, Colditz GA*, et al.* Biopsy confirmed benign breast disease, postmenopausal use of exogenous female hormones, and breast carcinoma risk. Cancer 2000;89(10):2046-52.

33. Dupont WD, Page DL. Relative risk of breast cancer varies with time since diagnosis of atypical hyperplasia. Hum Pathol 1989;20(8):723-5.

34. Thomas DB, Persing JP, Hutchinson WB. Exogenous estrogens and other risk factors for breast cancer in women with benign breast diseases. Journal of the National Cancer Institute 1982;69(5):1017-25.

35. Dupont WD, Page DL, Parl FF*, et al.* Estrogen replacement therapy in women with a history of proliferative breast disease. Cancer 1999;85(6):1277-83.

36. Brinton LA, Hoover R, Fraumeni JF, Jr. Menopausal oestrogens and breast cancer risk: an expanded case-control study. British Journal of Cancer 1986;54(5):825-32.

37. Brinton LA, Hoover R, Fraumeni JF, Jr. Interaction of familial and hormonal risk factors for breast cancer. Journal of the National Cancer Institute 1982;69(4):817-22.

38. Tamimi RM, Byrne C, Baer HJ*, et al.* Benign breast disease, recent alcohol consumption, and risk of breast cancer: a nested case-control study. Breast Cancer Res 2005;7(4):R555-62.

39. Ishitani K, Lin J, Manson JE*, et al.* Caffeine consumption and the risk of breast cancer in a large prospective cohort of women. Archives of Internal Medicine 2008;168(18):2022-31.

40. Chun J, Joseph KA, El-Tamer M*, et al.* Cohort study of women at risk for breast cancer and gross cystic disease. Am J Surg 2005;190(4):583-7.

41. Chun J, Pocock B, Joseph KA*, et al.* Breast cancer risk factors in younger and older women. Ann Surg Oncol 2009;16(1):96-9.

42. Work ME, Reimers LL, Quante AS*, et al.* Changes in mammographic density over time in breast cancer cases and women at high risk for breast cancer. Int J Cancer 2014.

43. Millsap RE, Maydeu-Olivares A. *The SAGE handbook of quantitative methods in psychology*. Los Angeles ; London: SAGE; 2009.

44. Raghunathan T, Lepkowski J, Van Hoewyk J*, et al.* A Multivariate Technique for Multiply Imputing Missing Values Using a Sequence of Regression Models. Survey Methodology 2001;27(1):85-95.

45. Hosmer DW, Lemeshow S, May S. *Applied survival analysis : regression modeling of time-to-event data*. 2nd ed. Hoboken, N.J.: Wiley-Interscience; 2008.

46. Allison PD, SAS Institute. *Survival analysis using the SAS system : a practical guide*. Cary, NC: SAS Institute; 1995.

47. Rod NH, Lange T, Andersen I*, et al.* Additive interaction in survival analysis: use of the additive hazards model. Epidemiology 2012;23(5):733-7.

48. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 3rd edition. ed. Philadelphia, Pennsylvania,: Lippincott Williams & Wilkins; 2008.

49. Russo J, Russo IH. Differentiation and breast cancer development. Advances in Oncobiology 1998;2:1-10.

50. Wang DY, Fentiman IS. Epidemiology and endocrinology of benign breast disease. Breast Cancer Res Treat 1985;6(1):5-36.

51. Catsburg C, Gunter MJ, Chen C*, et al.* Insulin, estrogen, inflammatory markers, and risk of benign proliferative breast disease. Cancer Research 2014;74(12):3248-58.

52. Bernstein L, Pike MC, Ross RK*, et al.* Estrogen and sex hormone-binding globulin levels in nulliparous and parous women. J Natl Cancer Inst 1985;74(4):741-5.

53. Clevenger CV, Chang WP, Ngo W*, et al.* Expression of prolactin and prolactin receptor in human breast carcinoma. Evidence for an autocrine/paracrine loop. Am J Pathol 1995;146(3):695-705.

54. Clevenger CV, Furth PA, Hankinson SE*, et al.* The role of prolactin in mammary carcinoma. Endocr Rev 2003;24(1):1-27.

55. Hankinson SE, Willett WC, Michaud DS*, et al.* Plasma prolactin levels and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst 1999;91(7):629-34.

56. Tworoger SS, Eliassen AH, Zhang X*, et al.* A 20-year prospective study of plasma prolactin as a risk marker of breast cancer development. Cancer Research 2013;73(15):4810-9.

57. Tikk K, Sookthai D, Johnson T*, et al.* Circulating prolactin and breast cancer risk among pre- and postmenopausal women in the EPIC cohort. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2014;25(7):1422-8.

58. Tworoger SS, Rice MS, Rosner BA*, et al.* Bioactive prolactin levels and risk of breast cancer: a nested case-control study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2014.

59. Yu MC, Gerkins VR, Henderson BE*, et al.* Elevated levels of prolactin in nulliparous women. Br J Cancer 1981;43(6):826-31.

60. Faupel-Badger JM, Sherman ME, Garcia-Closas M*, et al.* Prolactin serum levels and breast cancer: relationships with risk factors and tumour characteristics among pre- and postmenopausal women in a population-based case-control study from Poland. British journal of cancer 2010;103(7):1097-102.

61. Eliassen AH, Tworoger SS, Hankinson SE. Reproductive factors and family history of breast cancer in relation to plasma prolactin levels in premenopausal and postmenopausal women. Int J Cancer 2007;120(7):1536-41.

62. Tikk K, Sookthai D, Johnson T*, et al.* Prolactin Determinants in Healthy Women: A Large Cross-Sectional Study within the EPIC Cohort. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2014.

63. Cole EN, Sellwood RA, England PC*, et al.* Serum prolactin concentrations in benign breast disease throughout the menstrual cycle. Eur J Cancer 1977;13(6):597-603.

64. Peters F, Schuth W, Scheurich B*, et al.* Serum prolactin levels in patients with fibrocystic breast disease. Obstet Gynecol 1984;64(3):381-5.

65. Rose DP, Berke B, Cohen LA*, et al.* A comparison of serum and breast duct fluid-immunoassayable prolactin and growth hormone with bioassayable lactogenic hormones in healthy women and patients with cystic breast disease. Cancer 1987;60(11):2761-5.

66. Rose DP. Hormones and growth factors in nipple aspirates from normal women and benign breast disease patients. Cancer Detect Prev 1992;16(1):43-51.

67. Johansson H, Gandini S, Bonanni B*, et al.* Relationships between circulating hormone levels, mammographic percent density and breast cancer risk factors in postmenopausal women. Breast Cancer Res Treat 2008;108(1):57-67.

68. Gill S, Peston D, Vonderhaar BK*, et al.* Expression of prolactin receptors in normal, benign, and malignant breast tissue: an immunohistological study. J Clin Pathol 2001;54(12):956-60.

69. Gertig DM, Stillman IE, Byrne C*, et al.* Association of age and reproductive factors with benign breast tissue composition. Cancer Epidemiol Biomarkers Prev 1999;8(10):873-9.

70. Tarquini A, di Martino L, Malloci A*, et al.* Abnormalities in evening plasma prolactin levels in nulliparous women with benign or malignant breast disease. Int J Cancer 1978;22(6):687-90.

71. Terry MB, Zhang FF, Kabat G*, et al.* Lifetime alcohol intake and breast cancer risk. Annals of Epidemiology 2006;16(3):230-40.

72. Chen WY, Rosner B, Hankinson SE*, et al.* Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. JAMA 2011;306(17):1884-90.

73. McDonald JA, Goyal A, Terry MB. Alcohol Intake and Breast Cancer Risk: Weighing the Overall Evidence. Curr Breast Cancer Rep 2013;5(3).

74. Rohan TE, Cook MG. Alcohol consumption and risk of benign proliferative epithelial disorders of the breast in women. Int J Cancer 1989;43(4):631-6.

75. Cui Y, Page DL, Chlebowski RT*, et al.* Alcohol and folate consumption and risk of benign proliferative epithelial disorders of the breast. Int J Cancer 2007;121(6):1346-51.

76. Byrne C, Webb PM, Jacobs TW*, et al.* Alcohol consumption and incidence of benign breast disease. Cancer Epidemiol Biomarkers Prev 2002;11(11):1369-74.

77. Rohan TE, Jain M, Miller AB. Alcohol consumption and risk of benign proliferative epithelial disorders of the breast: a case-cohort study. Public Health Nutr 1998;1(3):139-45.

78. Smith-Warner SA, Spiegelman D, Yaun SS*, et al.* Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA 1998;279(7):535-40.

79. Seitz HK, Pelucchi C, Bagnardi V*, et al.* Epidemiology and pathophysiology of alcohol and breast cancer: Update 2012. Alcohol Alcohol 2012;47(3):204-12.

80. Dumitrescu RG, Shields PG. The etiology of alcohol-induced breast cancer. Alcohol 2005;35(3):213-25.

81. Fernandez SV. Estrogen, alcohol consumption, and breast cancer. Alcohol Clin Exp Res 2011;35(3):389-91.

82. Suga S, Kato K, Ohgami T*, et al.* An inhibitory effect on cell proliferation by blockage of the MAPK/estrogen receptor/MDM2 signal pathway in gynecologic cancer. Gynecol Oncol 2007;105(2):341-50.

Chapter 4:

Comparison of breast cancer risk assessment models in high-risk women and women with benign breast disease

4.1 Abstract

Introduction: An integral component of care of women with BBD is accurate assessment of breast cancer risk. Three of the most widely used in the clinic setting are Gail model, International Breast Cancer Intervention Study (IBIS) model, and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA). We validated these models within a high-risk cohort of women with BBD.

Methods: We used the Women At Risk (WAR) registry from 1991 to 2011. We used Poisson regression analysis to estimate incidence rates of breast cancer. We compared mean 8.5-year breast cancer risk estimates to compare across the three risk models. We assessed model calibration by comparing the predicted-to-observed ratio. Discrimination was measured using logistic regression analysis to examine the area under the curve (AUC).

Results: There were 120 incident breast cancers identified, breast cancer incidence in women with BBD was 98.71 per 10,000 woman years compared to 47.20 per 10,000 woman years. Mean IBIS risk was significantly higher for women with any BBD as compared mean predicted risk in Gail and BOADICEA models (IBIS 5.84%, Gail 4.79%, and BOADICEA 3.71%; $p<0.001$ for all pairwise comparisons). After restricting the estimates to women with atypical hyperplasia, the IBIS model still estimated the highest risk (8.77%). All three models tend to under predict the number of breast cancer events in our cohort.

Conclusions: Overall calibration with the IBIS model and better overall discrimination with the Gail model. Based on these findings it would be of benefit to healthcare providers to improve the IBIS model by incorporating additional risk factors, such as modifiable factors and/or biomarkers, to enhance its performance in women with BBD.

4.2 Introduction

An integral component of care of women with BBD is accurate assessment of breast cancer risk. Based on a woman's risk of disease, prevention and clinical management can be individually tailored. For example, the American Society of Clinical Oncology recommends tamoxifen in women 35 years or older who have a 5-year absolute breast cancer risk equal to or greater than 1.67% or to women with LCIS [1].

A number of models have been developed to estimate breast cancer risk. Three of the most widely used in the clinic setting are Gail model, International Breast Cancer Intervention Study (IBIS) model, and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA). The Gail model, or breast cancer risk assessment tool (BCRAT), was developed from the Breast Cancer Detection and Demonstration Project [2]. The Gail model incorporates current age, age at menarche, age at first live birth, race, first-degree family history, BRCA1/2 mutation status, number of breast biopsies, and atypical hyperplasia (**Table 4.1**) [2]. The IBIS model incorporates these factors, besides number of biopsies, and includes other factors, such as menopausal status, HRT use, height/weight, and personal history of hyperplasia, LCIS, and ovarian cancer [3]. In addition, the IBIS model improved upon the Gail model by including extensive family history data [3]. BOADICEA is another risk prediction model that takes into account specific data from relatives [4, 5]. However, it does not include any of the reproductive characteristics in the other two models. It also does not include breast biopsies, hyperplasia, or atypical hyperplasia.

To our knowledge, the Gail model and IBIS model have only been validated in women with atypical hyperplasia, and none have validated the model in a population of high-risk women with BBD. Both of these validation studies were conducted in women from the Mayo Benign Breast Disease (BBD) cohort [6, 7]. The authors found that the Gail model significantly underestimated and had poor discrimination of breast cancer risk in women with atypical hyperplasia [6], whereas the IBIS model overestimated the risk of breast cancer in women with atypia with poor concordance [7]. It is important to determine the performance of these models in other populations to understand which are important in clinical management of women with BBD. We followed a cohort of high-risk women to investigate the

development of invasive breast cancer and evaluate the performance of the Gail, IBIS, and BOADICEA models in predicting invasive breast cancer risk.

4.3 Methods

The Women At Risk (WAR) registry at Columbia University Medical Center (CUMC) is a prospectively followed cohort of women at high risk from breast cancer. This study has been previously described [8-10]. Initiated in 1991, the WAR registry continued to enroll patients until July 2011. Eligible participants met one or more of the following criteria: 1) one or more first-degree relatives (mother, daughter, or sister) with premenopausal breast cancer, 2) two or more first-degree relatives with postmenopausal breast cancer, and/or 3) history of biopsy-proven lobular carcinoma *in situ*, atypical ductal hyperplasia (ADH), or atypical lobular hyperplasia (ALH). Follow-up involved passive monitoring of patient outcomes by medical chart review and tracking breast cancer outcomes through linkage with New York-Presbyterian Cancer Registry.

In total, 2,674 women were included in the WAR registry. We excluded women whose breast cancer diagnosis was less than 6 months after enrollment (N=3) to account for potential misdiagnosis. In addition, we excluded 14 women who had no follow-up. Follow-up time was from time of enrollment to either breast cancer diagnosis, mastectomy, death, or date of last follow-up (July 1, 2013). Women with ductal carcinoma *in situ* (DCIS) were censored at their date of DCIS diagnosis, these models assess the risk of invasive breast cancer and therefore DCIS diagnosis after risk assessment would not affect the calibration or discrimination of these risk models. BBD diagnosis was determined by chart review of biopsy and/or surgical specimens. If a patient had multiple different types of BBD listed in her chart, the most progressive breast histology was selected for that woman. BBD diagnosis had to have occurred prior to the first visit in order for the woman to be classified as BBD at baseline. A detailed questionnaire administered at baseline provided information on demographics and breast cancer risk factors. We used the information from the baseline questionnaire to identify each individual's risk factors and family history. All information used was self-reported, except for the identification of women with BBD.

We used Poisson regression analysis, with log-transformed person-years, as the offset to assess risk of invasive breast cancer [11]. Incidence rates of breast cancer are reported per 10,000 person-years at risk. A SAS macro was used to obtain cumulative incidence function plots by BBD status and

atypical hyperplasia status [12]. The average follow-up of our cohort was 8.5 years; we calculated 8.5-year risk for each individual using three different models: Gail model, IBIS, and BOADICEA. Risk estimates for the Gail risk model were obtained using the SAS macro provided on the breast cancer risk assessment tool (BCRAT) website (version 3.0, December 2012) [2]. We randomly selected 10 patients, calculated their 5-year risk, and compared this estimate to those obtained through the website. For the IBIS model we used a computer program developed by the original authors (personal communication, October 2014). The risk estimates from this program were also compared to the website for accuracy (IBIS risk evaluator version 7.0). The BOADICEA website allows for batch processing of patients in groups of 500. We divided the patients into six groups and used the upload function (version 3). BOADICEA was the only model that did not allow adjustment of the number of years of risk estimation. Instead it provided yearly estimates for five years then estimated risk in five-year intervals till age 80. Therefore, we multiplied the 1-year estimated risk by 8.5 to get the risk based on 8.5 years of follow-up. The IBIS and BOADICEA models incorporate detailed family history of breast and ovarian cancer, so we used patient responses to family history questions to reconstruct pedigrees.

Risk factors used in each of these models were summarized using counts and percentages or means and standard deviations. Chi-square test or t test was used to compare those who remained unaffected to those diagnosed with invasive breast cancer on follow-up. We calculated the predicted number of breast cancer cases based on average risk for the total population adjusting for person-years of observation. Our person-year of follow-up was less than the total person-years of follow-up that would have been recorded if all women were followed for all 8.5 years. We adjusted the estimated risk from the models by dividing it by the person-years for complete follow-up and then multiplying it by the actual person-years of follow-up we observed. This risk was then multiplied by the number of women in our cohort to get the predicted number of breast cancer cases. We compared mean 8.5-year breast cancer risk estimates using analysis of variance (ANOVA) to compare across the three models. We assessed model calibration by comparing the predicted-to-observed ratio and calculating tests of significant and 95% confidence intervals (CIs). In addition, we examined model performance across risk factors included in each model.

We also used logistic regression analysis to obtain the concordance statistic or c-statistic to assess the discrimination of each of the models within our population. This statistic is the same as the area under the curve (AUC) and measures from 0.5 to 1 with 1 indicating perfect discrimination. This was also done for each risk factor to examine if there were different groupings of patients where the models had better discrimination. We compared the AUC for each of the models using a chi-square test. All analyses were performed using SAS software version 9.3 (Cary, NC). We used the Risk Model Assessment Program (RMAP), an R package, to assess the three risk models by quartile of assigned risk [13, 14]. Women were stratified into quartile of assigned risk and survival data was used to estimate the observed 8.5 year risk. Competing risk theory was used to estimate the probability in the presence of censoring due to incomplete follow-up. We evaluated cumulative mortality in addition to breast cancer risk.

4.4 Results

4.4.1 Incidence of breast cancer

Over 22,000 woman-years of observation, there were 120 incident breast cancers identified. We identified 26 invasive breast cancers among women with BBD; breast cancer incidence is 98.71 per 10,000 woman years, compared to 47.20 per 10,000 woman years among women without BBD (**Table 4.2**). Prevalent BBD resulted in an excess incidence of 51.51 per 10,000 woman years. Age-adjusted risk of invasive breast cancer was 1.94 times higher in women with prevalent BBD as compared to women without BBD (Relative Risk (RR): 1.94, 95% CI: 1.26-3.00). A plot of cumulative incidence of breast cancer by BBD status shows that women with BBD had a greater cumulative incidence throughout follow-up (**Figure 4.1a**).

We also examined incidence of breast cancer by atypical hyperplasia. Among women with atypical hyperplasia, breast cancer incidence is 48.75 per 10,000 woman years, compared to 53.43 per 10,000 woman years among women without atypical hyperplasia (**Table 4.2**). Upon adjustment for age, risk of invasive breast cancer was similar between women with atypical hyperplasia and women without atypical hyperplasia, including high-risk women within WAR and other subtypes of BBD (RR: 0.82, 95% 0.33-2.01). **Figure 4.1b** shows that throughout follow-up these groups had similar cumulative incidence of breast cancer.

4.4.2 Breast cancer risk assessment models

In **Table 4.3**, we present the distribution of characteristics for 2,657 women. At baseline, their average age was 47.4 years, 62% were white, 10.5% had two or more relatives with breast cancer, and 53.9% had at least one breast biopsy. Hyperplasia without atypia was previously diagnosed in 1.8% and 6.3% had been diagnosed with atypical hyperplasia. We included 107 women who had previously been diagnosed with LCIS.

We identified 120 subsequent invasive breast cancers in 2,657 women after 8.5 years of follow-up. Average breast cancer risk was significantly higher for the IBIS model (4.13%; P<0.001 as compared to both models), and the average risks were similar for the Gail and BOADICEA models (p=0.74; **Table 4.4**). The IBIS model predicted that 116.3 women in our cohort would be diagnosed with breast cancer after 8.5 years of follow-up. The ratio of predicted-to-observed (P:O) events for the IBIS model was 0.97, which was not significantly different than our observed cases (95% CI: 0.80-1.16, p=0.74). Both Gail and BOADICEA models under-predicted the number of breast cancer cases (P:O: 0.79, 95% CI: 0.64-0.97 and P:O 0.78, 95% CI: 0.63-0.95, respectively). However, the concordance between predicted and observed values was highest in the Gail model (c-statistic: 0.59, 95% CI: 0.54-0.64). **Figure 4.2a** shows the comparison of ROCs for the prediction breast cancer classification in the entire population for each of the three risk models. Comparing the IBIS model to the Gail model there is a slight difference in the curves (p=0.05). No difference is seen when comparing the BOADICEA model to the Gail model (p=0.08) or to the IBIS model (p=0.37).

Mean IBIS risk was significantly higher for women with any BBD as compared mean predicted risk in Gail and BOADICEA models (IBIS 5.84%, Gail 4.79%, and BOADICEA 3.71%; p<0.001 for all pairwise comparisons, **Table 4.4**). The IBIS model predicted that 19.2 women with any BBD in our cohort would be diagnosed with breast cancer, whereas the Gail predicted 15.8, and BOADICEA only predicted 12.2. The P:O ratio for the IBIS model slightly under-predicted the number of cases, but was not different than our observed cases (P:O: 0.74, 95% CI: 0.45-1.15). Both the Gail and BOADICEA models significantly under-predicted the number of breast cancer events (P:O: 0.61, 95% CI: 0.35-0.99 and P:O: 0.47, 95% CI: 0.24-0.82, respectively). Concordance between predicted and observed values was highest in the IBIS model – however, all of the models showed modest discrimination. **Figure 4.2b** shows

the comparisons of ROCs for the three different risk models in women with any BBD. No difference between any of the curves was observed (Gail vs. IBIS, p=0.68; Gail vs. BOADICEA, p=0.57; and IBIS vs. BOADICEA, p=0.33).

After restricting the estimates to women with atypical hyperplasia, the IBIS model still estimated the highest risk (8.77%; **Table 4.4**). All three models had significantly different average estimated risks for women with atypical hyperplasia (p<0.001). For the BOADICEA model the average risk estimate increased only slightly from the estimated breast cancer risk for the total population (3.49% vs. 3.32%). However, the BOADICEA model predicted 4.5 events: a P:O ratio of 0.90 (95% CI: 0.27-2.19). Both the Gail and IBIS models over-predicted the number of breast cancer events (8.4 and 11.2, respectively). Concordance between the observed and predicted values was the same for the IBIS and Gail models and higher than what we observed for the total population (c-statistic: 0.62, 95% CI: 0.29-0.96 and c-statistic: 0.62, 95% CI: 0.35-0.89, respectively). **Figure 4.2c** shows the comparisons of ROCs for the three different risk models in women with any BBD. No difference between any of the curves was observed (Gail vs. IBIS, p=1.0; Gail vs. BOADICEA, p=0.81; and IBIS vs. BOADICEA, p=0.86).

Table 4.4 shows that all three models tend to under-predict the number of breast cancer events in our cohort. A few notable exceptions are among minorities; all three models tended to over predict the number of breast cancer events (Appendix B, Table B1). Women with late age at menarche (≥14 years) and women with young age at first live birth (<20 years) were both over-predicted in all three models. The Gail and IBIS models over-predicted the risk in women with 3 or more first-degree relatives with breast cancer (P:O: 1.36, 95% CI: 0.24-4.16 and P:O 1.30, 95% CI: 0.22-4.07, respectively). IBIS, the only model to include LCIS in its risk estimate, over-predicted the number of breast cancer events among women with LCIS by 5.14 (P:O: 5.14, 95% CI: 3.49-7.30).

The top panel of **Figure 4.3** displays the three models based on quartiles of model-assigned risk. A well calibrated model would have the points close to the diagonal line, as we can see the observed risk exceed the mean assigned risks in all quartiles of all three models. The next three panels (from top to bottom) represent the standardized residuals by outcome: combined (both breast cancer and death due to other causes), breast cancer alone, and mortality due to other causes alone. In a well calibrated model the standardized residuals would line within the dashed lines at 2 and -2. These panels show that certain

quartiles within Gail, specifically the higher quartiles (q2 – q3), are higher than those observed in our high-risk women. In the IBIS model, show an excess of observed deaths, specifically within the second quartile of risk. Finally, the BOADICEA model also has an excess number of observed deaths as shown by the positive standardized residuals.

4.5 Discussion

Comparing three commonly-used breast cancer risk assessment models, Gail, IBIS, and BOADICEA, we observed better overall calibration with the IBIS model and better overall discrimination with the Gail model. However, regardless of model, agreement between predicted and observed breast cancer events was still low, with a c-statistic ranging from 0.51 to 0.59. In subgroup analysis of women with BBD, the IBIS model maintained superior calibration – however, the BOADICEA model had the best discrimination. All three models had the best discrimination in women with atypical hyperplasia – however, both the IBIS and Gail models over-predicted the number of breast cancer cases among women with atypical hyperplasia, and BOADICEA had good calibration. It is not surprising that IBIS would have superior calibration than the other two models given that it includes both reproductive and extensive family history. The Gail model includes mostly reproductive factors and summary family history data, whereas the BOADICEA includes only detailed family history data.

Each of these models often under-predicted risk; to evaluate this more closely, we did a subgroup analysis to see how these models performed to see if there were certain factors driving the prediction (Appendix B, Table B1). For all the variables, women classified as 'Unknown' were over-predicted in each of the three models, which reflects the confounding and residual uncertainty in women who do not have complete risk factor profiles. We saw differences in demographic characteristics between women with invasive breast cancer and unaffected women (**Table 4.3**). Specifically, there were differences by age, race, age at menarche, and menopausal status. These models were all developed in fairly homogeneous white populations, with some recent additions to account for risk differences by race [15, 16]. Race is both an important predictor of breast cancer risk and mutation prevalence differs by race [17, 18]. It was unexpected to find that each of these models over-predicted the number of breast cancer events for all minority populations. The only exception was Gail model, which had similar calibration in whites and African Americans; this is expected as the Gail model was recently updated to include revised

estimates for African American women [15]. Of note, the two models that actually incorporated breast biopsy information over-predicted the number of cancers for women with either hyperplasia without atypia or lobular carcinoma *in-situ* (LCIS). This reflects the over-prediction of women with atypical hyperplasia. With the IBIS model, there is a monotonic increase in the predicted-to-observed ratio as severity of benign disease increases (P:O hyperplasia without atypia: 1.49; P:O atypical hyperplasia: 2.24; and P:O LCIS: 5.14). However, this was not seen with the Gail or BOADICEA models, which do not incorporate hyperplasia or LCIS. In the original validation of the Gail model, they found over-prediction of breast cancer events in women with AH, as well as an over prediction with increasing number of biopsies [19].

Two previous studies validating the Gail model and IBIS model in women with atypical hyperplasia also found that the model over predicted the number of invasive breast cancers in the first 5 to 10 years. However, they had a lower c-statistic [6, 7]. After longer term follow-up (>10 years), the Gail model under-predicted the number of invasive breast cancer events in women with atypia [6]. Atypia in the Gail model was incorporated using estimates of the population prevalence of atypia from Carter *et al.* [20], with a prevalence of 7.8%, and used a relative risk of 1.96 for breast cancer in women with atypical hyperplasia [2]. In our population, the prevalence of atypical hyperplasia was slightly less (6.3%) and unexpectedly the relative risk showed an inverse association between atypical hyperplasia and breast cancer risk. The underlying prevalence of atypia in the Mayo Cohort was 3.5% [6]. Different underlying prevalence of risk factors influence how well these models will fit for different populations. The IBIS model used a relative risk of 4.0 [3]; similar to prevalence, this higher risk estimate is likely driving the over-prediction of breast cancer events for our population. A difference between our validation population and the Mayo Cohort is the higher incidence of breast cancer, although we had a slightly shorter follow-up time (8.5 vs. 10 years); our incidence was only 3.0% compared to 9.4%.

Compared to other populations used to validate these risk models, calibration ranged from 0.93 to 1.01, whereas ours was slightly lower [21]. The c-statistic was within a similar range in other validation studies as ours (range: 0.56-0.63) [21]. Our c-statistic was also very similar – however, it was slightly lower than what was found in high-risk populations with strong family history [13]. Previous studies showed that prediction models cannot be both perfectly-calibrated and perfectly discriminatory [22, 23]. How closely the predicted and observed risks for breast cancer agree – calibration – is important to public

health interventions and good decision making. In high-risk populations we ought to be more concerned with calibration. For example, in a poorly-calibrated model a woman may be assigned a low predicted probability (*i.e.,* <1.67%) where her actual risk is much higher. Therefore, her clinical care provider would not recommend chemoprevention to her even though it could actually reduce her breast cancer risk. Whereas over-prediction can lead to unnecessary use of risk-reduction strategies, *i.e.,* women using chemoprevention and potentially having unnecessary side effects. Discrimination is important to understand how well the model and variables included in it separates those with breast cancer from those without. Discrimination depends on the average risk in the population; it has been shown that populations with higher average risk have lower discrimination than populations with lower average risk [24].

There are certain limitations to our study. Our population is biased in that these are high-risk women who are already receiving care by a beast surgeon. Therefore, they are a specialized population seeking care and do not reflect the normal distribution of risk. However, this is an ideal population to test how these models discriminate risk and can therefore inform preventive care, as these are the patients that are actually getting prevention recommendations from surgeons and oncologists. We validated all of these models in the entire population regardless of their eligibility for use in the model, which may influence the calibration and discrimination. However, we conducted sensitivity analyses to examine if there were differences in model calibration and discrimination when populations were limited to women eligible for the Gail model (Appendix B, Table B2) and not including women with any unknown risk factors (Appendix B, Table B3). Even after excluding women for which Gail model use is not recommended (*i.e.,* age <35 years, *BRCA1/2* mutation carriers and women with LCIS), we still saw better calibration in the IBIS model than in the Gail model. BOADICEA was still the worst predictor (*i.e.,* lowest calibration) of number of breast cancer events than the other two models, with the exception of the atypical hyperplasia population, in which the BOADICEA model does a superior job of predicting breast cancer events. Of note, none of these models include modifiable risk factors, (besides HRT use in IBIS). A model developed by Colditz *et al.* is the only model to incorporate potentially modifiable factors [25]. In future validation studies, the Rosner-Colditz model should be included in the comparison of the models to see how the addition of modifiable factors can improve risk prediction.

Based on these findings it would be of benefit to healthcare providers to improve the IBIS model by incorporating additional risk factors, such as modifiable factors and/or biomarkers, to enhance its performance in women with benign breast disease. Enhancing the calibration and appropriate risk estimates of women can help providers offer better prevention recommendations. As there are a number of risks and benefits to chemoprevention use, decisions to use a chemopreventive agent should not be based on a single risk prediction number, but incorporate individual factors (*i.e.,* woman's age and specific risk factors for breast cancer) [26, 27]. Furthermore, biomarkers may reflect the current state of at-risk tissue and lead to more accurate risk predictions.

Figure 4.1. Cumulative incidence of breast cancer a) for total population by BBD status and b) by atypical hyperplasia (AH) status over WAR cohort follow-up time.

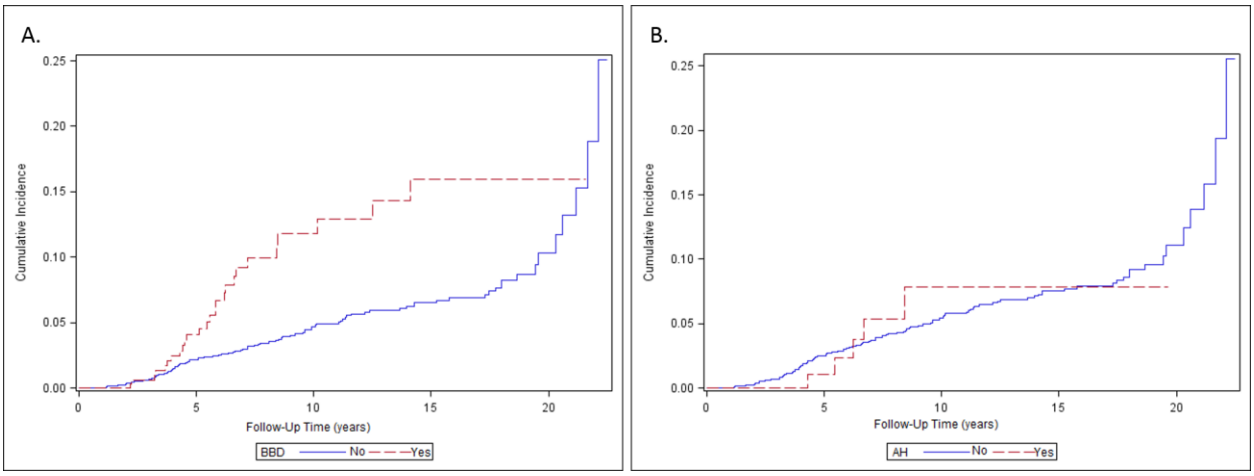

Figure 4.2. Receiver operator curves (ROCs) for each of the three risk models a) in the total population, b) within women with BBD, and c) within women with atypical hyperplasia (AH).

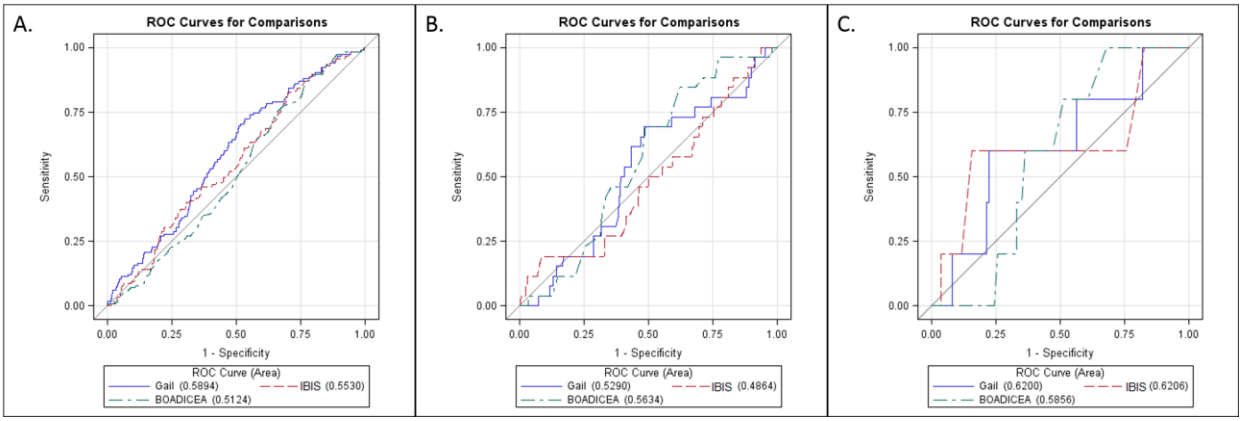

Figure 4.3. Attribute diagrams and plots of standardized residuals for Gail model, IBIS model, and BOADICEA model as applied to the WAR cohort by quartile of assigned risk. Top panel displays the three models on the basis of quartiles of model-assigned risk by observed risk. Well calibrated model the dots would lie close to the red diagonal line. The bottom 3 panels show the standardized residulals, a well calibrated model would have the standardized residuals between -2 and 2.

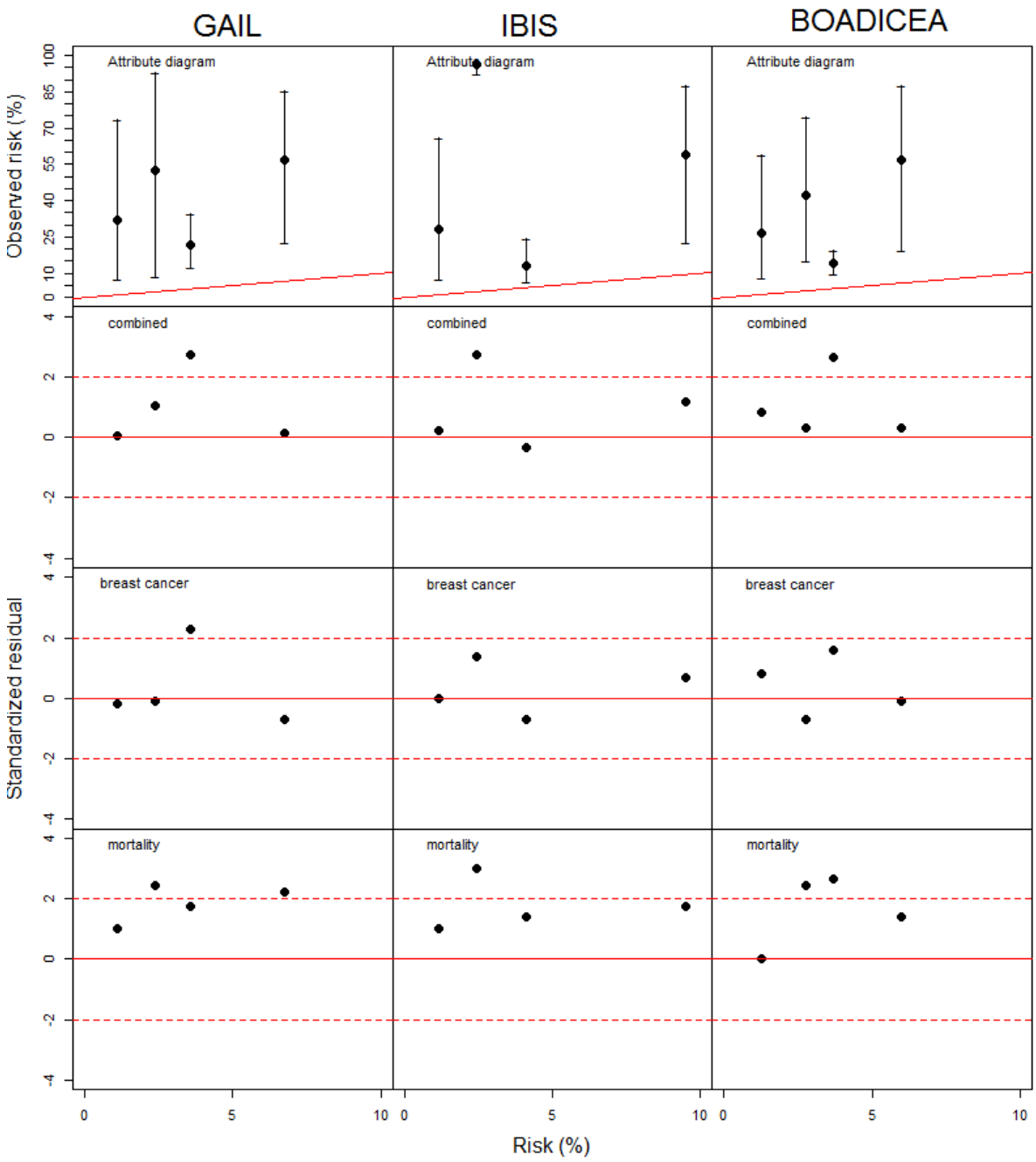

Table 4.1. Comparison of inputs used in breast cancer risk assessment models

Features	GAIL (BCRAT)	IBIS	BOADICEA
Age	>35 yrs	Continuous, any age	Continuous, 20-70 yrs; Year of Birth
Age at Menarche	7-11, 12-13, 14+ yrs, Unknown	Continuous	
Parity		Nulliparous, Parous, Unknown	
Age at First Live Birth	No Births, <20, 20-24, 25-29, 30+ yrs, Unknown	Continuous	
Race/Ethnicity	White, African American, Hispanic, Asian-American, American Indian/Alaska Native, Unknown		
Menopausal Status		Pre-, Peri-, or Post-menopausal	
Age at Menopause		Continuous	
HRT Use		Never, 5+ yrs ago, <5 yrs ago, Current User	
HRT Type		Oestrogen, Combined, Unknown	
Length of time taking HRT		Continuous, number of years	
Time since HRT last used		Continuous, number of years	
Height/Weight		Continuous, meters and kg	
Family History	First-degree only: 0, 1, >1, Unknown	Maternal (breast and ovarian, age at diagnosis, laterality); Sister (breast and ovarian, age at diagnosis, laterality); Paternal Grandmother; Maternal	First-degree, second-degree, third-degree relatives and their age at onset for both breast and ovarian cancer.

		Grandmother; Paternal aunts; Maternal aunts; Daughters	
BRCA1/2 Mutation	Yes, No, Unknown	Untested, Negative, BRCA1, BRCA2, Unknown	Untested, Negative, BRCA1, BRCA2, BRCA1 and BRCA2
Ashkenazi Jewish Heritage		Yes, No, Unknown	Yes, No
Breast Biopsy	Yes, No, Unknown		
Number of Breast Biopsies	1, >1		
Atypical Hyperplasia	Yes, No, Unknown	Yes, No, Unknown	
History of Hyperplasia (non-atypia)		Yes, No, Unknown	
History of LCIS		Yes, No, Unknown	
History of Ovarian Cancer		Yes, No, Unknown	
Father genetic Testing		Untested, Negative, BRCA1, BRCA2, Unknown	
Family Pedigree		Full, including ovarian cancer	Full, including ovarian, prostate and pancreatic cancer, tumor markers (ER/PR/HER2/CK14/Ck56

Table 4.2. Poisson regression estimates of age-adjusted rate ratios for breast cancer among women diagnosed with BBD

	Person-years	No of BC	Incidence rate /10,000 p-y	Excess Incidence	Crude RR (95% CI)	Age-adjusted RR (95% CI)
Benign Breast Disease						
No BBD	19913.86	94	47.20	-	1.0	1.0
BBD	2633.95	26	98.71	51.51	2.09 (1.35-3.23)	1.94 (1.26-3.00)
Atypical Hyperplasia						
Yes	1025.62	5	48.75	-4.68	0.91 (0.37-2.23)	0.82 (0.33-2.01)
No	21522.2	115	53.43	-	1.0	1.0

Table 4.3. Characteristics of 2657 women in WAR registry by breast cancer status

Characteristic	Total Population (n=2657) N (%)	Unaffected (n=2537) N (%)	Invasive Breast Cancer (n=120) N (%)	p-value
Age, years (mean±std)	47.4 (12.1)	47.2 (12.0)	51.3 (12.6)	0.001
Race				0.001
White	1646 (62.0%)	1150 (61.1%)	96 (80%)	
African American	85 (3.2%)	82 (3.2%)	3 (2.5%)	
Hispanic	204 (7.7%)	199 (7.8%)	5 (4.2%)	
Asian	59 (2.2%)	58 (2.3%)	1 (0.8%)	
Other	663 (25.0%)	648 (2.5%)	15 (12.5%)	
Age at menarche, years (mean±std)	12.6 (1.4)	12.6 (1.4)	12.3 (1.3)	0.03
Parity				0.10
Nulliparous	679 (25.6%)	640 (25.2%)	39 (32.5%)	
Parous	1893 (71.3%)	1813 (71.5%)	80 (66.7%)	
Unknown	85 (3.2%)	84 (3.3%)	1 (0.8%)	
Age at first live birth, years (mean±std)	26.9 (5.3)	26.9 (5.3)	27.0 (5.5)	0.93
Menopausal Status				0.01
Premenopausal	1350 (50.8%)	1297 (51.1%)	53 (44.2%)	
Postmenopausal	1122 (42.2%)	1058 (41.7%)	64 (53.3%)	
Unknown	185 (7.0%)	182 (7.2%)	3 (2.5%)	
Menopause age, years (mean±std)	49.9 (1.3)	49.9 (1.3)	50.0 (0.1)	0.06
Height, meters	1.63 (0.1)	1.63 (0.1)	1.63 (0.1)	0.90
Weight, kgs	62.1 (13.6)	62.0 (13.5)	63.8 (14.6)	0.21
Menopausal hormone therapy use				0.05
Never	2270 (85.4%)	2178 (85.9%)	92 (76.7%)	
>5 years ago	325 (12.2%)	301 (11.9%)	24 (20.0%)	
<5 years ago	30 (1.1%)	28 (1.1%)	2 (1.7%)	
Current user	32 (1.2%)	30 (1.2%)	2 (1.7%)	
*Menopausal hormone therapy type**				N/A
Estrogen only	62 (100%)	58 (100%)	4 (100%)	
Combined	0 (0%)	0 (0%)	0 (0%)	
*Menopausal hormone therapy length of use (mean±std)***	1.11 (0.54)	1.1 (0.6)	1.4 (0.4)	0.002
No. first-degree relatives with breast cancer				0.27
0-1	2284 (86.0%)	2184 (86.1%)	100 (83.3%)	
2	245 (9.2%)	229 (9.0%)	16 913.3%)	
3+	35 (1.3%)	33 (1.3%)	2 (1.7%)	
Unknown	93 (3.5%)	91 (3.6%)	2 (1.7%)	
Number of biopsies				0.22
0	544 (20.5%)	516 (20.3%)	28 (23.3%)	
1	888 (33.4%)	842 (33.2%)	46 (38.3%)	
2+	1225(46.1%)	1179 (46.5%)	46 (38.3%)	
Hyperplasia (no atypia)				0.17
Yes	48 (1.8%)	44 (1.7%)	4 (3.3%)	
No	2609 (98.2%)	2493 (98.3%)	116 (96.7%)	
Atypical Hyperplasia				0.33
Yes	167 (6.3%)	162 (6.4%)	5 (4.2%)	
No	2490 (93.7%)	2375 (93.6%)	115 (95.8%)	
LCIS				0.58
Yes	107 (4.0%)	101 (4.0%)	6 (5.0%)	
No	2550 (96.0%)	2436 (96.0%)	114 (95.0%)	

*use within 5 years or current users
**former users

Table 4.4. Comparison of performance of Gail (BCRAT), IBIS, and BOADICEA models in WAR Cohort

Model	Predicted 8.5-year Breast Cancer Risk Risk (Range)	Person-Years	Observed Events	Person-Years	Adjusted risk	Predicted Events	Predicted:Observed Ratio	95% CI	p-value	c-statistic	95% CI
Gail											
Total Population (n=2657)	3.38% (0.05%-18.09%)	22547.82	120	21256	3.59%	95.3	0.79	0.64-0.97	0.02	0.59	0.54-0.64
Any BBD (n=406)	4.79% (0.13%-16.47%)	2633.95	26	3248	3.88%	15.8	0.61	0.35-0.99	0.05	0.53	0.42-0.64
Atypical Hyperplasia (n=167)	6.47% (0.34%-16.47%)	1025.62	5	1336	5.05%	8.4	1.68	0.74-3.26	0.13	0.62	0.35-0.89
IBIS											
Total Population (n=2657)	4.13% (0.001%-35.99%)	22547.82	120	21256	4.38%	116.3	0.97	0.80-1.16	0.74	0.55	0.50-0.60
Any BBD (n=406)	5.84% (0.10%-22.73%)	2633.95	26	3248	4.73%	19.2	0.74	0.45-1.15	0.18	0.49	0.37-0.60
Atypical Hyperplasia (n=167)	8.77% (0.36-22.73%)	1025.62	5	1336	6.73%	11.2	2.24	1.13-3.99	0.006	0.62	0.29-0.96
BOADICEA											
Total Population (n=2657)	3.32% (0.0%-21.92%)	22547.82	120	21256	3.52%	93.6	0.78	0.63-0.95	0.02	0.51	0.47-0.56
Any BBD (n=406)	3.71% (0.0%-18.80%)	2633.95	26	3248	3.01%	12.2	0.47	0.24-0.82	0.007	0.56	0.47-0.66
Atypical Hyperplasia (n=167)	3.49% (0.24-18.80%)	1025.62	5	1336	2.68%	4.5	0.90	0.27-2.19	0.82	0.59	0.44-0.74

4.6 References:

1. Visvanathan K, Hurley P, Bantug E*, et al.* Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;31(23):2942-62.

2. Gail MH, Brinton LA, Byar DP*, et al.* Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989;81(24):1879-86.

3. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004;23(7):1111-30.

4. Antoniou AC, Cunningham AP, Peto J*, et al.* The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer 2008;98(8):1457-66.

5. Antoniou AC, Pharoah PP, Smith P*, et al.* The BOADICEA model of genetic susceptibility to breast and ovarian cancer. Br J Cancer 2004;91(8):1580-90.

6. Pankratz VS, Hartmann LC, Degnim AC*, et al.* Assessment of the accuracy of the Gail model in women with atypical hyperplasia. Journal of Clinical Oncology 2008;26(33):5374-9.

7. Boughey JC, Hartmann LC, Anderson SS*, et al.* Evaluation of the Tyrer-Cuzick (International Breast Cancer Intervention Study) model for breast cancer risk prediction in women with atypical hyperplasia. J Clin Oncol 2010;28(22):3591-6.

8. Chun J, Joseph KA, El-Tamer M*, et al.* Cohort study of women at risk for breast cancer and gross cystic disease. Am J Surg 2005;190(4):583-7.

9. Chun J, Pocock B, Joseph KA*, et al.* Breast cancer risk factors in younger and older women. Ann Surg Oncol 2009;16(1):96-9.

10. Work ME, Reimers LL, Quante AS*, et al.* Changes in mammographic density over time in breast cancer cases and women at high risk for breast cancer. Int J Cancer 2014.

11. Fleiss JL, Levin B, Paik MC. *Statistical methods for rates and proportions*. 3rd ed. Hoboken, N.J.: Wiley-Interscience; 2003.

12. Klein JP, Moeschberger ML. *Survival analysis : techniques for censored and truncated data*. 2nd ed. New York: Springer; 2003.

13. Quante AS, Whittemore AS, Shriver T*, et al.* Breast cancer risk assessment across the risk continuum: genetic and nongenetic risk factors contributing to differential model performance. Breast Cancer Res 2012;14(6):R144.

14. Gong G, Quante AS, Terry MB*, et al.* Assessing the goodness of fit of personal risk models. Stat Med 2014;33(18):3179-90.

15. Gail MH, Costantino JP, Pee D*, et al.* Projecting individualized absolute invasive breast cancer risk in African American women. J Natl Cancer Inst 2007;99(23):1782-92.

16. Matsuno RK, Costantino JP, Ziegler RG*, et al.* Projecting individualized absolute invasive breast cancer risk in Asian and Pacific Islander American women. J Natl Cancer Inst 2011;103(12):951-61.

17. Liu L, Zhang J, Wu AH*, et al.* Invasive breast cancer incidence trends by detailed race/ethnicity and age. Int J Cancer 2012;130(2):395-404.

18. Huo D, Senie RT, Daly M*, et al.* Prediction of BRCA Mutations Using the BRCAPRO Model in Clinic-Based African American, Hispanic, and Other Minority Families in the United States. J Clin Oncol 2009;27(8):1184-90.

19. Costantino JP, Gail MH, Pee D*, et al.* Validation studies for models projecting the risk of invasive and total breast cancer incidence. J Natl Cancer Inst 1999;91(18):1541-8.

20. Carter CL, Corle DK, Micozzi MS*, et al.* A prospective study of the development of breast cancer in 16,692 women with benign breast disease. Am J Epidemiol 1988;128(3):467-77.

21. Anothaisintawee T, Teerawattananon Y, Wiratkapun C*, et al.* Risk prediction models of breast cancer: a systematic review of model performances. Breast Cancer Res Treat 2012;133(1):1-10.

22. Diamond GA. What price perfection? Calibration and discrimination of clinical prediction models. J Clin Epidemiol 1992;45(1):85-9.

23. Gail MH, Pfeiffer RM. On criteria for evaluating models of absolute risk. Biostatistics 2005;6(2):227-39.

24. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation 2007;115(7):928-35.

25. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol 2000;152(10):950-64.

26. Gail MH, Costantino JP, Bryant J*, et al.* Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 1999;91(21):1829-46.

27. Freedman AN, Yu B, Gail MH*, et al.* Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. J Clin Oncol 2011;29(17):2327-33.

Chapter 5:

Importance of benign breast disease, family history, and mammographic density in breast cancer risk assessment

Breast cancer continues to be the most common cancer, estimated to account for 29% of all new cancers in women in the United States, and the second most common cause of death [1]. Mammography was originally introduced with the intent of detecting breast cancer earlier, before progression. Over time, however, breast cancer screening has brought about some unintended consequences, specifically the number of women with false-positive results and unnecessary biopsies. In a 10-year period it is estimated for 10,000 women in their 40s undergoing annual screening mammography the number with more than one false positive result is 6130 (95% CI: 5940-6310) and the number with more than one unnecessary biopsy is 700 (95% CI: 610-780) [2]. The number of unnecessary biopsies actually increases with age for women in their 50s 940 (95% CI: 740-1150) and women in their 60s 980 (95% CI: 840-1130) [2]. These excessive biopsies will often result in a diagnosis of benign breast disease (BBD). The purpose of this dissertation research was to investigate the interactions between BBD and established breast cancer risk factors, specifically family history and mammographic breast density, as it is largely unknown how all three interact to affect risk. This research was designed to improve upon prior studies through assessment of both multiplicative and additive interactions. In addition, we have provided one of the few validation studies of current risk factor models in a high-risk population that includes a large proportion of women with a history of BBD. Risk assessment models are not well validated and management for women with BBD is inconsistent. The objective is that this research can inform whether BBD is a causal intermediary or a susceptibility marker.

5.1 Modifiers of breast cancer risk

Mammographic density is a strong risk factor for breast cancer. In Chapter 2, we assessed the association between BBD and mammographic density. We found that BBD is associated with higher percent density, even 9 years after BBD diagnosis. We also showed that these associations may change over time, for age at BBD diagnosis and BBD with parity analyses we only found associations with the mammographic measures at the most recent mammogram. It is unknown, the underlying mechanisms linking histological and mammographic measures. Unfortunately, in the longitudinal birth cohort used for this analysis, we do not have enough breast cancers to look at interaction. However, in the Women At Risk (WAR) cohort we had 1,256 women with at least one pre-diagnostic mammogram with reported

Breast Imaging Reporting and Data System (BIRADS) at least 6 months prior to breast cancer diagnosis. BIRADS density categories [3] are: 1=almost entirely fat (<25%), 2=scattered fibroglandular densities (25-50%), 3=heterogeneously dense (51-75%), and 4=extremely dense (>75%). We used Poisson modeling to calculate the relative risks of breast cancer based on BIRADS and BBD, using women with low density (BIRADS 1/2) and no BBD as the reference group. In the fully adjusted model, women with low density and BBD or high density (BIRADS 3/4) and no BBD have an approximately 2-fold risk of breast cancer as compared to women with low density and no BBD ($RR_{1/2 \text{ and } BBD}$: 1.94, 95% CI: 0.50-7.55; $RR_{3/4 \text{ and No } BBD}$: 1.85, 95%CI: 0.50-6.90). Women with both high density and BBD have a 3.63-fold higher risk of breast cancer as compared to women with low density and no BBD ($RR_{3/4 \text{ and } BBD}$: 3.63, 95% CI: 1.07-12.31). Due to the differences in risk of breast cancer between nonproliferative disease and those that are proliferative with and without atypia we conducted a sensitivity analysis excluding those women with nonproliferative disease. Our results were similar to those above ($RR_{1/2 \text{ and } BBD}$: 1.55, 95% CI: 0.72-3.34; $RR_{3/4 \text{ and No } BBD}$: 2.18, 95%CI: 1.11-4.29; $RR_{3/4 \text{ and } BBD}$: 3.73, 95% CI: 1.97-7.06). We found no evidence of multiplicative interaction between mammographic density and BBD (p=0.99). The adjusted rate of breast cancer was 18.6 per 10,000 women who had both factors compared to 9.94 per 10,000, 9.49 per 10,000, and 5.13 per 10,000 for women who had BBD without high mammographic density, high mammographic density without BBD, and neither, respectively. We also saw similar effect modification when including only women with atypical hyperplasia (**Figure 5.1**).

Breast cancer risk is an interaction between environmental, hormonal, and genetic factors. In Chapter 3, we found significant interactions between parity and alcohol consumption in women with BBD, both of which may be related to hormonal changes in women. Progression of disease in women with BBD may depend on their hormonal promotion [4], as differences in endogenous hormones have been found between parous and nulliparous women [5-7]. Alcohol consumption is an important effect modifier of risk between BBD and breast cancer as it is a modifiable risk factor. One proposed mechanism of alcohol consumption is through alcohol increasing estrogen levels and potentially acting as a tumor promoter [8-10]. Of note, our models did not detect a significant interaction between family history and BBD on breast cancer risk. However, we did see a 5-fold higher risk of breast cancer in women with both a strong first-degree family history and BBD compared to women with no first-degree family history and

no BBD. This suggests that there is a potential interaction between these two factors and our study may not have been powered to detect an interaction. Indeed, our population was oversampled for women at high-risk meaning that most women had a first-degree relative with breast cancer. Furthermore, it is known that if two factors have an effect on risk, there will always be interaction on either the multiplicative or additive scale [11, 12]. Therefore, additional studies in BBD populations with varying degrees of family history should be assessed to gain a better understanding of their interactions. Our findings support that BBD may be more likely to be a susceptibility marker rather than a true precursor lesion, meaning that genetic and epigenetic changes at BBD diagnosis may be important to determining breast cancer risk.

Our results have implications on risk assessment models for breast cancer. Although some risk models incorporate prior breast biopsy; few incorporate breast density [13-15]. A recent revision of the Gail model incorporated mammographic density and had improvements in discriminatory power and found higher predicted risks among women with dense breasts [16]. No model that we are aware of incorporates interaction effects between these two factors, which would need to include interaction terms even in multiplicative models if additive interaction is observed.

5.2 Risk assessment

Risk assessment for breast cancer is complex, lacking consistent definitions or thresholds for high-risk. Individualized risk assessment is a crucial component to effective assessment of women with BBD. In Chapter 4, we found moderate calibration and discrimination among the Gail, IBIS, and BOADICEA models. Overall, this IBIS model had better calibration whereas the Gail model had better discrimination. Highlighting the limitations to current risk assessment models, specifically within women with a history of BBD. First, only two of these models include BBD, the Gail and IBIS models. Each of these captures BBD in a different manner. Specifically, the Gail model uses having had a breast biopsy (yes/no), number of breast biopsies (1 or >1), presence of atypical hyperplasia, but not lobular carcinoma *in situ* (LCIS). IBIS includes hyperplasia with or without atypical and LCIS. Even within women with just atypical hyperplasia, the models did not fit well in our population or in the Mayo Cohort [17, 18]. Second, risk factors that are non-familial are not included, such as mammographic density. Mammographic density is a strong breast cancer risk factor. Women with 75% or greater dense tissue have a 4-6 fold

risk of breast cancer compared to women with 25% or less dense tissue [19-21]. Mammographic density is such a strong factor of breast cancer risk that it is considered an intermediate marker of breast cancer risk [22]. Finally, as we have shown these models should also consider incorporation of the interactions between strong breast cancer risk factors, such as BBD, family history, and mammographic density. All three of these factors strongly influence breast cancer and are likely to have both biological interactions as well as statistical interactions.

We have shown that BBD is a susceptibility marker that may represent tissue changes in the breast that make a woman more susceptible to other breast cancer risk factors. Therefore, genetic and epigenetic changes are important to the initiation of these breast changes and potentially determine which women get BBD and which of these women progress to breast cancer. Accumulation of genetic alterations plays a key role in carcinogenesis of breast tumors. Molecular epidemiologic, specifically epigenetic studies of tissue biomarkers may provide tissue and/or blood based biomarkers that can improve risk assessment models. Epigenetics is the study of heritable changes in gene expression; these changes do not modify the actual genetic sequence. DNA methylation is an epigenetic modification that usually occurs in cytosine-guanine dinucleotide-rich areas (CpG islands) in gene promoter regions [23, 24]. Conservation of DNA methylation patterns in normal cells help to control gene expression. CpG island promoter methylation affects genes involved in cell cycle regulation, cell-adherence, and apoptosis [23]. Methylation can initiate breast cancer carcinogenesis in a number of ways: through activation of proto-oncogenes by hypomethylation of promoter regions, inactivation of tumor suppressor genes by hypermethylation, or alteration of estrogen receptor gene methylation [24]. Epigenetic gene silencing through promoter hypermethylation of normally unmethylated CpG islands occurs in major tumor suppressor genes [23, 24]. During carcinogenesis, maintenance of normal DNA methylation patterns is disrupted and CpG islands become susceptible to methyltransferase activity, resulting in epigenetic modifications that promote cancer initiation and progression. Epigenetic markers show promise for distinguishing between malignant and benign disease. Gene-specific promoter methylation, the addition or removal of a methyl group at promoter regions of genes is a potential tool for examining BBD as a susceptibility marker and as a potential target for interventions to reduce breast cancer risk in high-risk women and women with BBD [25].

Previous studies of benign breast disease tissue have assessed methylation of genes involved in DNA repair, cell invasion, cell-cycle regulation and apoptosis [26-49]. However, what remains unclear from these analyses is if methylation is related to breast cancer risk. It remains to be determined if methylation is a cause or consequence of breast proliferation. All of these previous studies were cross-sectional designs [26-49]. Therefore, comparisons of methylation levels within-individual at different stages of disease were not available. In addition, there has been no comparison of breast cancer risk by methylation levels in tissue in women with BBD.

Therefore, methylation changes that occur early in the benign tissue may help us to understand how epigenetic changes influence carcinogenesis in breast cancers. Specifically, methylation may influence tissue changes and make the breast more susceptible to environmental or lifestyle factors. Based on studies assessing adjacent normal tissue, epigenetic changes can provide prognostic information [35, 44, 50]. Furthermore, these epigenetic markers could be incorporated into existing breast cancer risk assessment models to improve accuracy of risk assessment.

5.3 Screening and Prevention

Currently, guidelines for screening and chemoprevention of breast cancer vary and are limited to women at high-risk (as defined by risk assessment models). **Table 5.1** summarizes the current guidelines broken down by screening method, mammography, clinical breast exam (CBE), breast self-exam (BSE), and magnetic resonance imaging (MRI). While these guidelines are inconsistent, even in their recommendations for average risk women, we want to emphasize the guidelines for women at high-risk. Two of the guidelines specifically define high-risk women as women with a lifetime risk of greater than 20% (based on models dependent on family history [51, 52]). The third concludes that it is unclear how to identify women at an increased risk [53]. Over the past few years, MRI has been used as an adjunct to mammographic screening, especially in high-risk patients. For American Cancer Society (ACS) and National Comprehensive Cancer Network (NCCN) those patients that should have MRI as an adjunct are women with greater than 20% lifetime risk (based on models dependent on family history). As we have shown in Chapter 4, models dependent on family history do not consistently predict a woman's risk, and in fact she may be defined as high risk in one model and not in another [figure/table of

mean difference in risk by IBIS and BOADICEA]. Furthermore, women with atypical hyperplasia have a 30% cumulative incidence after 25 years [54]. However, current guidelines either recommend against MRI or conclude there is insufficient evidence to make a decision regarding MRI screening in women with atypical hyperplasia [51, 55], even though these women are at an almost 30% higher risk of breast cancer. Risk models need to be improved so that clinical recommendations regarding MRI as an adjunct can be appropriately applied to the correct high-risk populations and to be able to clearly define a high-risk woman.

Mammographic density is known to respond to changes in hormones [56]. Tamoxifen has also been shown to decrease mammographic density [57, 58]. Effectiveness of chemoprevention may be measured by reductions in density among tamoxifen users [58]. However, guidelines for chemoprevention do not currently recommend chemoprevention for women with BBD. NCCN guidelines define high-risk women for consideration for tamoxifen use, using a 5-year absolute risk of ≥1.7% [59]. Tamoxifen is currently recommended to women with atypical ductal or lobular hyperplasia by the American Society for Clinical Oncology (ASCO) [60, 61], yet tamoxifen may not be appropriate for all women with atypical hyperplasia [62]. However, tamoxifen is not recommended for women with other benign lesions, unless indicated by Gail risk score. Risk models that do not incorporate mammographic density or BBD may underestimate risk in women who could benefit from chemoprevention.

5.4 Future directions

If replicated in larger studies, the findings of this dissertation suggest incorporation of BBD and mammographic density into risk assessment models, which may improve patient care and implementation of prevention strategies. This dissertation did not address the relationship between BBD and mammographic density by subtype of BBD (nonproliferative disease, proliferative disease without atypia, and atypical hyperplasia); as Chapter 3 showed there are varying degrees of risk with varying severity of BBD. Therefore, future studies should examine this association in a large cohort of women with all three subtypes using continuous mammographic density measures. In addition, this dissertation did not attempt to create a new risk model that incorporated mammographic density, BBD, and their interaction. Additionally, one new model developed within BBD populations has recently been published [63],

however we were not able to incorporate this into our comparison of risk models. It would be interesting to know if a model created specifically within a BBD population provides any better calibration or discrimination than current risk models across populations. We plan to assess these models using a high-risk cohort of women with BBD.

In conclusion, BBD is an important risk factor for breast cancer and may modify the association between other risk factors and breast cancer risk. Therefore, BBD represents a susceptibility marker and not a causal intermediary of breast cancer. Furthermore, these results suggest that risk assessment in high-risk populations, specifically women with BBD, is not ideal. Potentially including BBD and mammographic density in these risk models and/or creating a risk model within a cohort of women with BBD could improve risk assessment and as a result improve screening and clinical care of these women.

Figure 5.1. Cumulative incidence of breast cancer by mammographic density and atypical hyperplasia (AH) measured using Breast Imaging-Reporting Data System (BIRADS) scale. Category 1: almost entirely fatty, 2: scattered areas of fibroglandular densities, 3: heterogeneously dense, and 4: extremely dense

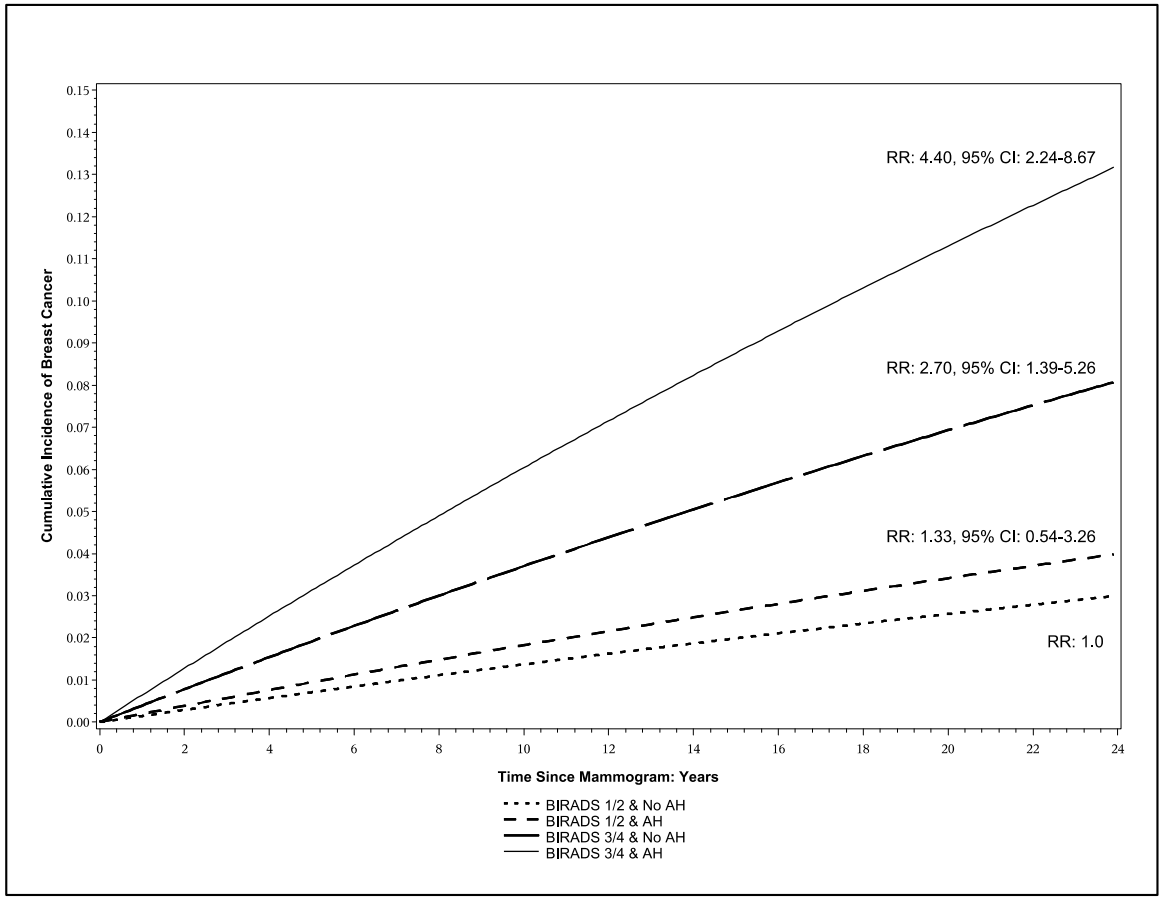

Table 5.1. Comparison of Guidelines for Breast Cancer Detection in high-risk women

	ACS	USPSTF	NCCN
Mammogram	age 40+ years; annually	age <50 years; biennial taking patient context into account age 50-74 years; biennial age 75+ years; insufficient evidence	age 40+ years; annually age 35+ yrs w/5-year risk ≥1.7%; annually lifetime risk >20% based on models dependent on family history; annually
Clinical Breast Exams (CBE)	age 20-39 years; every 3 years age 40+ years; annually	age 40+ years; insufficient evidence	age 25-40 years; every 1 to 3 years age 40+ years; annually age 35+ yrs w/5-year risk ≥1.7%; every 6 to 12 months lifetime risk >20% based on models dependent on family history; every 6 to 12 months
Breast Self-Exams (BSE)	age 20+ years; describe benefits and limitations of BSE, women can choose to do BSE or to do BSE irregularly	Against teaching BSE	age 25+ years; breast awareness encouraged
MRI Screening			
Annual MRI as adjunct to Mammography	BRCA mutation First-degree relative, BRCA carrier Lifetime risk 20-25% or greater, defined by BRCAPRO or other models dependent on family history		age 25+ years; Pedigree suggestive of or known genetic predisposition to breast cancer Lifetime risk >20% based on models dependent on family history; consider MRI

Insufficient Evidence to Recommend for or Against MRI Screening	Lifetime risk 15-20%, as defined by BRCAPRO or other models dependent on family history Atypical ductal (ADH) or lobular (ALH) hyperplasia Heterogeneously or extremely dense breasts on mammogram	All women insufficient evidence	
Chemoprevention		Recommended for women at increased risk for breast cancer; states not clear how to identify candidates for therapy	age 35+ years; life expectancy 10+ years; ≥1.7% 5-year risk for breast cancer by Gail model (premenopausal - Tamoxifen; postmenopausal - Raloxifene or Aromatase Inhibitor) age <35 years: insufficient data

5.5 References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA: a cancer journal for clinicians 2015;65(1):5-29.

2. Pace LE, Keating NL. A systematic assessment of benefits and risks to guide breast cancer screening decisions. JAMA 2014;311(13):1327-35.

3. D'Orsi C, Mendelson E, Berg W. *BI-RADS: Mammography, 4th edition*. 4th edition ed. Reston, VA: American College of Radiology; 2003.

4. Wang DY, Fentiman IS. Epidemiology and endocrinology of benign breast disease. Breast Cancer Res Treat 1985;6(1):5-36.

5. Bernstein L, Pike MC, Ross RK*, et al.* Estrogen and sex hormone-binding globulin levels in nulliparous and parous women. J Natl Cancer Inst 1985;74(4):741-5.

6. Yu MC, Gerkins VR, Henderson BE*, et al.* Elevated levels of prolactin in nulliparous women. Br J Cancer 1981;43(6):826-31.

7. Faupel-Badger JM, Sherman ME, Garcia-Closas M*, et al.* Prolactin serum levels and breast cancer: relationships with risk factors and tumour characteristics among pre- and postmenopausal women in a population-based case-control study from Poland. British journal of cancer 2010;103(7):1097-102.

8. Seitz HK, Pelucchi C, Bagnardi V*, et al.* Epidemiology and pathophysiology of alcohol and breast cancer: Update 2012. Alcohol Alcohol 2012;47(3):204-12.

9. Dumitrescu RG, Shields PG. The etiology of alcohol-induced breast cancer. Alcohol 2005;35(3):213-25.

10. Fernandez SV. Estrogen, alcohol consumption, and breast cancer. Alcohol Clin Exp Res 2011;35(3):389-91.

11. Darroch J. Biologic synergism and parallelism. American Journal of Epidemiology 1997;145(7):661-8.

12. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 3rd edition. ed. Philadelphia, Pennsylvania,: Lippincott Williams & Wilkins; 2008.

13. Gail MH, Brinton LA, Byar DP*, et al.* Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989;81(24):1879-86.

14. Tice JA, Cummings SR, Smith-Bindman R*, et al.* Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. Annals of internal medicine 2008;148(5):337-47.

15. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004;23(7):1111-30.

16. Chen J, Pee D, Ayyagari R*, et al.* Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. Journal of the National Cancer Institute 2006;98(17):1215-26.

17. Pankratz VS, Hartmann LC, Degnim AC*, et al.* Assessment of the accuracy of the Gail model in women with atypical hyperplasia. Journal of Clinical Oncology 2008;26(33):5374-9.

18. Boughey JC, Hartmann LC, Anderson SS*, et al.* Evaluation of the Tyrer-Cuzick (International Breast Cancer Intervention Study) model for breast cancer risk prediction in women with atypical hyperplasia. J Clin Oncol 2010;28(22):3591-6.

19. Boyd NF, Byng JW, Jong RA*, et al.* Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst 1995;87(9):670-5.

20. Boyd NF, Lockwood GA, Byng JW*, et al.* Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers Prev 1998;7(12):1133-44.

21. Byrne C, Schairer C, Wolfe J*, et al.* Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 1995;87(21):1622-9.

22. Boyd NF, Rommens JM, Vogt K*, et al.* Mammographic breast density as an intermediate phenotype for breast cancer. The Lancet. Oncology 2005;6(10):798-808.

23. Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. Nat Rev Genet 2002;3(6):415-28.

24. Jovanovic J, Ronneberg JA, Tost J*, et al.* The epigenetics of breast cancer. Mol Oncol 2010;4(3):242-54.

25. Heichman KA, Warren JD. DNA methylation biomarkers and their utility for solid cancer diagnostics. Clinical chemistry and laboratory medicine : CCLM / FESCC 2012;50(10):1707-21.

26. Umbricht CB, Evron E, Gabrielson E*, et al.* Hypermethylation of 14-3-3 sigma (stratifin) is an early event in breast cancer. Oncogene 2001;20(26):3348-53.

27. Lehmann U, Langer F, Feist H*, et al.* Quantitative assessment of promoter hypermethylation during breast cancer development. Am J Pathol 2002;160(2):605-12.

28. Pu RT, Laitala LE, Alli PM*, et al.* Methylation profiling of benign and malignant breast lesions and its application to cytopathology. Mod Pathol 2003;16(11):1095-101.

29. Parrella P, Poeta ML, Gallo AP*, et al.* Nonrandom distribution of aberrant promoter methylation of cancer-related genes in sporadic breast tumors. Clin Cancer Res 2004;10(16):5349-54.

30. Di Vinci A, Perdelli L, Banelli B*, et al.* p16(INK4a) promoter methylation and protein expression in breast fibroadenoma and carcinoma. International Journal of Cancer 2005;114(3):414-21.

31. Rody A, Holtrich U, Solbach C*, et al.* Methylation of estrogen receptor beta promoter correlates with loss of ER-beta expression in mammary carcinoma and is an early indication marker in premalignant lesions. Endocrine-Related Cancer 2005;12(4):903-16.

32. Kwon MS, Kim SJ, Lee SY*, et al.* Epigenetic silencing of the sulfotransferase 1A1 gene by hypermethylation in breast tissue. Oncology Reports 2006;15(1):27-32.

33. Lee JS. GSTP1 promoter hypermethylation is an early event in breast carcinogenesis. Virchows Arch 2007;450(6):637-42.

34. Ordway JM, Budiman MA, Korshunova Y*, et al.* Identification of novel high-frequency DNA methylation changes in breast cancer. PLoS ONE [Electronic Resource] 2007;2(12):e1314.

35. Pasquali L, Bedeir A, Ringquist S*, et al.* Quantification of CpG island methylation in progressive breast lesions from normal to invasive carcinoma. Cancer Lett 2007;257(1):136-44.

36. Kim SJ, Kang HS, Chang HL*, et al.* Promoter hypomethylation of the N-acetyltransferase 1 gene in breast cancer. Oncology Reports 2008;19(3):663-8.

37. Kioulafa M, Balkouranidou I, Sotiropoulou G*, et al.* Methylation of cystatin M promoter is associated with unfavorable prognosis in operable breast cancer. Int J Cancer 2009;125(12):2887-92.

38. Kioulafa M, Kaklamanis L, Mavroudis D*, et al.* Prognostic significance of RASSF1A promoter methylation in operable breast cancer. Clin Biochem 2009;42(10-11):970-5.

39. Kioulafa M, Kaklamanis L, Stathopoulos E*, et al.* Kallikrein 10 (KLK10) methylation as a novel prognostic biomarker in early breast cancer. Ann Oncol 2009;20(6):1020-5.

40. Zhao L, Wang L, Jin F*, et al.* Silencing of estrogen receptor alpha (ERalpha) gene by promoter hypermethylation is a frequent event in Chinese women with sporadic breast cancer. Breast Cancer Research & Treatment 2009;117(2):253-9.

41. Luo J, Feng J, Lu J*, et al.* Aberrant methylation profile of 14-3-3 sigma and its reduced transcription/expression levels in Chinese sporadic female breast carcinogenesis. Med Oncol 2010;27(3):791-7.

42. Son KS, Kang HS, Kim SJ*, et al.* Hypomethylation of the interleukin-10 gene in breast cancer tissues. Breast 2010;19(6):484-8.

43. Zhu W, Qin W, Hewett JE*, et al.* Quantitative evaluation of DNA hypermethylation in malignant and benign breast tissue and fluids. Int J Cancer 2010;126(2):474-82.

44. Park SY, Kwon HJ, Lee HE*, et al.* Promoter CpG island hypermethylation during breast cancer progression. Virchows Arch 2011;458(1):73-84.

45. Botla SK, Gholami AM, Malekpour M*, et al.* Diagnostic values of GHSR DNA methylation pattern in breast cancer. Breast Cancer Res Treat 2012;135(3):705-13.

46. Chen FM, Chang HW, Yang SF*, et al.* The mitogen-activated protein kinase phosphatase-1 (MKP-1) gene is a potential methylation biomarker for malignancy of breast cancer. Experimental & Molecular Medicine 2012;44(5):356-62.

47. Zhao L, Yu Z, Li Y*, et al.* Clinical implications of ERb methylation on sporadic breast cancers in Chinese women. Medical Oncology 2012;29(3):1569-1575.

48. Verschuur-Maes AH, de Bruin PC, van Diest PJ. Epigenetic progression of columnar cell lesions of the breast to invasive breast cancer. Breast Cancer Res Treat 2012;136(3):705-15.

49. van Hoesel AQ, Sato Y, Elashoff DA*, et al.* Assessment of DNA methylation status in early stages of breast cancer development. Br J Cancer 2013;108(10):2033-8.

50. Veeck J, Wild PJ, Fuchs T*, et al.* Prognostic relevance of Wnt-inhibitory factor-1 (WIF1) and Dickkopf-3 (DKK3) promoter methylation in human breast cancer. BMC cancer 2009;9:217.

51. Saslow D, Boetes C, Burke W*, et al.* American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57(2):75-89.

52. Bevers TB, Anderson BO, Bonaccio E*, et al.* NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. In. 1.2014 ed: National Comprehensive Cancer Network (NCCN); 2014.

53. Nelson HD, Smith ME, Griffin JC*, et al.* Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2013;158(8):604-14.

54. Hartmann LC, Degnim AC, Santen RJ*, et al.* Atypical hyperplasia of the breast--risk assessment and management options. The New England journal of medicine 2015;372(1):78-89.

55. Nelson HD, Tyne K, Naik A*, et al.* In. *Screening for Breast Cancer: Systematic Evidence Review Update for the US Preventive Services Task Force*. Rockville (MD); 2009.

56. Boyd NF, Stone J, Martin LJ*, et al.* The association of breast mitogens with mammographic densities. Br J Cancer 2002;87(8):876-82.

57. Cuzick J, Warwick J, Pinney E*, et al.* Tamoxifen and breast density in women at increased risk of breast cancer. Journal of the National Cancer Institute 2004;96(8):621-8.

58. Cuzick J, Warwick J, Pinney E*, et al.* Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. Journal of the National Cancer Institute 2011;103(9):744-52.

59. Bevers TB, Armstrong DK, Arun B*, et al.* Breast cancer risk reduction. J Natl Compr Canc Netw 2010;8(10):1112-46.

60. Visvanathan K, Lippman SM, Hurley P*, et al.* American Society of Clinical Oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. Gynecol Oncol 2009;115(1):132-4.

61. Chemoprevention of breast cancer: recommendations and rationale. Annals of internal medicine 2002;137(1):56-8.

62. Tice JA, O'Meara ES, Weaver DL*, et al.* Benign Breast Disease, Mammographic Breast Density, and the Risk of Breast Cancer. J Natl Cancer Inst 2013;105(14):1043-9.

63. Pankratz VS, Degnim AC, Frank RD*, et al.* Model for Individualized Prediction of Breast Cancer Risk After a Benign Breast Biopsy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015.

Appendix A: Supporting Analyses for Chapter 3

Table A1. Association between BBD and no BBD showing that missing variables do not depend on BBD status, as BBD is our exposure of interest

	No BBD	BBD	p-value
Menopausal Status			0.14
Premenopausal	704 (56.7%)	610 (53.7%)	
Postmenopausal	538 (43.3%)	527 46.4%)	
BMI (mean±std)			0.50
<25 kg/m^2	477 (67.7%)	574 (66.1%)	
≥25 kg/m^2	228 (32.3%)	295 (33.9%)	
Age at Menarche			0.64
≤11 years	214 (19.3%)	210 (18.5%)	
≥12 years	897 (80.7%)	926 (81.5%)	
Oral Contraceptive Use			0.35
Yes	461 (48.2%)	496 (50.4%)	
No	495 (51.8%)	489 (49.6%)	
Duration of Use			0.75
<2 years	211 (23.2%)	220 (23.7%)	
≥2 years	203 (22.3%)	218 (23.5%)	
None	495 (51.8%)	489 (49.6%)	
Current Alcohol Use			0.28
Yes	471 (68.3%)	523 (65.6%)	
No	219 (31.7%)	274 (34.4%)	
Frequency of Consumption			0.12
<1 - 3 times per month	203 (30.5%)	207 (27.3%)	
1-3 times per week	187 (28.1%)	192 (25.4%)	
Daily to 2-3 times per day	56 (8.4%)	84 (11.1%)	
None	219 (31.7%)	274 (34.4%)	
Ever Smoker			0.01
Yes	308 (50.0%)	280 (42.8%)	
No	308 (50.0%)	374 (57.2%)	
Duration of Smoking (among Yes)			0.07
<5 years	88 (15.0%)	75 (12.0%)	
6-10 years	45 (7.7%)	41 (6.6%)	
>10 years	146 (24.9%)	133 (21.4%)	
None	308 (52.5%)	374 (60.0%)	

Table A2. Comparison of association with breast cancer between variables that were imputed, compared to the results if the variables were not imputed.

	Imputed				Non-Imputed			
	No. of Women (n=2560), No. (%)	**No. of women with breast cancer (n=119)**	**No. of person-years of follow-up**	**HR (95% CI)**	**No. of Women (n=2379), No. (%)**	**No. of women with breast cancer (n=119)**	**No. of person-years of follow-up**	**HR (95% CI)**
Menopausal Status								
Premenopausal	1416 (55.3%)	56	12725.27	1.00	1314 (55.2%)	53	12029.05	1.00
Postmenopausal	1144 (44.7%)	63	9353.19	1.53 (1.07-2.20)	1065 (44.7%)	63	8907.38	1.60 (1.11-2.31)
BMI (mean±std)								
<25 kg/m^2	1640 (64.1%)	68	14323.21	1.00	1051 (55.8%)	50	8934.46	1.00
≥25 kg/m^2	920 (35.9%)	51	7755.25	1.37 (0.95-1.97)	523 (33.2%)	36	4257.77	1.47 (0.96-2.26)
Age at Menarche								
≤11 years	490 (19.1%)	26	4220.72	1.19 (0.77-1.85)	424 (18.9%)	25	3354.24	1.27 (0.82-1.99)
≥12 years	2070 (80.9%)	93	17857.74	1.00	1823 (91.1%)	89	14853.54	1.00
Oral Contraceptive Use								
Yes	1273 (49.7%)	47	10828.88	0.67 (0.46-0.97)	957 (49.3%)	38	7722.46	0.68 (0.46-1.03)
No	1287 (50.3%)	72	11249.58	1.00	984 (50.7%)	61	8282.35	1.00
Duration of Use								
<2 years	625 (24.4%)	19	5738.1	0.51 (0.31-0.84)	431 (23.5%)	14	3821.35	0.50 (0.28-0.90)
≥2 years	648 (25.3%)	28	5090.78	0.86 (0.55-1.33)	421 (22.9%)	19	3189.93	0.84 (0.50-1.40)
None	1287 (50.3%)	72	11249.58	1.00	984 (53.6%)	61	8282.35	1.00
Current Alcohol Use								
Yes	1677 (65.5%)	79	14387.19	1.06 (0.73-1.56)	994 (66.9%)	57	8063.18	1.02 (0.67-1.59)

No	883 (34.5%)	40	7691.27	1.00	493 (33.2%)	30	4272.36	1.00
Frequency of Consumption								
<1 - 3 times per month	703 (27.5%)	33	6137.8	1.05 (0.66-1.66)	410 (28.8%)	23	3486.97	0.94 (0.55-1.62)
1-3 times per week	710 (27.7%)	31	6100.78	0.98 (0.61-1.56)	379 (26.7%)	19	3091.53	0.91 (0.51-1.63)
Daily to 2-3 times per day	264 (10.3%)	15	2148.61	1.36 (0.75-2.46)	140 (9.9%)	11	1113.39	1.42 (0.71-2.84)
None	883 (34.5%)	40	7691.27	1.00	493 (34.7%)	30	4272.36	1.00
Ever Smoker								
Yes	1164 (45.5%)	53	9914.60	1.00 (0.70-1.43)	588 (46.3%)	33	5059.46	0.81 (0.52-1.27)
No	1396 (54.5%)	66	12163.85	1.00	682 (53.7%)	48	6124.86	1.00
Duration of Smoking (among Yes)								
<5 years	430 (16.8%)	19	3629.53	0.98 (0.59-1.63)	163 (13.5%)	8	1405.28	0.73 (0.35-1.55)
6-10 years	190 (7.4%)	14	1608.82	1.61 (0.90-2.86)	86 (7.1%)	11	699.4	2.05 (1.06-3.96)
>10 years	544 (21.3%)	20	4676.26	0.80 (0.49-1.32)	279 (23.1%)	11	2503.21	0.50 (0.26-1.00)
None	1396 (54.5%)	66	12163.85	1.00	682 (56.3%)	48	6124.86	1.00

Table A3. Comparing association with breast cancer and BBD using BBD as a time-varying covariate or modeling BBD as a non-time-varying covariate.

		BBD as time-varying covariate			BBD as Non-time-varying covariate
	No. of Women (n=2560), No. (%)	**No. of women with breast cancer (n=119)**	**No. of person-years of follow-up**	**HR (95% CI)**	**HR (95% CI)**
Benign Breast Disease					
Yes	1240 (48.4%)	74	9895.79	2.75 (1.90-3.98)	2.07 (1.43-3.01)
No	1320 (51.6%)	45	12182.67	1.00	1.00
Histology					
No BBD	1320 (51.6%0	45	12182.67	1.00	1.00
Nonproliferative disease	400 (15.6%)	25	3450.75	1.96 (1.20-3.20)	1.96 (1.20-3.20)
Proliferative disease without atypia	309 (12.1%)	16	2393.37	1.82 (1.03-3.22)	1.82 (1.03-3.22)
Atypical Hyperplasia	531 (20.7%)	33	4051.66	2.33 (1.49-3.67)	2.33 (1.49-3.67)
Age					
≤35 years	357 (14.0%)	10	3258.56	1.00	1.00
36-45 years	836 (32.7%)	34	7463.38	1.49 (0.74-3.01)	1.49 (0.74-3.01)
46-55 years	801 (31.3%)	36	6948.19	1.73 (0.86-3.49)	1.73 (0.86-3.49)
>55 years	564 (22.1%)	39	4372.87	2.95 (1.47-5.90)	2.95 (1.47-5.90)
Race/Ethnicity					
Caucasian	1907 (74.5%)	98	17012.46	1.00	1.00
Hispanic	243 (9.5%)	7	1840.46	0.65 (0.30-1.40)	0.43 (0.06-3.09)
African American	98 (3.8%)	4	777.86	0.91 (0.34-2.49)	0.67 (0.21-2.13)
Asian	84 (3.3%)	2	537.67	0.70 (0.17-2.82)	0.60 (0.24-1.47)
Other	228 (8.9%)	8	1910.01	0.73 (0.36-1.50)	0.65 (0.28-1.48)
Menopausal Status					
Premenopausal	1416 (55.3%)	56	12725.27	1.00	1.00

Postmenopausal	1144 (44.7%)	63	9353.19	1.53 (1.07-2.20)	1.63 (1.14-2.34)
BMI (mean±std)					
<25 kg/m^2	1640 (64.1%)	68	14323.21	1.00	1.00
≥25 kg/m^2	920 (35.9%)	51	7755.25	1.37 (0.95-1.97)	1.20 (0.83-1.73)
Age at Menarche					
≤11 years	490 (19.1%)	26	4220.72	1.19 (0.77-1.85)	1.39 (0.91-2.14)
≥12 years	2070 (80.9%)	93	17857.74	1.00	1.00
Parity					
Nulliparous	737 (28.8%)	39	6390.8	1.00	1.00
Parous	1823 (71.2%)	80	15687.66	0.84 (0.58-1.24)	0.84 (0.58-1.24)
Age at First Birth					
<30 years	1243 (48.6%)	54	10788.6	0.84 (0.55-1.26)	0.89 (0.59-1.34)
≥30 years	580 (22.7%)	26	4899.06	0.86 (0.52-1.41)	0.77 (0.47-1.26
No Births	737 (28.8%)	39	6390.8	1.00	1.00
Number of Births					
1 birth	597 (23.3%)	19	5175.58	0.59 (0.34-1.01)	0.56 (0.33-0.98)
≥2 births	1226 (47.9%)	61	10512.08	0.98 (0.65-1.47)	1.00 (0.67-1.50)
No Births	737 (28.8%)	39	6390.8	1.00	1.00
Age at Last Live Birth					
<35 years	1305 (51.0%)	60	11249.95	0.89 (0.59-1.33)	0.90 (0.60-1.34)
≥35 years	518 (20.2%)	20	4437.71	0.74 (0.43-1.27)	0.69 (0.40-1.21)
No Births	737 (28.8%)	39	6390.8	1.00	1.00
Interval between Age at Menarche and Age at First Birth					
<15 years	958 (37.4%)	42	8249.06	0.85 (0.55-1.32)	0.96 (0.62-1.49)
≥15 years	865 (33.8%)	38	7438.6	0.83 (0.53-1.30)	1.16 (0.75-1.81)
No Births	737 (28.8%)	39	6390.8	1.00	1.00

Breastfeeding (among parous)					
Yes	980 (53.8%)	45	8407.08	1.08 (0.69-1.68)	0.89 (0.57-1.38)
No	843 (26.2%)	35	7280.58	1.00	1.00
Duration of Breastfeeding (among parous)					
<2 years	723 (39.7%)	35	6163.96	1.14 (0.71-1.82)	0.74 (0.34-1.59)
≥2 years	257 (14.1%)	10	2243.12	0.92 (0.46-1.87)	1.05 (0.666-1.67)
None	843 (46.2%)	35	7280.58	1.00	1.00
Oral Contraceptive Use					
Yes	1273 (49.7%)	47	10828.88	0.67 (0.46-0.97)	0.68 (0.47-0.99)
No	1287 (50.3%)	72	11249.58	1.00	1.00
Duration of Use					
<2 years	625 (24.4%)	19	5738.1	0.51 (0.31-0.84)	0.58 (0.35-0.94)
≥2 years	648 (25.3%)	28	5090.78	0.86 (0.55-1.33)	0.79 (0.51-1.22)
None	1287 (50.3%)	72	11249.58	1.00	1.00
Current Alcohol Use					
Yes	1677 (65.5%)	79	14387.19	1.06 (0.73-1.56)	0.89 (0.62-1.30)
No	883 (34.5%)	40	7691.27	1.00	1.00
Frequency of Consumption					
<1 - 3 times per month	703 (27.5%)	33	6137.8	1.05 (0.66-1.66)	0.91 (0.58-1.42)
1-3 times per week	710 (27.7%)	31	6100.78	0.98 (0.61-1.56)	0.76 (0.47-1.24)
Daily to 2-3 times per day	264 (10.3%)	15	2148.61	1.36 (0.75-2.46)	1.21 (0.67-2.18)
None	883 (34.5%)	40	7691.27	1.00	1.00
Ever Smoker					
Yes	1164 (45.5%)	53	9914.60	1.00 (0.70-1.43)	0.94 (0.65-1.35)
No	1396 (54.5%)	66	12163.85	1.00	1.00
Duration of Smoking (among Yes)					
<5 years	430 (16.8%)	19	3629.53	0.98 (0.59-	0.82 (0.50-1.36)

				1.63)	
6-10 years	190 (7.4%)	14	1608.82	1.61 (0.90-2.86)	1.62 (0.91-2.88)
>10 years	544 (21.3%)	20	4676.26	0.80 (0.49-1.32)	0.79 (0.47-1.35)
None	1396 (54.5%)	66	12163.85	1.00	1.00
First Degree Family History of Breast Cancer					
No First Degree Family History	905 (36.6%)	49	7182.19	1.00	1.00
1 First Degree Family Member	1267 (51.3%)	47	11982.1	0.54 (0.36-0.81)	0.54 (0.36-0.81)
>1 First Degree Family Member	299 (12.1%)	21	2401.78	1.29 (0.77-2.15)	1.29 (0.77-2.15)

Table A4. Examination of potential collider bias due to family history selection into the cohort, effect modification of BBD results shown only in women with a family history of breast cancer

	Benign Breast Disease, No (n = 988)			Benign Breast Disease, Yes (n = 578)		
	No. of person-years of follow-up	No. of women with breast cancer (n=119)	Multivariable adjusted HR (95% CI)	No. of person-years of follow-up	No. of women with breast cancer (n=119)	Multivariable adjusted HR (95% CI)
Age						
≤35 years	1957.03	3	1.0	791.62	5	5.49 (1.30-23.10)
36-45 years	2976.41	10	2.17 (0.59-7.97)	1999	11	5.15 (1.41-18.85)
46-55 years	2403.3	9	2.59 (0.68-9.79)	1537.5	9	4.38 (1.15-16.64)
>55 years	1888.26	13	4.88 (1.34-17.77)	813.49	8	7.01 (1.77-27.80)
Menopausal Status						
Premenopausal	7183.70	16	1.0	5541.57	19	2.63 (1.33-5.18)
Postmenopausal	4998.97	19	1.43 (0.63-3.25)	4354.21	14	2.26 (0.97-5.31)
BMI						
<25 kg/m^2	6092.35	23	1.0	3425.69	15	1.37 (0.71-2.66)
≥25 kg/m^2	3149.92	12	0.91 (0.45-1.86)	1715.92	18	3.18 (1.68-6.01)
Age at Menarche						
≤11 years	1855.21	8	1.16 (0.52-2.57)	1032.22	4	2.26 (1.33-3.86)
≥12 years	7387.06	27	1.0	4109.40	29	1.47 (0.51-4.26)
Parity						
Nulliparous	2894.08	9	1.00	1486.8	12	3.47 (1.45-8.32)
Parous	6348.18	26	1.60 (0.59-4.36)	3654.81	21	2.61 (0.96-7.07)
Age at First Birth (among parous women)						
<30 years	4021.37	19	1.00	2305	14	1.50 (0.74-3.02)
≥30 years	23.26.81	7	0.99 (0.37-2.70)	1349.8	7	1.91 (0.70-3.02)

Number of Births (among parous women)						
1 birth	2551.93	5	1.00	1075.73	2	1.21 (0.23-6.26)
≥2 births	3796.26	21	2.68 (0.94-7.68)	2579.07	19	4.54 (1.58-13.04)
Age at Last Live Birth (among parous women)						
<35 years	4673.25	20	1.00	2511.68	15	1.57 (0.80-3.10)
≥35 years	1674.94	6	0.82 (0.31-2.29)	1143.13	6	1.43 (0.52-3.90)
Interval between Age at Menarche and Age at First Birth (among parous women)						
<15 years	3072.28	15	1.00	1750.84	10	1.53 (0.68-3.42)
≥15 years	3275.9	11	0.93 (0.41-2.13)	1903.97	11	1.60 (0.70-3.64)
Breastfeeding (among parous)						
Yes	3030.13	11	1.56 (0.69-3.55)	1425.28	7	2.53 (1.10-5.82)
No	3318.05	15	1.0	2229.52	14	1.48 (0.57-3.84
Duration of Breastfeeding (among parous)						
<2 years	2497.3	13	0.74 (0.16-3.49)	1677.14	11	1.78 (0.47-6.66)
≥2 years	820.75	2	1.83 (0.79-4.24)	552.38	3	2.76 (1.15-6.63)
None	3030.13	11	1.0	1425.28	7	1.48 (0.57-3.84)
Oral Contraceptive Use						
Yes	4734.89	16	0.97 (0.49-1.92)	2561.34	13	1.89 (0.92-3.89)
No	4507.38	19	1.0	2580.27	20	2.14 (1.13-4.08)
Duration of Use						
<2 years	2242.21	5	0.63 (0.23-1.69)	1269.08	6	1.74 (0.68-4.46)
≥2 years	2492.68	11	1.31 (0.61-2.79)	1292.26	7	2.03 (0.85-4.85)
None	4507.38	19	1.0	2580.27	20	2.14 (1.13-4.07)
Current Alcohol Use						
Yes	6528.07	21	0.63 (0.31-1.25)	3270.1	21	1.59 (0.73-3.49)
No	2714.202	14	1.00	1871.51	12	1.50 (0.75-3.00)
Frequency of Consumption						

<1 - 3 times per month	3206.27	8	0.48 (0.20-1.16)	1291.21	11	1.60 (0.73-3.50)
1-3 times per week	2495.01	10	0.80 (0.35-1.84)	1428.91	6	1.92 (0.86-4.32)
Daily to 2-3 times per day	826.79	3	0.65 (0.18-2.34)	549.98	4	1.00 (0.38-2.65)
None	2714.20	14	1.00	1871.51	12	1.82 (0.59-5.62)
Ever Smoker						
Yes	4295.56	19	1.44 (0.73-2.84)	2107.87	11	2.20 (1.01-4.81)
No	4946.71	16	1.00	3033.74	22	2.63 (1.36-5.07)
Duration of Smoking						
<5 years	1891.16	6	1.02 (0.40-2.63)	1046.80	7	2.65 (1.37-5.11)
6-10 years	759.86	6	2.68 (1.04-6.92)	323.44	2	2.70 (1.10-6.67)
>10 years	1644.53	7	1.37 (0.55-3.39)	737.63	2	2.47 (0.56-10.89)
None	4946.71	16	1.00	3033.74	22	1.25 (0.28-5.50)

*adjusted for: age, race, for reproductive variables also adjusted for current alcohol use, age at first birth, number of live births and age last birth, for alcohol use also adjusted for age at first birth, number of live births and age at last birth.

Appendix B: Supporting Analyses for Chapter 4

Table B1. Comparison of performance of Gail (BCRAT), Tyrer-Cuzick (IBIS), and BOADICEA models in WAR Cohort by characteristics used in risk assessment models

Characteristic	N Total	Person-Years	Observed Events	Gail Predicted Events	IBIS Predicted Events	BOADICEA Predicted Events	P:O Gail	95% CI	P:O IBIS	95% CI	P:O BOADICEA	95% CI
Age, years												
<35	363	3319.80	10	2.45	3.72	3.92	0.25	0.04-0.79	0.37	0.09-0.98	0.39	0.10-1.01
35-44	739	6567.32	27	18.34	21.19	20.01	0.68	0.40-1.07	0.78	0.49-1.20	0.74	0.45-1.14
45-54	890	7681.58	40	29.37	38.46	32.33	0.73	0.49-1.05	0.96	0.68-1.32	0.81	0.55-1.14
55-64	403	3049.44	18	20.25	27.78	17.84	1.13	0.69-1.73	1.46	0.97-2.12	0.99	0.59-1.57
65-75	213	1650.00	20	12.84	12.24	8.52	0.64	0.34-1.10	0.61	0.32-1.06	0.43	0.19-0.82
>75	49	279.68	5	3.65	3.09	2.32	0.73	0.18-1.95	0.62	0.13-1.78	0.46	0.07-1.54
Race												
White	1646	13485.66	96	59.77	72.46	54.42	0.62	0.47-0.80	0.75	0.59-0.95	0.57	0.43-0.74
African American	85	630.34	3	1.98	3.19	3.06	0.66	0.07-2.40	1.06	0.23-3.02	1.02	0.21-2.95
Hispanic	204	1276.16	5	6.55	10.85	9.60	1.31	0.50-2.76	2.17	1.08-3.90	1.92	0.90-3.57
Asian	59	350.77	1	1.98	2.25	2.94	1.98	0.22-7.19	2.25	0.31-7.62	2.94	0.58-8.68
Other	663	6804.90	15	15.72	17.38	15.58	1.05	0.60-1.71	1.16	0.67-1.85	1.04	0.59-1.70
Age at menarche, years												
7-11	439	3418.98	25	17.19	20.03	15.54	0.69	0.40-1.10	0.80	0.49-1.24	0.62	0.35-1.02
12-13	1431	11544.54	75	49.66	60.51	47.76	0.66	0.49-0.87	0.81	0.62-1.04	0.64	0.47-0.84
≥14	470	3704.64	15	15.32	19.91	16.52	1.02	0.58-1.68	1.33	0.81-2.05	1.10	0.64-1.78
Unknown	317	3879.66	5	5.18	6.20	5.68	1.04	0.34-2.38	1.24	0.46-2.67	1.14	0.40-2.52
Parity												
Nulliparous	679	6003.96	39	16.33	23.07	16.46	0.42	0.24-0.68	0.59	0.38-0.89	0.42	0.24-0.68
Parous	1893	16020.01	80	66.21	76.87	63.73	0.83	0.64-1.05	0.96	0.76-1.20	0.80	0.61-1.02
Unknown	85	523.84	1	2.24	3.63	3.54	2.24	0.30-7.60	3.63	0.89-9.70	3.54	0.85-9.57
Age at first live birth, years (mean±std)												
No Birth	679	6003.96	39	16.33	23.07	16.46	0.42	0.24-0.68	0.59	0.38-0.89	0.42	0.24-0.68
<20	87	545.91	3	4.05	4.63	4.45	1.35	0.37-	1.54	0.47-	1.48	0.44-

								3.44		3.71		3.63
20-24	518	4372.41	23	19.03	21.41	17.38	0.83	0.50-1.29	0.93	0.58-1.42	0.76	0.44-1.20
25-29	566	4658.33	26	20.75	25.07	19.30	0.80	0.49-1.22	0.96	0.62-1.42	0.74	0.45-1.16
≥30	479	3939.05	23	17.18	20.30	16.29	0.75	0.44-1.19	0.88	0.54-1.36	0.71	0.41-1.15
Unknown	328	3028.16	6	8.26	9.74	10.18	1.38	0.60-2.68	1.62	0.77-3.01	1.70	0.82-3.10
Menopausal Status												
Premenopausal	1350	12222.72	53	30.93	38.62	33.89	0.58	0.40-0.83	0.73	0.52-1.00	0.64	0.44-0.89
Postmenopausal	1122	9177.77	64	48.56	58.24	42.92	0.76	0.56-1.00	0.91	0.69-1.18	0.67	0.49-0.90
Unknown	185	1147.32	3	6.45	8.21	8.13	2.15	0.82-4.56	2.74	1.19-5.35	2.71	1.18-5.31
Menopausal hormone therapy use												
Never	2270	19013.45	92	70.29	86.58	70.57	0.76	0.60-0.96	0.94	0.75-1.16	0.77	0.60-0.97
>5 years ago	325	2985.93	24	11.74	13.61	10.38	0.49	0.25-0.86	0.57	0.31-0.96	0.43	0.21-0.79
<5 years ago	30	223.07	2	1.45	2.12	1.28	0.73	0.04-3.16	1.06	0.13-3.71	0.64	0.02-3.02
Current user	32	325.37	2	1.07	1.07	1.01	0.54	0.01-2.84	0.54	0.01-2.84	0.51	0.01-2.79
No. first-degree relatives with breast cancer												
0-1	2284	19767.64	100	62.67	83.59	66.83	0.63	0.48-0.80	0.84	0.67-1.04	0.67	0.52-0.85
2	245	1973.30	16	17.29	13.71	11.36	1.08	0.63-1.72	0.86	0.46-1.45	0.70	0.36-1.26
3+	35	284.55	2	2.71	2.59	1.75	1.36	0.24-4.16	1.30	0.22-4.07	0.88	0.08-3.41
Unknown	93	522.34	2	2.81	3.91	4.20	1.41	0.26-4.24	1.96	0.52-5.06	2.10	0.59-5.26
Number of biopsies												
0	1225	11600.59	46	29.34	35.76	33.21	0.64	0.43-0.91	0.78	0.54-1.08	0.72	0.50-1.01
1	544	4672.97	28	15.86	25.76	16.89	0.57	0.32-0.92	0.92	0.60-1.35	0.60	0.35-0.97
2+	888	6274.26	46	43.01	44.87	34.84	0.94	0.68-1.26	0.98	0.71-1.31	0.76	0.53-1.05
Hyperplasia (no atypia)												
Yes	48	204.62	4	4.29	5.94	3.90	1.07	0.31-2.66	1.49	0.54-3.24	0.98	0.26-2.52
No	2609	22343.19	116	81.79	99.44	80.49	0.71	0.56-0.88	0.86	0.70-1.04	0.69	0.55-0.86
LCIS												
Yes	107	495.44	6	6.65	30.85	6.05	1.11	0.43-	5.14	3.49-	1.01	0.37-

No	2550	22052.38	114	79.56	84.88	78.40	0.70	2.32 0.55-0.87	0.74	7.30 0.59-0.92	0.69	2.19 0.54-0.86

Table B2. Comparison of performance of Gail (BCRAT), Tyrer-Cuzick (IBIS), and BOADICEA models in WAR Cohort, excluding women who the Gail model is not recommended for

Model	Predicted 8.5-year Breast Cancer Risk Risk (Range)	Person-Years	Observed Events	Person-Years	Adjusted risk	Predicted Events	Predicted:Observed Ratio	95% CI	p-value	c-statistic	95% CI
Gail											
Total Population (n=2173)	3.77% (0.48%-18.09%)	18675.4	104	17384	4.05%	87.9	0.85	0.68-1.04	0.11	0.58	0.52-0.63
Any BBD (n=359)	5.04% (0.71%-16.47%)	2388.97	22	2872	4.19%	15.1	0.69	0.38-1.13	0.14	0.55	0.42-0.67
Atypical Hyperplasia (n=150)	6.68% (1.170%-16.47%)	967.72	4	1200	5.39%	8.1	2.03	0.88-3.97	0.04	0.65	0.31-0.98
IBIS											
Total Population (n=2657)	3.92% (0.58%-35.99%)	18675.4	104	17384	4.21%	91.4	0.88	0.71-1.08	0.22	0.54	0.49-0.60
Any BBD (n=359)	5.69% (1.02%-17.20%)	2388.97	22	2872	4.73%	17.0	0.77	0.45-1.24	0.29	0.58	0.47-0.70
Atypical Hyperplasia (n=150)	8.55% (2.77%-12.33%)	967.72	4	1200	6.90%	10.3	2.58	1.25-9.92	0.002	0.54	0.13-0.94
BOADICEA											
Total Population (n=2657)	3.60% (0.64%-21.20%)	18675.4	104	17384	3.86%	83.9	0.81	0.64-1.00	0.05	0.52	0.46-0.57
Any BBD (n=359)	3.76% (0.80%-15.92%)	2388.97	22	2872	3.12%	11.2	0.51	0.26-0.91	0.02	0.54	0.44-0.64
Atypical Hyperplasia (n=150)	3.51% (0.88%-10.96%)	967.72	4	1200	2.83%	4.2	1.05	0.29-2.63	0.82	0.59	0.40-0.78

Table B3. Comparison of performance of Gail (BCRAT), Tyrer-Cuzick (IBIS), and BOADICEA models in WAR Cohort, excluding women with any unknown data

Model	Predicted 8.5-year Breast Cancer Risk Risk (Range)	Person-Years	Observed Events	Person-Years	Adjusted risk	Predicted Events	Predicted:Observed Ratio	95% CI	p-value	c-statistic	95% CI
Gail											
Total Population (n=1395)	3.66% (0.07%-18.09%)	11630.75	82	11160	3.81%	101.3	1.24	1.01-1.50	0.03	0.59	0.53-0.65
Any BBD (n=236)	5.17% (0.13-16.45%)	1501.83	18	1888	4.11%	9.7	0.54	0.25-1.00	0.05	0.56	0.42-0.71
Atypical Hyperplasia (n=106)	6.86% (0.34%-16.45%)	610.31	2	848	4.94%	5.3	2.65	0.89-6.04	0.02	0.83	0.67-0.99
IBIS											
Total Population (n=1395)	4.47% (0.0%-35.99%)	11630.75	82	11160	4.66%	123.8	1.51	1.26-1.80	<0.0001	0.46	0.40-0.53
Any BBD (n=236)	6.20% (0.10%-22.73%)	1501.83	18	1888	4.93%	11.6	0.64	0.33-1.14	0.13	0.60	0.47-0.73
Atypical Hyperplasia (n=106)	9.02% (0.36%-22.73%)	610.31	2	848	6.49%	6.9	3.45	1.37-7.14	0.001	0.50	0.0-1.00
BOADICEA											
Total Population (n=1395)	3.38% (0.0%-21.20%)	11630.75	82	11160	3.53%	49.2	0.60	0.44-0.79	0.0003	0.49	0.43-0.55
Any BBD (n=236)	3.75% (0.0%-18.0%)	1501.83	18	1888	2.98%	7.0	0.39	0.16-0.80	0.01	0.59	0.47-0.71
Atypical Hyperplasia (n=106)	3.67% (0.24%-18.80%)	610.31	2	848	2.64%	2.8	1.40	0.26-4.23	0.57	0.59	0.20-0.98