ISSUES IN BREAST CANCER PREVENTION:

BODY MASS INDEX, BREAST DENSITY, AND FRACTURES

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Submitted to the Graduate Faculty of

the Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2012

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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Breast cancer is the most frequently diagnosed cancer besides skin and the second leading cause of cancer death among American women. Breast cancer prevention comprises all techniques that lower the risk for developing breast cancer, thereby lowering population incidence and mortality. This dissertation used breast cancer prevention clinical trials data from the National Surgical Adjuvant Breast and Bowel Project to evaluate important issues related to breast cancer prevention. Some breast cancer risk factors are modifiable and can be changed with lifestyle adjustments. For example, high body weight has been associated with increased breast cancer risk among postmenopausal women, but the relationship in premenopausal women has remained unclear. In the first analysis, we found a significant association between overweight and obesity and increased breast cancer risk in premenopausal women, and a nonsignificant association among postmenopausal women. Other risk factors are not modifiable and require more complex interventions such as chemopreventive therapies. The Gail model is the most popular risk prediction model to determine who might benefit from these therapies, but it does not include breast density which is an established breast cancer risk factor. In a second analysis, high breast density was significantly associated with increased breast cancer risk when considered with the Gail score, but provided only slight improvement in discriminatory accuracy. Despite the

success and availability of tamoxifen and raloxifene as chemopreventive agents, they have been underused in clinical settings. Providing more information about these drugs may help to increase their popularity. A final analysis expanded on prior findings about tamoxifen and bone fractures, and showed that tamoxifen reduced osteoporotic fracture risk for all subgroups of women. The public health significance of this dissertation is realized in the clarification and expansion of knowledge surrounding important issues in breast cancer prevention for both clinicians and patients. We showed that maintaining a healthy weight is likely beneficial for all women at high-risk for developing breast cancer, and that women receiving tamoxifen will gain the added benefit of fracture risk reduction. Furthermore, among postmenopausal women, a single assessment of breast density does not provide substantial risk prediction improvement.

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1.0 INTRODUCTION

Clinical research has led to great improvements in the detection, diagnosis, and treatment of breast cancer resulting in a steady decline in mortality over the past 20 years. However, breast cancer continues to be the most commonly diagnosed cancer other than skin among women[1]. Although the search for new and improved breast cancer treatment continues, it has broadened to include methods for breast cancer prevention. Finding effective methods for identifying women at high risk for developing breast cancer, and subsequently determining safe options for lowering that risk, remain crucial yet challenging areas of breast cancer research.

The objective of this dissertation was to examine some unresolved issues related to breast cancer prevention including the identification of women who are at high risk for developing breast cancer, as well as possible concomitant benefits of chemopreventive drugs. Specifically, a series of three research articles addressed the following questions:

1. Is body mass index related to invasive breast cancer among postmenopausal and premenopausal women at high risk for developing breast cancer?
2. Does baseline mammographic breast density improve the predictive capability of the Gail model for invasive breast cancer?
3. Is the effect of tamoxifen on both osteoporotic and all clinical fractures consistent across different categories of fracture risk among women at high risk for breast cancer?

Data from two large randomized clinical trials from the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Breast Cancer Prevention Trial (BCPT, P-1) and the Study of Tamoxifen and Raloxifene (STAR, P-2), were used to address the above questions.

2.0 BACKGROUND

2.1 BREAST CANCER

2.1.1 Overview and Descriptive Epidemiology

In 2012, over 226,000 women in the United States are expected to be diagnosed with invasive breast cancer[1]. The current incidence reflects a long-term underlying increase since 1975 when population-based surveillance of breast cancer began. Between 1980 and 1987, breast cancer incidence rates rose by about four percent per year[2]. This rapid increase has been attributed to the growing popularity of mammography use during that time because more cancers that were too small to be detected otherwise were diagnosed. There was another slight increase during the 1990s (1.6% per year) that was likely due to the continued rise of mammographic screening in addition to growing rates of obesity and the use of postmenopausal hormone therapy (PHT). In 2002, we began to see a decline in incidence rates among postmenopausal women following the release of results from the Women's Health Initiative (WHI) which revealed detrimental effects of estrogen plus progestin on breast cancer risk[3,4].

Breast cancer mortality also ranks high relative to other cancers. Behind lung cancer, it is the second leading cause of cancer death among females. In 2012, an estimated 40,000 breast cancer deaths will occur in the United States[1]. Despite these statistics, research has led to vast improvements in breast cancer survival. Early detection through mammography screening,

available and approved chemopreventive agents, and improvements in breast cancer treatment have led to a steady decline in death rates for breast cancer over the past 20 years. According to the American Cancer Society, relative survival at five years after diagnosis is estimated to be 89% overall. However, survival rates are dissimilar according to stage at diagnosis with estimates as high as 99% for those diagnosed at an early stage with localized disease, 84% for regional disease, and 23% for late-stage distant disease. Survival rates are also lower among younger women diagnosed before age 40 compared to older women (84% vs. 90%) and among African American women compared to white women (77% vs. 90%)[2].

In addition to the United States, the impact of breast cancer can be seen throughout the world. Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women[5]. Incidence rates are generally higher in developed countries including North America, Australia, and Northern and Western Europe, but low screening rates and incomplete reporting in developing countries may contribute to the discrepancy. Although recent years have brought a decline in breast cancer incidence and mortality in the United States, these trends are not consistent worldwide. Breast cancer incident rates have continued to rise in many African and Asian countries, most likely due to changes in obesity, physical inactivity, reproductive patterns, and the introduction of breast cancer screening. Furthermore, westernized lifestyle changes and lack of widespread breast cancer screening programs have also contributed to an increase in breast cancer mortality in many Asian countries[5].

There are two main characteristics of breast cancer that are often used to describe a diagnosis, noninvasive and invasive. Both of these originate in the lobules which are the milk-producing glands in the breast, or the ducts which are the tiny tubes that carry milk from the lobules to the nipple. Noninvasive breast cancers are currently referred to as lobular carcinoma

in situ (LCIS) or ductal carcinoma *in situ* (DCIS), and are less severe since they are confined within the walls of the lobules or ducts. In fact, nearly all noninvasive breast cancers can be cured[6]. Invasive breast cancer occurs when the cancer cells break through the glandular or ductal walls and infiltrate the surrounding breast tissue. Invasive breast cancer comprises the majority of breast cancers diagnosed and are more severe in prognosis and survival. Within invasive breast cancer, the severity is determined by the stage of the disease which is based on the size of the tumor, the spread of the cancer at first diagnosis, and characteristics identified through laboratory tests. The stage of breast cancer can range from completely confined to the breast, to spreading to the surrounding tissue and lymph nodes, or to metastasizing to distant organs. Invasive lobular cancer is more difficult to diagnose and therefore usually presents at a more advanced stage than invasive ductal cancer. However, invasive lobular cancer has been associated with better survival and disease-free survival than ductal cancers[7,8].

Once a diagnosis of breast cancer is made, cancer cells removed during biopsy or surgery are tested for estrogen receptor (ER) and progesterone receptor (PR) status. Receptors are proteins found inside and on the surface of cells that can attach to certain substances that circulate in the blood[6]. Normal breast cells have hormone receptors that attach to estrogen and progesterone and act as initiators for the biological chain of events for the particular hormone. It is believed that when a malignant transformation of a normal breast cell occurs, the cell may retain all or part of the normal population of receptor sites (i.e., hormone receptor-positive)[9]. If the cell does not retain the receptor sites, then it is no longer influenced by hormonal control (i.e., hormone receptor-negative). Therefore, estrogen promotes tumor growth in only breast cancers that are found to be positive for hormone receptors. Women with hormone receptor (ER and/or PR) positive breast cancer tend to have lower-grade tumors that grow slowly and respond

well to hormonal therapy, and thus have a better prognosis than women with hormone receptor-negative cancer. ER and/or PR-positive breast cancers account for approximately 65 percent of all diagnosed breast cancers and occur more frequently in older, postmenopausal women. Likewise, ER and PR-negative cancers are diagnosed more often in younger, premenopausal women. Differences by race also exist with ER and/or PR-positive cancers being more common among white women compared to African American[10].

Invasive breast cancer tumors are also assessed for the human epidermal growth factor receptor 2 (HER2). Normal cells have one copy of the HER2 gene on each chromosome 17, which instructs cells to make the growth-promoting HER2 protein. Women with HER2-positive breast cancers have too many copies of the HER2 gene leading to an increased number of receptors at the tumor-cell surface. This leads to excessive cellular division and the formation, proliferation, and survival of tumors[11]. About 25 percent of invasive breast cancers test positive for increased levels of HER2[6,11]. HER2-positive cancers tend to grow and spread more aggressively than HER2-negative breast cancers[11].

2.1.2 Risk Factors for Breast Cancer

Many factors have been identified that are associated with an increased risk of breast cancer. Some of these factors are modifiable through lifestyle changes. However, there are also many strong risk factors associated with breast cancer that are not modifiable. It is important for all women to be aware of breast cancer risk factors and understand the impact they may individually and collectively have on breast cancer risk. Understanding why and how all risk factors (both modifiable and not modifiable) influence the development of breast cancer is important for

finding ways to reduce risk and prevent the disease. Table 2-1 lists personal, lifestyle, reproductive, and medical factors that have been associated with an increased risk of breast cancer. They are grouped by the strength of the association[2,12].

Table 2-1. Summary of breast cancer risk factors

Strength of Association	Risk Factor
Relative Risk > 2.0	Older age Family history of breast cancer (first-degree relatives) History of atypical hyperplasia Higher breast density Higher bone density
Relative Risk ≤ 2.0	Race Number of breast biopsies Late age (>30 years) of first live birth Early menarche (<12 years) Late menopause (>55 years) Nulliparity Never breastfed a child Recent oral contraceptive use Recent PHT use with combined estrogen and progestin Obesity Low physical activity Alcohol consumption Cigarette smoking

One of the most important risk factors for breast cancer is age. A woman's risk increases steadily until around the age of 85 years. The majority of breast cancers are diagnosed among women over age 40 (95%), with a median age at diagnosis of 61 years[2]. However, women diagnosed before the age of 40 often have more aggressive tumors that are unresponsive to treatment. Race is another important risk factor with white women being more likely to develop breast cancer than African American women. However, despite their lower incidence rate, African American women are more likely to die from the disease. A positive family history of

breast cancer also increases the risk for developing breast cancer. Having one first-degree relative (i.e., mother, sister, or daughter) with breast cancer doubles the risk and having two relatives increases the risk 5-fold.

Lifestyle factors such as alcohol use, cigarette smoking, physical activity, and obesity have also been studied in relation to breast cancer risk. There is substantial evidence in the literature that alcohol consumption increases breast cancer risk by about 10% with one alcoholic beverage per day[13,14]. Furthermore, alcohol may be more strongly related to ER-positive breast cancer than ER-negative cancers, and the relationship is more pronounced for lobular subtypes compared to ductal[15,16]. Recent findings have also provided evidence of an increased risk for breast cancer among active cigarette smokers, and the risk appears to be greater with a longer duration of smoking years and for those who started to smoke at a younger age[17-19]. Physical activity in the form of exercise appears to play a role in the development of breast cancer as well. Evidence in the literature has been somewhat inconsistent and further study is needed. However, in general, increased levels of physical activity have been associated with a reduction in breast cancer risk[15,20]. Related to physical activity, obesity has also been associated with breast cancer risk. Specifically, a protective effect among premenopausal women and a detrimental effect after menopause has been suggested throughout the literature. This relationship will be discussed further in section 2.1.3.

Various reproductive factors are strongly associated with an increased risk for breast cancer. These include age of menarche, age of menopause, nulliparity, and age of first live birth. Both an early age of menarche (i.e., onset of menstruation at age 12 or younger) and an older age of menopause (i.e., discontinuation of menstruation at age 55 or older) are associated with an increased risk for breast cancer. This increased risk is believed to relate to levels of endogenous

estrogen circulating in a woman's body. Estrogen is primarily responsible for the growth and differentiation of normal breast tissue, and in premenopausal women, nearly all of circulating estrogen is of ovarian origin. Thus, it is believed that the risk for breast cancer is directly related to the cumulative number of ovulatory menstrual cycles in a woman's life. Also related to the total number of menstrual cycles throughout a woman's lifetime is the number of times she has been pregnant, with an inverse relation between the number of pregnancies and breast cancer risk. Moreover, the risk for breast cancer is increased for nulliparous women and those who experienced their first full-term pregnancy after the age of 30 years. Breastfeeding has been associated with a decreased risk for breast cancer and is more protective with longer cumulative durations of breastfeeding[21].

Exogenous estrogen exposure is also associated with an increased risk for breast cancer. PHT with combined estrogen and progestin was once commonly prescribed to alleviate hot flashes and osteoporosis in postmenopausal women. However, in 2002, the WHI released results from a randomized controlled trial of over 16,000 women confirming that combined estrogen plus progestin use increased the risk for invasive breast cancer[3,4]. However, the increased risk diminished after 5 years of stopping the combined PHT and subsequent studies found no increased risk with estrogen-only therapies for women post-hysterectomy[22-25]. Since the original findings were reported, the use of this type of PHT has decreased substantially. Studies have also shown a slight increase in breast cancer risk for women who take combined estrogen and progestin oral contraceptives; however, after 10 years of discontinuation there was no increased risk for invasive breast cancer[26].

Clinical factors such as the number of previous breast biopsies, history of atypical hyperplasia, bone mineral density (BMD), and mammographic breast density have also been

associated with an increased risk of invasive breast cancer. Unsurprisingly, since a breast biopsy is an indicator of previous benign breast disease, a greater number of previous breast biopsies is associated with an increased risk for breast cancer. Likewise, women who have a history of atypical hyperplasia, which is a type of benign breast disease where there is excessive growth of abnormal breast tissue cells, have a risk of invasive breast cancer that is four to five times higher than women without such a history. BMD is a measure of bone strength and risk of fracture that is positively correlated with estrogen exposure. Thus, older women with increased levels of BMD have been shown to have an increased risk for breast cancer[27], possibly because BMD is a marker of higher lifetime estrogen exposure. Mammographic breast density is the proportion of the breast that is composed of glandular and connective tissue relative to fatty tissue that shows up as white area on a mammogram. Many studies have found mammographic breast density to be a strong independent risk factor for breast cancer with an increased risk that is about three to five times greater in women with dense breasts compared to women with less dense or mostly fatty breasts[28-30]. This relationship is discussed in greater detail in section 2.1.4.

2.1.3 Association between Obesity and Breast Cancer Risk

Obesity is defined as excessive accumulation of body fat, but is often quantified as excess body weight for ease of measurement. Body mass index (BMI) is the most common measure of excess body weight used in epidemiologic studies. It is calculated as weight in kilograms divided by height in meters squared. Despite its ubiquitous use, BMI may not always be a precise measure of obesity in clinical studies. Measurements may be inaccurate if they are based on self-reported data since respondents typically overestimate their height and underestimate

their weight, the latter being true particularly among women[31]. Therefore, it is recommended that trained clinical staff perform measurements of weight and height. BMI also does not account for losses in height caused by osteoporosis or variations in lean body mass, which can affect the measurement of BMI without an actual change in body fat mass. Thus, older women will usually have a higher percentage of body fat at a given BMI than younger women[31,32]. Despite its limitations, BMI is quickly and easily attainable and has been deemed satisfactory for clinical and epidemiological purposes[32]. Classifications of BMI from the World Health Organization are as follows: <18.5 as underweight, 18.5-24.9 as normal, 25.0-29.9 as overweight, and ≥30 as obese.

The relationship between BMI and breast cancer has been extensively reported in the literature; however, conflicting and inconsistent results have led to speculation regarding its true nature. Associations between obesity and breast cancer risk are believed to differ based on menopausal status. Studies have identified BMI as a risk factor for breast cancer among postmenopausal women[33-35], and as a protective factor among premenopausal women[36-38]. In an early meta-analysis of 19 case-control and four cohort studies conducted among premenopausal women, Ursin and colleagues[39] found a modest inverse association between BMI and premenopausal breast cancer. Furthermore, a meta-analysis conducted by van den Brandt and colleagues in 2000[40] that used data from seven prospective studies supported a significant, inverse association between BMI and premenopausal breast cancer and a significant, positive association among postmenopausal breast cancer. However, other studies have been inconsistent among premenopausal women and were unable to find an association[35,41-43].

The most widely accepted explanation for the paradoxal relationship between BMI and breast cancer risk by menopausal status involves estrogen availability. After menopause, most of

the circulating estrogen in a woman's body comes from the aromatization of adrenal androgens in adipose tissue. Therefore, excess fat results in higher circulating estrogen levels in a woman's body, which stimulates the growth and progression of breast cancer. However, in premenopausal women, the level of circulating estrogen is controlled by the ovaries and therefore may not be greatly affected by the amount of excess fat. The estrogen connection in postmenopausal women is based on sound biological plausibility and clinical findings. In 2003, the Endogenous Hormones and Breast Cancer Collaborative Group pooled individual data from postmenopausal participants of eight different prospective studies and found that controlling for serum hormone concentrations attenuated the positive association between an increased risk of breast cancer and BMI[44]. Multiple hormones were tested, but the greatest effect was seen with concentrations of free estradiol for which the relative risk per 5 kg/m^2 increase in BMI was reduced from 1.19 to 1.02. They concluded that the increase in risk with high BMI was due to a corresponding increase in estrogens[44]. Furthermore, among postmenopausal women obesity has been more strongly related to ER-positive breast cancer than with ER-negative breast cancer thereby supporting the theory that greater amounts of circulating estrogen in obese women can increase the risk of tumor development[45].

Unfortunately, mechanisms for explaining the protective effect of obesity on premenopausal breast cancer are not as clear. The principal explanation has been anovulation among obese women. However, a study conducted by Michels et al.[38], which used data from premenopausal participants of the Nurses' Health Study (NHS) II, found that the inverse association between BMI and breast cancer risk was not explained by menstrual cycle characteristics, infertility due to ovulatory disorders, or probable polycystic ovary syndrome because adjustment for these factors did not attenuate the association. Although they could not

measure anovulation directly, they concluded that it was unlikely that anovulation was the primary reason that premenopausal women with a high BMI had a lower risk for breast cancer. Furthermore, premenopausal breast cancers are more likely to be ER and PR-negative and therefore not dependent on estrogen. When looking at premenopausal breast cancers by receptor status, studies have shown that obese women have a lower risk for developing ER or PR-positive breast cancers, but not ER and PR-negative cancers[32,46]. A recent study by Harris et al.[47] used NHS II data to look at the relationship between body fat distribution and risk for invasive breast cancer by subtype of cancer. They found that among their premenopausal population, abdominal adiposity increased the risk of developing ER-negative breast cancer but was not associated with ER-positive breast cancer. Therefore, the effect of obesity on breast cancer risk in premenopausal women may be acting through other pathways besides estrogen. A recent study showed that women with triple-negative breast cancers (i.e., negative for ER, PR, and HER2) also had a high prevalence of metabolic syndrome, characterized by obesity and insulin resistance[48]. Insulin resistance leads to hyperinsulinemia and stimulated synthesis of insulin-like growth factor-I (IGF-I) which both may contribute to tumor development and tumor growth[32,49,50]. Links between these factors and obesity are being explored for biological mechanisms explaining the obesity and breast cancer risk relationship, particularly among premenopausal women[50].

Certain individual factors have been shown to affect the relationship between BMI and breast cancer risk. A study from the WHI that examined obesity, body size, and the risk of postmenopausal breast cancer found that PHT use (either formerly or currently) attenuated the association of BMI and risk of breast cancer among postmenopausal women[34]. The authors theorized that taking PHT would raise the amount of circulating estrogen in the body to such a

degree that any additional amount made available by the conversion of androgens to estrogens in adipose tissue would be negligible. Based on their findings, they concluded that obesity increased risk only among postmenopausal women who had never taken PHT. Other studies have supported these findings[35]. Similarly, among premenopausal women, studies have shown that having a family history of breast cancer or a history of oral contraceptive use may attenuate the inverse relationship between obesity and breast cancer risk[40,45].

When studying the relationship between BMI and breast cancer risk, detection bias cannot be ruled out as an explanation for inconsistent results. Obese women are less likely to partake in breast cancer screening[38]. Furthermore, it may be difficult to palpate lumps in obese women with larger breasts, [51]. Therefore, unless an obese woman is undergoing regular mammographic screening, cancer may go undiagnosed for some time until the tumor is large enough to palpate. Cui and colleagues found that high BMI was significantly associated with a later stage of breast cancer at diagnosis and larger tumor size[51]. They also found that this association was stronger among younger women compared to older women. It is possible that if diagnoses are delayed among heavier women, then the detection will occur in the postmenopausal stage of life instead of prior to menopause, causing the association to appear stronger among postmenopausal women[38].

2.1.4 Association between Breast Density and Breast Cancer Risk

Differences in breast tissue composition among women are reflected in mammography. Fat appears dark on a mammogram since it is radiologically lucent, allowing x-rays to easily pass through. However, connective and epithelial tissues such as those comprising milk ducts and

lobules are radiologically dense and block the x-rays from passing through. Thus, they appear white on a mammogram. Mammographic breast density is usually expressed as the percentage of breast area that is occupied by connective and epithelial tissues (i.e., the proportion appearing white on a mammogram)[28]. There are various methods for classifying mammographic breast density. Dr. John Wolfe developed the earliest classifications in 1976, and was the first to show the existence of a relationship between breast density and breast cancer risk. He described four distinct parenchymal patterns for classification: N1 (predominantly fat), P1 (ductal prominence in less than one-fourth of the breast), P2 (ductal prominence in more than one-fourth of the breast), and DY (severe involvement with dysplasia)[28,52]. Wolfe's categories became commonly used for classifying breast density. However, subsequent studies were not able to replicate and support Wolfe's findings, most likely because of a lack of consistency in applying the parenchymal pattern classifications. Therefore, in the United States, his classifications fell out of use as researchers began to look for new, more precise methods for measuring breast density. They began basing categorizations on quantitative estimations of the percentage of density in the breast instead of on strictly qualitative estimates. Using these quantitative methods, studies began to consistently show a positive association between breast density and the risk of breast cancer, leading to the acceptance of breast density as a risk factor for breast cancer. Women with high mammographic breast density were found to have a breast cancer risk that was three to five times larger than women with less dense breasts[28-30]. Studies also found that both past and current breast density were associated with risk, and that although masking bias does occur it likely has only a small and short-lived effect[28,52,53].

Currently in the United States, the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) provides a commonly used classification system of

breast density in clinical practice[54]. It was developed to standardize mammography reporting terminology as a way to estimate breast density and mammography accuracy. BI-RADS categories were not originally defined by percentage of density, but in 2003, quantitative percentage ranges were added to the descriptive categories[55]. The current BI-RADS density classifications are defined as follows: Grade 1 – the breast is almost entirely fat (<25% glandular), Grade 2 – there are scattered fibroglandular densities (approximately 25-50% glandular), Grade 3 – the breast tissue is heterogeneously dense, which could obscure detection of small masses (approximately 51-75% glandular), and Grade 4 – the breast tissue is extremely dense (>75% glandular). The BI-RADS breast density classifications have been shown to have only moderate interobserver agreement[28,55], but their widespread use and availability allow for convenient use in large study populations. More consistent methods of classification include computer-assisted planimetry and the use of thresholding methods with digitized mammograms[28,52]; however, all of these methods, including BI-RADS, require the input of trained observers and are therefore subjective in nature. Newer objective methods take the thickness of the breast into account to calculate volumetric breast density and appear to be more accurate and consistent. They include the use of Standard Mammogram Form (SMF) on digitized film screen mammograms, the use of full-field digital mammography (FFDM), and the use of magnetic resonance imaging (MRI) and ultrasound. However, all of these methods have not been studied in relation to breast cancer risk, and for those that have been studied, results are preliminary[28,56,57]. Furthermore, methods such as MRI can be costly and may not be appropriate for widespread use.

Breast density has been associated with certain host characteristics that may also be related to breast cancer. For example, BMI and percent breast density are largely interrelated

such that women with high BMI are more likely to have a low percent breast density. This is because BMI is positively related to total breast area, which is the denominator for percent breast density[57]. Because a high BMI may increase risk for breast cancer, especially among postmenopausal women, it is believed that the effect of parenchymal patterns estimated by percent breast density on risk will tend to be underestimated when not adjusted for BMI[58]. Preliminary studies have suggested that other measures of density, such as the absolute area of dense tissue or the volumetric breast density may eliminate this interrelationship. A recent study using a measure of volumetric breast density through FFDM instead of percent breast density showed that density volume was greater in women with high BMI[56].

In addition to BMI, high breast density is more common among white women compared to African-American women. It is also associated with nulliparity, late age at first birth, and younger age due to breast involution and density decreases that occur with age, the greatest of which occur after menopause[59,60]. Certain medication use has been shown to affect breast density as well. For example, PHT slows normal breast involution in postmenopausal women and causes an increase in mammographic density in 17-73% of women. On the other hand, both tamoxifen and raloxifene have been found to decrease mammographic density[52]. Despite all of the above listed characteristics, genetic factors are believed to account for a large proportion (approximately 50-70%) of the variation in mammographic breast density[61]. A few small studies that focused on mother-daughter sets, twins, and segregation analyses have supported this hypothesis[28]. Specifically, segregation analyses suggest that a major autosomal gene influences breast density, with a likely Mendelian transmission of a dominant gene (possibly on chromosome 6). In addition, women with BRCA1 and BRCA2 mutations have been shown to

have more dense breast tissue that is coarser and lower in contrast than women at low risk for developing breast cancer[52].

2.2 GAIL MODEL

2.2.1 Background and History

The Gail model incorporates a multivariate logistic regression model that was originally developed in 1989 by Mitchell Gail and colleagues using data from the Breast Cancer Detection Demonstration Project (BCDDP)[62]. The purpose of the model, referred to here as model 1, was to estimate the probability of developing invasive or noninvasive breast cancer among women receiving regular mammographic screenings. In addition to the age of the participant dichotomized into above or below 50 years, the model included age at menarche, age at first live birth, the number of previous breast biopsies, presence of atypical hyperplasia, and the number of affected first-degree female relatives. The relative risks associated with these factors were combined with estimates of the baseline hazard rates and attributable risks in the BCDDP population. Statisticians at the NSABP later modified model 1 to project the probability of developing invasive breast cancer only[63,64]. This modification, referred to as model 2, replaced the breast cancer incidence rates from the BCDDP with age and race-specific invasive breast cancer rates from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) and used attributable risk estimates from SEER to obtain the baseline hazard rates.

The Gail model has been validated in multiple study populations including the Cancer and Steroid Hormone (CASH) Study, NHS, and BCPT. Using data from the CASH Study, Gail and Benichou found that model 1 overpredicted breast cancer risk in younger women[65]. Spiegelman and colleagues concluded similar findings using NHS data[66]. However, both of these studies looked at women who were not undergoing regular mammographic screening. When considering women who were receiving regular screening, model 1 provided reasonable agreement between observed (*O*) and expected (*E*) cases in younger women (137 vs. 126.91, respectively)[63,67]. Costantino and colleagues assessed the validity of model 2 using white women who were assigned to the placebo arm of BCPT[63]. They found that the model was well calibrated in this population (*E/O* ratio of 1.03). Rockhill and colleagues further assessed the validity of model 2 using data from white women participating in NHS to evaluate discriminatory accuracy in addition to model calibration[68]. They concluded that model 2 was well calibrated (*E/O* ratio of 0.94) with modest discriminatory accuracy (c-statistic of 0.58). Although research continued for possible methods of improvement, model 2 became the most reliable and widely used model for risk prediction.

The Gail model could be applied to African Americans and women of other races and ethnicities; however, the projections were based on assumptions instead of empirical data. So in more recent years, the model was updated to provide more accurate predictions among African Americans[69] and Asians[70]. In 2007, Gail and colleagues used data from almost 2,300 African American women participating in the Women's Contraceptive and Reproductive Experiences (CARE) Study to build a model for predicting absolute invasive breast cancer for African Americans. They compared the projections from the new model with those from the previous model and calibrated the new model using data from African American women in the WHI. The

final CARE model was more parsimonious than the original and was well calibrated with good agreement between the number of predicted and observed cases in the WHI population. The CARE model also projected larger estimates of invasive breast cancer for African Americans than the prior model, which enabled more women to be eligible for and benefit from chemopreventive therapies and future clinical trials[69]. In 2011, the model was updated to provide more accurate predictions for Asian and Pacific Islander American women. Data from 589 cases and 952 controls participating in the Asian American Breast Cancer Study were used to create a model, and data from Asian and Pacific Islander American participants of the WHI were used to assess model calibration and discrimination. The new model was more parsimonious, had good fit, and gave smaller estimates of invasive breast cancer risk for Asian and Pacific Islander American women than the original model[70].

When model 2 was first developed, the age-specific breast cancer incidence rates were based on SEER data from 1983 to 1987. Since then, breast cancer incidence rates have changed substantially and so the rates used in the Gail model were not representative of more contemporary study populations. In 2010, Schonfeld and colleagues used more recent SEER rates from the 1995 to 2003 period to create an updated version of the Gail model[71]. They then compared their updated model to model 2, which was based on the earlier SEER rates. They used data from white, postmenopausal women participating in the National Institutes of Health – AARP Diet and Health Study, and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO). Almost all of the follow-up for both of these cohorts occurred after 1995, which corresponded to the more recent SEER rates. They found that the original Gail model based on the earlier SEER rates underpredicted invasive breast cancer in these two contemporary populations, and that using the updated SEER rates improved the calibration of the model. Thus,

they showed the importance of updating risk prediction models to reflect recent trends in incidence rates in order to remain relevant for use in the clinical setting.

2.2.2 Use in Clinical Practice and Research

Many women, especially those with a family history of breast cancer, tend to overestimate their risk for developing breast cancer. The Gail model was originally developed for the primary purpose of providing these women with a realistic estimate of their chance for developing breast cancer over different periods of their life[65]. Women and their doctors could then use these individualized estimates to aid in decisions regarding the management and control of risk. In the late 1990s, the NCI distributed a computer program to health care providers that computed the risk of invasive breast cancer based on model 2 and later posted this Breast Cancer Risk Assessment Tool on their website[72,73]. Since then, the tool has been updated to reflect the modifications for African Americans and Asian Americans, and will soon be updated to reflect the most recent breast cancer incidence rates from SEER and specific projections for Hispanic women. The tool provides an estimate of risk for developing invasive breast cancer over the next five years and over the lifetime of each woman if she were to live to age 90. For comparison, the tool also provides the 5-year and lifetime risk estimates for a woman of the same age who is at average risk for developing breast cancer[73]. A 5-year risk of invasive breast cancer of 1.66% or greater is considered to be the cut-point for identifying high versus low risk individuals. Any woman with a score above 1.66% should be evaluated further to determine whether she would benefit from prophylactic surgeries or chemoprevention.

Despite the fact that any woman can go online and calculate her own risk for developing breast cancer, it is important that the results are reviewed by and discussed with clinicians or counselors. Understanding the concept of risk may be difficult for most of the general public. Therefore, it is important that each assessed woman understands that no model is perfect, and that there may be some personal characteristics, such as having a breast cancer gene, that could affect individual risk despite what was predicted by the Gail model[65]. Clear communication is necessary so that each woman understands that although the Gail model may classify her as high risk, that does not mean that she is likely to get cancer in the near future, but only that her risk is high enough to consider some form of preventive action including chemoprevention[68].

In addition to its recommended use in clinical practice, the Gail model has also been used in research to identify women with an increased risk for breast cancer. The number of invasive breast cancers developed during a study affects the statistical power of the trial. Therefore, the Gail model has become a useful tool in the planning of breast cancer chemoprevention studies[65]. The Gail model was used to assess eligibility for participation in both the Breast Cancer Prevention Trial (BCPT) and the Study of Tamoxifen and Raloxifene (STAR), which were large, randomized breast cancer chemoprevention clinical trials conducted by the NSABP. The desired population for both trials was women at high risk for developing breast cancer, and a Gail score of 1.66% or higher was a criterion for eligibility.

2.2.3 Limitations and Possible Improvements

The Gail model is a powerful and useful tool for breast cancer risk prediction in both the clinical setting as a guide for counseling and risk-reduction recommendations, and in research as a

method to identify eligible, high-risk participants. The model has good calibration and accurately predicts incidence of breast cancer in groups of women. However, the Gail model does have some limitations. As with most risk prediction models for relatively rare diseases, it has low to moderate discrimination (c-statistic ranging from 0.58 – 0.62)[74], and therefore only modestly predicts incidence at the individual level. The model may also not perform well for all races. Although, it has been validated in the United States for white, African American, and Asian women, there remain some races for which there has been very little data such as Hispanics.

It has also been suggested that different models might be better for different subgroups of women within races (i.e., premenopausal vs. postmenopausal) or for different types of breast cancer (i.e., ER-positive vs. ER-negative)[75]. Chlebowski and colleagues used data from the WHI to validate and possibly improve the Gail model for estimating risk for invasive breast cancer by ER status in postmenopausal women[75,76]. They determined that in their population the Gail model had moderate discrimination for ER-positive breast cancers (c-statistic of 0.58) and that adding additional risk factors did not provide a significant improvement in prediction. However, they found that a more parsimonious model predicting ER-positive breast cancers in postmenopausal women performed nearly as accurately as the Gail model with the same discriminatory accuracy. Their new model included only age, family history of breast cancer, and a history of a previous breast biopsy. They suggested that this model may be more accessible for rapid screening and better fitting for postmenopausal women likely to be diagnosed with ER-positive breast cancer; however, results need to be tested among other populations before being accepted and put into use.

Many researchers have focused on whether adding additional risk factors to the Gail model would improve its predictive capability. Chlebowski et al. assessed a number of personal characteristics such as parity, breastfeeding, smoking, alcohol, BMI, physical activity, and prior estrogen use and found that none added significant improvements to the model. However, they did not have the ability to assess breast density. Because breast density is a strong independent risk factor for breast cancer, speculation abounds regarding its use in predictive models. Using data from the BCDDP, Chen and colleagues[77] added a continuous measure of breast density to a model with weight, age of first live birth, number of affected relatives and number of breast biopsies. This new model showed improved risk discrimination (c-statistic of 0.64) when compared to the Gail model; however, it has not been validated in different populations and a continuous measure of breast density may not be realistic in clinical practice. Three other studies[29,78,79] used data from the Breast Cancer Surveillance Consortium (BCSC), which comprises information from over one million women from seven mammography registries, to develop breast cancer risk prediction models that included traditional risk factors as well as breast density. Barlow et al.[78] looked at pre- and postmenopausal women separately and found that a model including BI-RADS breast density and hormone therapy had greater predictive accuracy than the same model without breast density (c-statistic of 0.63 vs. 0.60). However, it was only a short-term model based on breast cancers diagnosed within one year after the initial mammogram. In 2005, Tice and colleagues[79] used data from one of the BCSC mammography registries in San Francisco and found that adding breast density to the Gail model slightly improved the predictive accuracy of the model (c-statistic of 0.68 vs. 0.67). Furthermore, they found that a simpler model with BI-RADS breast density, age, and ethnicity performed similarly to the Gail model in their population. In 2008, Tice et al.[29] aimed to improve upon their original

findings by including data from all seven BCSC mammography registries. This time they included family history of breast cancer and history of breast biopsy in addition to BI-RADS breast density, age, and ethnicity. They found that the model was well-calibrated (*E/O* ratio of 1.01) and had modest discriminatory accuracy (c-statistic of 0.66). Existing literature supports the idea that including a measure of mammographic breast density may increase the capability of a model to predict risk for invasive breast cancer; however, researchers agree that these models need to be studied in multiple independent populations before put into clinical use.

2.3 BREAST CANCER CHEMOPREVENTION

2.3.1 History and Current Methods of Chemoprevention

Chemoprevention is the use of medicines, vitamins, or other agents to delay or prevent the diagnosis of cancer. Chemoprevention of breast cancer has primarily focused on the use of selective estrogen receptor modulators (SERMs). SERMs are selective in that they act as estrogen agonists in some tissues and antagonists in others. Therefore, they can either stimulate or inhibit estrogen-like action in various tissues. Tamoxifen is the most well-known of these drugs. Tamoxifen use inhibits estrogen-like action in the breast, but stimulates it in the bone and uterus. This selective activity is why tamoxifen lowers the risk of incident and recurrent breast cancer, but increases bone density in postmenopausal women and is associated with an increased risk of endometrial cancer. More recently, a second generation SERM, raloxifene, also received recognition for the prevention of invasive breast cancer, but only in postmenopausal women.

Raloxifene demonstrates anti-estrogenic activity on the breast, but unlike tamoxifen, it also has anti-estrogenic actions on the uterus. Therefore, it is not associated with an increased risk of endometrial cancer.

The possible role of tamoxifen in breast cancer prevention became of great interest due to its success in lowering the incidence of contralateral breast cancer after adjuvant therapy. Four large placebo-controlled trials designed to investigate tamoxifen for lowering the incidence of invasive breast cancer began around the early 1990s. The largest of these trials was the NSABP BCPT[80]. A total of 13,388 high-risk women were randomized and followed for an average of 4 years at the time of the initial report. Women were considered to be high-risk if they were 60 years of age or older, had a 5-year predicted risk of developing breast cancer of at least 1.66% based on the Gail model, or had a history of LCIS. Results showed that tamoxifen compared to placebo reduced the incidence of invasive breast cancer by 49% and the incidence of noninvasive breast cancer by 50%. When looking at the type of invasive breast cancer, tamoxifen reduced the incidence of ER-positive breast cancer by 69% but did not significantly affect ER-negative cancers. The International Breast Cancer Intervention Study (IBIS-I)[81] also found a significant reduction with tamoxifen compared to placebo with a 32% lower overall risk with tamoxifen. Similarly to BCPT, findings from IBIS-I showed a reduction for ER-positive invasive breast cancers (31%) but no effect for ER-negative invasive cancers. The remaining two trials, the Italian Tamoxifen Prevention Study[82,83] and the Royal Marsden Hospital trial[84], did not find a statistically significant reduction in breast cancer with tamoxifen use, but both of the studies' results trended toward a lower risk in the tamoxifen arm. Differing study populations and designs may have contributed to the insignificant results; however, after combining data from all four trials, a significant reduction of 38% in breast incidence was seen with tamoxifen use[85,86].

Furthermore, long-term follow-up (median time of 13 years) of the RMH study showed a highly significant reduction in ER-positive breast cancer with tamoxifen[84].

Based primarily on the results of BCPT, tamoxifen received approval from the United States Food and Drug Administration (FDA) for the risk reduction of invasive breast cancer among women aged 35 years and older who are at high risk for developing the disease. However, the drug was not without side effects. Secondary endpoints of BCPT included evaluating the effect of tamoxifen on the risk of endometrial cancer, heart disease, thromboembolic events, cataracts, osteoporotic fractures (hip, spine and Colles), and several others in order to obtain a thorough risk/benefit analysis. Although tamoxifen did not increase the risk for heart disease and trended toward a lower incidence of osteoporotic fractures (this relationship will be discussed further in section 2.3.2), it significantly increased the risk for endometrial cancer, thromboembolic events, and cataracts[80]. Therefore, older women at high risk for endometrial cancer or vascular-related events are likely not good candidates for tamoxifen therapy. Updated results from BCPT after seven years of follow-up were consistent with the original findings in relation to breast cancer and side effects[87]. The updated data confirmed the reduction in risk of invasive breast cancer with tamoxifen therapy, and showed that the benefit remained for at least two years after women received tamoxifen.

Although tamoxifen was found to be beneficial for many women at high risk for developing breast cancer, the search continued for a therapy with an improved profile of side effects. In 1999, results were released from the Multiple Outcomes of Raloxifene (MORE) trial, which was a randomized, placebo controlled trial designed to test whether raloxifene reduces the risk of fracture among postmenopausal women[88,89]. A secondary endpoint of the trial was breast cancer for which they found a 72% reduction in invasive breast cancer with raloxifene compared

to placebo after four years of follow-up. Based on these promising findings, three trials were launched to investigate the possible preventive effect of raloxifene on invasive breast cancer. The Continuing Outcomes Relevant to Evista (CORE) trial[90] added four additional years of raloxifene therapy to women from MORE who agreed to participate. They found that after approximately 8 years of therapy, raloxifene reduced the risk of invasive breast cancer by 66% compared to placebo. They also found that the increase in thromboembolic events with raloxifene use was insignificant and that there was no increased risk for endometrial cancer. The Raloxifene Use for The Heart (RUTH) trial[91,92] was a double-blind, placebo-controlled, randomized trial designed to determine whether raloxifene reduced the risk of coronary events and invasive breast cancer in postmenopausal women at risk for a major coronary event. Results showed a 44% reduction in total invasive breast cancers and a 55% reduction in risk of ER-positive invasive breast cancer with raloxifene compared to placebo. They found no effect on ER-negative breast cancers.

The NSABP's second breast cancer prevention trial, STAR[93], was designed to determine the relative efficacy of raloxifene versus tamoxifen in the prevention of invasive breast cancer among postmenopausal women at high risk for developing breast cancer. It was the only one of the randomized clinical trials involving raloxifene that compared it directly to tamoxifen instead of a placebo. After four years of follow-up, STAR data showed that raloxifene was as effective as tamoxifen in preventing invasive breast cancer (RR 1.02, 95% CI 0.82-1.28). Raloxifene also had a lower risk of endometrial cancer and a significantly lower risk of thromboembolic events and cataracts. Although not significant, raloxifene did not perform as well as tamoxifen in preventing noninvasive breast cancer. The combined results demonstrated that raloxifene provided an alternative to tamoxifen in preventing invasive breast cancer among postmenopausal

women at high risk for developing breast cancer, and FDA approval of raloxifene for this indication followed. A recently released update of the STAR trial[94] showed that after a median of 81 months (60 months of treatment and 21 months of follow-up) raloxifene retained approximately 76% of the effectiveness of tamoxifen representing a 38% reduction when compared to an untreated group. The results also showed that the difference between tamoxifen and raloxifene in preventing noninvasive breast cancer narrowed and that raloxifene remained less toxic than tamoxifen. The authors recommended that postmenopausal women with an intact uterus and an increased risk for breast cancer, osteoporosis, and fracture may be good candidates for raloxifene and that continuing raloxifene therapy after five years might be beneficial.

Despite the success of tamoxifen and raloxifene in breast cancer prevention clinical trials and the FDA approval of the drugs, few women are estimated to be actually taking the drugs for chemoprevention. Disparities in access to treatment facilities and insurance coverage among racial/ethnic minority groups, low socioeconomic groups, and those in remote geographic areas of residence may be contributing to the underuse of chemoprevention[95]. Several studies have been conducted to identify other reasons for the underuse of these chemopreventive drugs. One study used an individually tailored decision aid to adequately inform women about their increased breast cancer risk based on the Gail score, and the benefits and risks of tamoxifen therapy[96]. They found that even though high risk women in their study understood that tamoxifen would lower their breast cancer risk, they still had no interest in taking the drug and this reluctance was mostly due to concerns about side effects and beliefs that the risks would outweigh the benefits. Another recent study[97] reported that in the 10 years since the BCPT trial, the prevalence of tamoxifen use for chemoprevention in the United States was well below 1%. They indicated that in addition to patient concerns about side effects, part of the explanation

could be due to physician reluctance. Neither primary care physicians nor oncologists have accepted the responsibility of assessing risk, providing counseling, and prescribing therapies for breast cancer chemoprevention[98]. In a recent report[99], Ravdin examined the number of filled prescriptions for tamoxifen and raloxifene from 1995 to 2008 and found concerning results. In the two years following FDA approval for tamoxifen, its use for chemoprevention only slightly increased and has since declined in more recent years. At the time of FDA approval of raloxifene in 2007, prescriptions for the drug in the United States were already declining and have continued to do so at the same rate. Physician education regarding risk reduction options and internet-based decision-making tools may be beneficial and should be investigated in future research[97,99]. Currently an exploratory, descriptive study (Decision Making for Prevention, DMP-1) is being conducted by the NSABP to gain a better understanding of the social and psychological factors involved in decisions about SERMs and breast cancer risk reduction so that tools to facilitate decision-making can be provided.

In 2010, results were released regarding lasofoxifene, which is a third-generation SERM found to be effective in reducing the risk of breast cancer and fractures among postmenopausal women at risk for osteoporosis[100]. The results showed a 79% decrease in breast cancer risk, a 32% decrease in coronary events, and a 36% decrease in risk of stroke with 0.5 mg of lasofoxifene. The study was limited with a small number of breast cancer events and further research is necessary, but researchers are hopeful that it could be an effective agent with a favorable risk/benefit profile that would be widely accepted by the public[98]. Arzoxifene is another SERM that has been recently found to reduce the risk for breast cancer among postmenopausal women with osteoporosis or low bone mass. There was a 56% reduction in breast cancer with arzoxifene compared to placebo, but similarly to other SERMs, arzoxifene

increased the risk of thromboembolic events and gynecologic adverse events[101]. Other agents believed to have potential in breast cancer chemoprevention are aromatase inhibitors (i.e., anastrozole and exemestane) and retinoids (i.e., fenretinide)[95]. Aromatase inhibitors have been successful in breast cancer treatment and are currently being compared to placebo for the prevention of ER-positive breast cancer among postmenopausal high risk women in two different clinical trials[102,103]. Retinoids have been shown to reduce ER-negative breast cancer in animal models, making them ideal to use in combination therapy with SERMs to prevent both ER-positive and ER-negative breast cancer[95]. However, results of one study showed that the combination of low-dose tamoxifen and fenretinide did not reduce breast neoplastic events compared to placebo[104]. Despite the possibilities for the future of chemoprevention, tamoxifen and raloxifene remain the only FDA approved chemopreventive agents recommended for use outside of the investigational setting.

2.3.2 Association between Tamoxifen and Fracture Risk

There are millions of women in the United States who are at risk for both breast cancer and osteoporosis[98]. Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength is a reflection of BMD which is determined by peak bone mass and amount of bone loss, and bone quality which refers to architecture, turnover, damage accumulation, and mineralization[105]. As mentioned before, tamoxifen has estrogen-agonist effects on the bone. Consequently, the relationship between tamoxifen and BMD has been extensively studied in the literature, particularly in the adjuvant setting. A review of 27 peer-reviewed articles focusing on the relationship between tamoxifen

and BMD concluded that tamoxifen increased BMD by approximately 2-4% in the hip and spine, but did not affect the wrist[106]. Although tamoxifen has been shown to prevent bone loss in postmenopausal women, studies have found significant bone loss in patients who have remained premenopausal following tamoxifen therapy for breast cancer[107-109]. The exact mechanisms for the different effects of tamoxifen by menopausal status remain unclear; however, it is believed to relate to the differing levels of endogenous estrogen before and after menopause. In their 1996 study of BMD in pre- and postmenopausal women, Powles et al. suggested that the effect of tamoxifen on the bone might be mediated by estrogen receptors in osteoblasts. Thus the high premenopausal levels of estrogen may be modifying the sensitivity of the receptors causing tamoxifen to have an antagonist effect before menopause compared to an agonist effect after menopause[107].

Since BMD is a surrogate for osteoporotic fractures, one would also expect a decrease in fractures with tamoxifen use among postmenopausal women. However, this relationship has not been studied as extensively, since using fractures as an endpoint requires longer follow-up time and larger sample sizes than studies of BMD. A case-control study by Cooke et al.[110] found a significant association between fewer fractures and current tamoxifen use (OR 0.69, 95% CI 0.54 – 0.88); however, they did not find an association when considering tamoxifen use in the remote or recent past. BCPT, which compared tamoxifen to placebo, looked at the effect of tamoxifen on fracture risk as a secondary endpoint[80]. Results indicated that tamoxifen significantly lowered the risk for osteoporotic fractures of the hip, spine and radius (Colles) after seven years of follow-up (RR 0.68, 95% CI 0.51 – 0.92)[87]. This represented five years of treatment followed by two years of additional follow-up, implying that protection persisted even after stopping therapy. Furthermore, evidence from the STAR trial indicated that there was no difference in the number

of fractures between those taking tamoxifen or raloxifene[93,94]. The primary indication for raloxifene is osteoporosis prevention and raloxifene is known to reduce vertebral fractures among postmenopausal women[111-113]. Therefore, the results of the STAR trial provide further evidence supporting a reduction in osteoporotic fractures with tamoxifen use. However, more research is needed to determine whether this benefit exists for all women and extends to all fractures in addition to hip, spine, and Colles fractures.

2.4 SUMMARY

Lifestyle modifications may be helpful in lowering breast cancer risk. For example, high body weight is believed to be associated with an increased risk for developing the disease, even though the biological explanations for this relationship are unclear. Therefore, maintaining a healthy lifestyle by following a balanced diet, exercising, and reducing alcohol intake is recommended to reduce breast cancer risk and provide substantial overall health benefits. However, we are uncertain whether the breast cancer benefit exists for all subtypes of breast cancer and among different subgroups of women. Therefore, gaining a better understanding of the true effect that body weight has on breast cancer development among different populations can provide important insight into the prevention of the disease for many women.

Other factors for increased breast cancer risk such as family history and those related to endogenous estrogen exposure (e.g., age at menarche, age at first live birth) are not easily modifiable. Chemoprevention, which is the use of drugs to reduce the risk of disease, has been successful among these high-risk women. Two drugs, tamoxifen and raloxifene, have been

found to reduce the risk of breast cancer among high risk women by 50% and 38% respectively[80,94], and both have been approved by the FDA for breast cancer prevention. However, they are not without risks of side effects and toxicities. Therefore, it is important to accurately predict who is at high risk for developing breast cancer and would benefit from preventive therapy. The Gail model is the most widely used and tested method for doing just that; however, improvement to its predictive capability by exploring the addition of risk factors such as mammographic breast density remains of great interest.

Despite the availability of tamoxifen and raloxifene as chemopreventive agents, few women in clinical practice who carry an increased risk for developing breast cancer are willing to use them. The majority of this reluctance is likely due to concerns and fear about side effects and believing that the risks outweigh the benefits of the drugs[96]. Although some concern is warranted and each woman's eligibility should be thoroughly evaluated by her physician through a risk-benefit analysis[64], the unwillingness of many women may be impeding the preventive power of these drugs. Understanding and providing more researched-based knowledge regarding some of the concerns surrounding breast cancer chemoprevention and highlighting concomitant benefits from the drugs may help to refine this area of research.

3.0 SPECIFIC AIMS

Research Article 1 used data from the NSABP STAR and BCPT (P-1) randomized clinical trials to explore whether BMI at baseline was associated with the risk for invasive breast cancer. This association was first explored among the STAR population, which consisted of women who were postmenopausal at the time of study entry, and subsequently among the postmenopausal women who participated in P-1. Since P-1 also contained a group of women who were premenopausal at study entry, the relationship was explored among this population as well to determine whether the effect of BMI differed by menopausal status. We tested for important explanatory variables including treatment group, Gail score, age, history of estrogen use, history of oral contraceptive use, history of diabetes, and years of cigarette smoking at entry. We also explored whether the relationship between BMI and breast cancer risk differed among women who were treated with chemopreventive therapies and those who were not treated.

Research Article 2 investigated whether mammographic breast density based on the BI-RADS classifications at baseline was associated with the risk of invasive breast cancer among STAR participants, and whether mammographic breast density improved the predictive capability of the Gail model. We adjusted for possible explanatory variables including age, treatment group, BMI, years of cigarette smoking, and history of diabetes at entry. We also investigated whether adding mammographic breast density to an abbreviated model improved the model's ability to predict the risk of ER-positive breast cancer.

Research Article 3 explored whether tamoxifen use lowered the risk of osteoporotic and all clinical fractures among participants of BCPT (P-1) at high risk for breast cancer, and if the effect of tamoxifen on fractures was consistent across subgroups of the population defined by the presence or absence of fracture risk factors. The subgroups were defined by age, Gail score, BMI, menopausal status, smoking status, alcohol use, leisure time physical activity, history of diabetes, history of bone fracture, history of osteoporosis, prior use of estrogen, prior use of oral contraceptive, use of thyroid replacement medication, use of cholesterol lowering agents, use of calcium supplements, and a summary fracture risk score.

4.0 BODY MASS INDEX AND THE RISK FOR DEVELOPING INVASIVE BREAST CANCER AMONG HIGH-RISK WOMEN IN NSABP P-1 AND STAR BREAST CANCER PREVENTION TRIALS

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***These studies were supported by*:** Public Health Service grants (U10-CA-12027, U10-CA-69651, U10-CA-37377, and U10-CA-69974) from the National Cancer Institute, Department of Health and Human Services and by AstraZeneca Pharmaceuticals LP and Eli Lilly and Company.

***Trial registration*:** P-1: PDQ: NSABP-P-1; P-2: ClinTrials.gov: NCT00003906

This manuscript has been published in Cancer Prevention Research

Cecchini RS, Costantino JP, Cauley JA, Cronin WM, Wickerham DL, Land SR, Weissfeld JL, Wolmark N. Body mass index and the risk for developing breast cancer among high-risk women in NSABP P-1 and STAR breast cancer prevention trials. *Cancer Prev Res*, 2012:5(4);583-92.

4.1 ABSTRACT

High body mass index (BMI) has been associated with an increased risk for breast cancer among postmenopausal women. However, the relationship between BMI and breast cancer risk in premenopausal women has remained unclear. Data from two large prevention trials conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) were used to explore the relationship between baseline BMI and breast cancer risk. The analyses included 12,243 participants with 253 invasive breast cancer events from the Breast Cancer Prevention Trial (P-1) and 19,488 participants with 557 events from the Study of Tamoxifen and Raloxifene (STAR). Both studies enrolled high-risk women (Gail score ≥ 1.66) with no breast cancer history. Women in P-1 were pre- and postmenopausal, while women in STAR (P-2) were all postmenopausal at entry. Using Cox proportional hazards regression, we found slight but nonsignificant increased risks of invasive breast cancer among overweight and obese postmenopausal participants in STAR and P-1. Among premenopausal participants, an increased risk of invasive breast cancer was significantly associated with higher BMI (P=0.01). Compared to BMI<25, adjusted hazard ratios for premenopausal women were 1.59 for BMI 25–29.9 and 1.70 for BMI≥30. Our investigation among annually screened, high-risk participants in randomized, breast cancer chemoprevention trials showed that higher levels of BMI were significantly associated with increased breast cancer risk in premenopausal women older than age 35, but not postmenopausal women.

4.2 INTRODUCTION

Despite efforts to promote healthy lifestyle choices and to raise awareness about the consequences of excess body weight, overweight and obesity remain important public health challenges in the United States. An alarming two-thirds of Americans are overweight or obese, and more than one-third is obese[114]. Excess weight has been linked to an array of medical problems including cardiovascular disease, type 2 diabetes, osteoarthritis, and various types of cancer[31,114]. Since body weight is a modifiable factor, understanding its relationship with breast cancer risk among women could provide helpful insight into the prevention of breast cancer.

In epidemiologic studies, body mass index (BMI) is often the standardized method used for classifying excess weight. BMI is calculated as weight in kilograms divided by height in meters squared. There is extensive evidence in the literature supporting a relationship between increased BMI and an increased risk for breast cancer among postmenopausal women[33-35,40]. However, studies among premenopausal women are sparse and inconsistent. Based on these limited results, some studies have suggested that obesity is protective among premenopausal women[36,38-40], while others have found no association[35,41,43].

The most widely accepted explanation for the BMI and breast cancer risk association among pre- and postmenopausal women is related to estrogen production. In premenopausal women, the ovaries are the primary source of estrogen in the body. After menopause, most circulating estrogen derives from the conversion of adrenal androgens by means of adipose aromatase. Therefore, women with higher amounts of body fat have higher levels of circulating estrogen. Studies have found a stronger relationship between obesity and estrogen receptor (ER)-positive breast cancers than between obesity and ER-negative cancers[45]. They have also

shown that a history of using postmenopausal hormone therapy (PHT) attenuates the relationship between obesity and breast cancer risk among postmenopausal women[34]. Both of these findings provide further evidence for the estrogen availability theory among postmenopausal women. Other biologically plausible explanations include insulin resistance, obesity-induced inflammation, and expression patterns of proteins in mammary epithelial cells[115,116].

Despite the above explanations, we do not yet know the exact biological mechanisms for the development of breast cancer in obese women. Due to this uncertainty, the proposed theories are laced with speculation[43]. Inconsistent results, combined with speculative explanations, underscore the need for more research to clarify the relationship between BMI and breast cancer risk with respect to menopausal status among different populations of women. In this report we use data from two large prospective chemoprevention trials [the Breast Cancer Prevention Trial (P-1) and the Study of Tamoxifen and Raloxifene (STAR, P-2)] conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) to explore the relationship between BMI and invasive breast cancer in both pre- and postmenopausal women who are at high risk for developing breast cancer.

4.3 METHODS

4.3.1 Description of P-1 and STAR

Both P-1 and STAR were two-arm, double-blinded, randomized clinical trials investigating the use of chemoprevention for breast cancer. P-1 opened to accrual June 1, 1992. One-hundred-

thirty-one clinical centers throughout North America enrolled 13,388 women by September 30, 1997. Each woman was randomly assigned to receive either placebo or tamoxifen for five years. In March of 1998, the trial was stopped and unblinded as a result of sufficiently strong findings indicating a 49% reduction in breast cancer risk with tamoxifen use[80]. A 2005 update of the results with seven years of follow-up showed that tamoxifen remained effective in reducing breast cancer risk for two years after stopping therapy[87].

The NSABP's second breast cancer prevention trial, STAR, was designed to compare the relative effects of raloxifene to tamoxifen on breast cancer risk as well as other diseases found to be associated with tamoxifen in the P-1 trial. Two hundred centers throughout North America enrolled and randomized 19,747 participants to STAR between July 1, 1999, and November 4, 2004. The trial results were reported in April 2006 and indicated that raloxifene was as effective as tamoxifen in preventing invasive breast cancer; however, the toxicity and side effect profiles favored raloxifene[93]. A 2010 update of the findings indicated that raloxifene maintained 76% of the effectiveness of tamoxifen in preventing invasive breast cancer (i.e., raloxifene was 24% inferior to tamoxifen) and continued to remain less toxic[94]. For both trials, all clinical centers obtained approval from institutional review boards, and all participants provided written informed consent.

To be eligible for enrollment into P-1 or STAR, women had to be at least 35 years of age with no history of invasive breast cancer. Women also had to be at high risk for developing breast cancer, which was defined as having a history of lobular carcinoma *in situ*, having a minimum projected 5-year probability of invasive breast cancer (based on the Gail model) of at least 1.66%[62,63], or, in P-1 only, being age 60 or older. There was no menopausal status exclusion criterion for P-1 participation, but STAR participants were required to be either

surgically or naturally postmenopausal. Women were excluded from P-1 and STAR if they had previously undergone a bilateral or unilateral prophylactic mastectomy. Women were also required to have discontinued all use of estrogen or progesterone replacement therapy, oral contraceptives, or androgens for at least three months before random assignment. Other inclusion and exclusion criteria, including certain medications and conditions, along with further details regarding the scientific rationale and additional aspects of the design and recruitment of P-1 and STAR have been previously published[80,93].

Participants were followed every six months for the first five years and annually thereafter. In order to capture all diagnoses of invasive breast cancer, they received a physical breast examination at each six-month follow-up appointment and bilateral mammograms annually. Staff members from the participating clinical centers were responsible for performing participant follow-up and were required to submit documentation for each event reported. The documentation was reviewed centrally by trained medical professionals at the NSABP to confirm the diagnosis of each event.

4.3.2 Study Design

The current study included all participants of P-1 and STAR with follow-up information and known menopausal status and BMI at entry. Because a large portion (almost 32%) of women assigned to placebo in P-1 crossed over to active treatment with tamoxifen at the time the findings were reported (March 31, 1998), follow-up data for all P-1 participants were censored at that time, representing an average of 4.1 years of follow-up. Follow-up for the STAR population is based on the data used in the most recent update of the trial (March 31, 2009), representing an

average of 6.4 years of follow-up. The flow of participants included in the current study is shown in Figures 1A and 1B. For P-1 participants, menopausal status was inferred from questions about menstrual history at entry. A woman was considered postmenopausal if she reported that both of her ovaries were removed or if she indicated that her menstrual periods had stopped for at least 12 months. For those women with missing information or who underwent a hysterectomy before entry but had at least one intact ovary and were menstruating at the time of their hysterectomy, menopausal status was classified based on each woman's age at entry. Women younger than age 50 were classified as premenopausal, and women aged 60 or older were considered postmenopausal. For women aged 50-59, we could not confidently make any assumptions based on age; consequently, their menopausal status at entry was considered unknown and they were excluded from this evaluation.

In both P-1 and STAR, each participant's height and weight were measured and recorded by clinical staff members at each participating clinical center. These measurements were used to calculate individual BMIs. For adults, BMI is usually grouped into four categories of weight classification: underweight (<18.5), normal (18.5 – 24.9), overweight (25.0 – 29.9), and obese (≥ 30.0). Because of the low numbers of women falling into the underweight category in our population, it was combined with the normal group to form three categories of BMI for this analysis.

Information about important explanatory variables was also collected at baseline. As an eligibility assessment, participants were required to complete a risk assessment form that gathered information regarding current age, race, age at menarche, age at first live birth, number of previous breast biopsies, presence of atypical hyperplasia, and number of first-degree relatives with a history of breast cancer. Using these responses, the 5-year predicted breast cancer risk

(Gail score) was centrally calculated by the NSABP Biostatistical Center. Other variables, including history of estrogen use, history of oral contraceptive use, history of diabetes, and smoking history, were assessed via questionnaires that had been administered at the time the women entered the original studies.

4.3.3 Statistical Analysis

We used the STAR population to first explore the relationship between BMI and invasive breast cancer in postmenopausal women. We then looked at postmenopausal women from P-1 to see if these results would be consistent. Since P-1 also enrolled women before menopause, we were able to use this group to explore the relationship between BMI and invasive breast cancer in premenopausal women. For each of the groups (i.e., STAR postmenopausal, P-1 postmenopausal, and P-1 premenopausal), we used Cox proportional hazards regression to calculate unadjusted and adjusted hazard ratios of developing invasive breast cancer for overweight (BMI 25.0 – 29.9) and obese (BMI $\geq$ 30.0) participants compared to those of normal or low weight (BMI < 25.0). Time to invasive breast cancer was calculated as time from randomization to diagnosis of invasive breast cancer or time of last follow-up. Time was censored for those who had undergone a bilateral mastectomy or died during follow-up. *P* values for tests for trend were obtained by including BMI as a single ordinal term (with values 0, 1, and 2) in the models and evaluating the global *P* value for the term. We first assessed the association between BMI and the risk of breast cancer on a univariable basis, and then we assessed the association utilizing two forms of adjustment for important explanatory variables. The first was achieved using Cox regression modeling that incorporated all key potential

variables including treatment, Gail score, age, history of diabetes, history of oral contraceptive use, history of estrogen use, and years of cigarette smoking at entry. We refer to this as the full multivariable model assessment. Because the majority of P-1 and STAR participants are white (94-97%) and race is incorporated into the Gail score, we did not include race/ethnicity as a potential factor. As a second form of adjustment, we used backward elimination to drop out all of the potential variables that did not reach a statistically significant level of $P<0.05$. We refer to this as the final multivariable model assessment. Based on results reported in the literature, we tested for an interaction between BMI and history of estrogen use among postmenopausal women, and an interaction between BMI and history of oral contraceptive use among premenopausal women. Since our populations consisted of women receiving chemopreventive therapy, we decided *a priori* to conduct analyses separately among treated and untreated women. To assess whether effects of BMI differed by receptor status of the tumor, we conducted separate analyses for ER-positive and ER-negative breast cancers among postmenopausal and premenopausal women. For the analysis of ER-positive breast cancer, we censored the ER-negative cancers and those with unknown ER status at the time of diagnosis. Similar logic was followed when ER-negative breast cancer was the outcome of interest. Assessments of the statistical significance of interactions and effects within treatment groups and by ER status were based on the final multivariable model for the respective study populations. *P* values used to assess the statistical significance of parameters in all modeling were determined using the likelihood ratio test. All tests were evaluated using a 2-sided $P = 0.05$. Analyses were performed using SAS version 9.2 software (SAS Institute, Inc).

4.4 RESULTS

Entry characteristics for the three groups of participants included in this analysis (i.e., STAR postmenopausal, P-1 postmenopausal, and P-1 premenopausal) by BMI are included in the top portion of Table 1. Among postmenopausal women in STAR and P-1, the mean ages were 58.5 (SD, 7.4) and 60.8 (SD, 7.5) years, respectively. Among the premenopausal women in P-1, the mean age was 46.3 (SD, 4.3) years. STAR participants had higher Gail scores, with a mean 5-year predicted breast cancer risk of 4.03% (SD, 2.2) compared to 3.87% (SD, 2.8) among postmenopausal women and 3.28% (SD, 2.0) among premenopausal women in P-1. Overall, obese women were more likely to have a history of diabetes and less likely to have smoked or to have used oral contraceptives. In addition, obese women tended to have slightly lower Gail scores than women of normal weight. More overweight and obese premenopausal women reported a history of estrogen use, while obese postmenopausal women were less likely to have used estrogen. The distributions of tumor characteristics of the cases by BMI are presented in the bottom portion of Table 1. Obese women were slightly more likely to have ER-positive breast cancer than women of normal weight.

The results of univariable and multivariable analyses of the association between BMI and the risk of developing invasive breast cancer are shown in Table 2 for postmenopausal women and Table 3 for premenopausal women. Of all the potential explanatory variables assessed, only treatment, Gail score, and age were statistically significant in STAR; and only treatment and Gail score were statistically significant in P-1. Among postmenopausal women in STAR, there was a slight but nonsignificant increased risk of invasive breast cancer with increasing levels of BMI (Table 2, first portion). Adjusting for all potential explanatory variables (full multivariable

model assessment) or for only those that were statistically significant in the study population (final multivariable model assessment) had negligible effects on the point estimates of the hazard ratios or on the conclusions regarding the tests of trend. Compared to the lowest group (BMI <25.0), the hazard ratios for the two increasing BMI categories from the final multivariable model were 1.04 and 1.16, and the *P* value for the trend test was 0.16.

When considering the results among P-1 postmenopausal women, the findings were similar to those seen in STAR in that there was no statistically significant trend of breast cancer risk across BMI categories (Table 2, second portion). Again, adjustment for possible explanatory variables had little effect on the point estimates of the hazard ratios or the tests of trend. The hazard ratios for the upper two categories of BMI from the final multivariable model were 1.22 and 1.09, and the *P* value for the test of trend was 0.68. Since the results were consistent for postmenopausal women from both STAR and P-1, these two populations were combined to obtain more precise estimates of hazard ratios and confidence intervals (Table 2, last portion). There were 710 participants on the placebo arm of P-1 who were also participants in STAR. These women were only included once in this combined analysis, using the information obtained from their P-1 participation. The hazard ratios across BMI categories from the final multivariable model for the combined population of postmenopausal women were 1.07 and 1.14, and the *P* value for the test of trend was 0.17.

The findings for premenopausal women were different than those found for postmenopausal women (Table 3). For this population, all assessments indicated a statistically significant trend of increasing breast cancer risk with increasing categories of BMI. As in the postmenopausal populations, adjustment for explanatory variables had very little effect on the hazard ratio estimates or the conclusions regarding the tests of trend. When considering the final

multivariable model, the hazard ratios for the upper BMI categories were 1.59 and 1.70, and the test of trend was statistically significant (P=0.01).

There was no evidence of a significant interaction between BMI and history of estrogen use among STAR/P-1 postmenopausal women (P=0.93), or between BMI and history of oral contraceptive use among premenopausal women (P=0.66). Results from analyses stratified by treatment group are shown in Table 4. When considering the untreated (placebo) group of postmenopausal women, the hazard ratios for the overweight and obese groups were elevated (1.77 and 1.28, respectively), but did not show a statistically significant trend (P=0.36). Among the treated (tamoxifen or raloxifene) groups of postmenopausal women, we found no association between BMI and invasive breast cancer. For raloxifene users, hazard ratios for the two upper categories of BMI were 0.92 and 1.07 (P value for trend 0.61) and for tamoxifen users, hazard ratios were 1.07 and 1.18 (P value for trend 0.26). A test of interaction between BMI category and treatment group (treated vs. untreated) among the postmenopausal women was not significant (P=0.09).

Among premenopausal women, there was also no evidence of an interaction between BMI and treatment group (P=0.59), although premenopausal obese women randomly assigned to tamoxifen had a greater risk of breast cancer than non-obese women. Among those who received tamoxifen therapy, the hazard ratios were 1.79 and 2.33 for overweight and obese women, respectively (P value for trend 0.02). In the placebo group, there was not a statistically significant association between the risk of breast cancer and BMI (P value for trend 0.17); but the hazard ratios for the upper two categories of BMI remained elevated (1.51 and 1.41, respectively).

Table 5 shows the results for ER-positive and ER-negative breast cancers separately. Among postmenopausal women, there was a nonsignificant positive association between BMI and ER-positive breast cancer (hazard ratios of 1.14 and 1.23 for the overweight and obese groups, respectively; *P* value for trend 0.07) and no association between BMI and ER-negative breast cancer. Among premenopausal women, there was a statistically significant trend for BMI and ER-positive breast cancer with hazard ratios for the two upper categories of BMI of 1.41 and 1.78 (*P* value for trend 0.04). For ER-negative breast cancers, the test of trend was not statistically significant; but the number of breast cancer events among premenopausal women in each BMI category by ER status was small.

4.5 DISCUSSION

Our results indicate a statistically significant positive association between the risk of invasive breast cancer and BMI among premenopausal women over age 35 who were already at high risk for developing breast cancer. Among high risk postmenopausal women in STAR and P-1, we found a slightly increased risk of invasive breast cancer among overweight and obese women, but the association was not significant.

Much concern has been previously raised about the association between estrogen-only and combined estrogen/progestin PHT and breast cancer risk. An observational study from the Women's Health Initiative (WHI) showed that PHT use, defined as an estrogen-containing pill or patch, attenuated the association between BMI and breast cancer risk among postmenopausal women[34], which is consistent with findings from other studies[35,40]. However, results from two

WHI clinical trials that compared estrogen plus progestin[4] and estrogen-only[117] therapy to placebo did not find an interaction between BMI and PHT. We did not have the ability to assess combined estrogen/progestin PHT in this study; but over half of the P-1 and STAR postmenopausal participants reported a history of estrogen use. This history may help to explain the increase in hazard ratio but lack of significant *P* value for obese postmenopausal women randomized to placebo in our study. However, consistent with results from the WHI clinical trials, we did not find a significant interaction between BMI and history of estrogen use among postmenopausal women in our study.

Similarly to PHT, oral contraceptive use has been a concern among premenopausal women. A pooled analysis by van den Brandt and colleagues[40] found that the inverse association between BMI and breast cancer risk was attenuated among women who had ever used oral contraceptives. However, we found no effect of a history of oral contraceptive use among the premenopausal women who participated in the P-1 trial. Researchers have also recently gained interest in exploring possible links between type 2 diabetes and the obesity/breast cancer risk relationship[49,50]. Our study had very small numbers of participants with a history of diabetes (3-6%), and although we tested for significance of this variable in our multivariable model, we were unable to further explore the relationship.

Prior research has suggested that high BMI is more strongly related to ER-positive than to ER-negative breast cancer, particularly among postmenopausal women[38,45,118,119]. We assessed whether the effects of BMI differed by receptor status of the tumor in both post- and premenopausal women. We found that among postmenopausal women, although neither reached statistical significance, BMI was more strongly associated with ER-positive breast cancer than ER-negative breast cancer. Among premenopausal women, elevated hazard ratios were seen for

both subtypes but a significant trend was only found for ER-positive cancers. These results are consistent and not surprising given that obesity is believed to raise levels of circulating estrogen thereby increasing the risk of ER-positive cancer. Conversely, a recent study found a direct association between abdominal adiposity and ER-negative breast cancer only[47]. Our findings for premenopausal women conflict with these results; however, it should be noted that the number of cases by ER status and BMI classifications for premenopausal women in our study were too small to conduct any meaningful evaluations.

According to existing literature, high BMI has been associated with a significantly increased breast cancer risk in postmenopausal women[33-35] and is believed to be protective in premenopausal women[33,36-38]. There are some possible explanations for why our results are inconsistent with these findings. One of the most striking differences is that most of the participants in our study were being treated with tamoxifen or raloxifene, which are selective estrogen receptor modulators (SERMs). SERMs reduce the risk of breast cancer by inhibiting estrogen-like activity in the breast. Because of this anti-estrogenic activity, it could be that the use of SERMs alters the biological pathway by which obesity leads to increased breast cancer risk. Although the trend remained nonsignificant, the hazard ratios among postmenopausal women were higher for those taking placebo than for those taking SERMs. The elevated hazard ratios in the placebo group likely concur with prior studies and with the estrogen availability theory. The interaction between BMI and treatment with SERMs was not significant, so we cannot make any definitive conclusions regarding differences by treatment groups. However, the results are suggestive of a possible treatment effect among postmenopausal women and perhaps warrant more investigation in future studies. In premenopausal women, it is unlikely that

chemoprevention was the primary reason for our contradictory results since we saw hazard ratios greater than 1.0 for overweight and obese women in both the placebo and treated populations.

Another important difference between the current study and those prior is that our population consisted of women with a high risk for developing breast cancer. Studies have shown that having a family history of breast cancer attenuates the inverse association between obesity and premenopausal breast cancer[40,45]. Thus, there may be some underlying difference in high risk women that influences the effect of BMI on breast cancer risk. Additionally, most studies have either censored premenopausal women at the time of menopause or assigned menopausal status at the time of diagnosis of breast cancer. We did not update menopausal status throughout our study, and thus premenopausal women at entry may have been postmenopausal by the time of diagnosis. Another difference is the age of our premenopausal women. A study by Peacock and colleagues found that the inverse effect of obesity on premenopausal breast cancer risk was present only among women age 35 and younger[120]. It is believed that this is likely due to anovulatory cycles and the subsequent decrease in progesterone and estradiol levels[121]. In P-1, all women were over age 35 and so may have already been experiencing anovulatory cycles thereby washing out the protective effect of obesity. However, a study conducted among premenopausal participants of the Nurses' Health Study II found that the inverse association between BMI and breast cancer risk was not explained by menstrual cycle characteristics, infertility due to ovulatory disorders, or probable polycystic ovary syndrome[38].

Finally, we cannot rule out detection bias in other studies. It is more difficult to palpate lumps in obese women with larger breasts than in other women[51]. Unless heavier women undergo regular mammographic screening, they may be more likely to have a delayed diagnosis compared to women of normal weight. This delay could push the detection of breast cancer to

the postmenopausal stage of life instead of before menopause, causing the association to look stronger among postmenopausal women[38]. Invasive breast cancer was the primary endpoint in STAR and P-1 and was therefore clearly defined and accurately documented. Furthermore, all participants were required to undergo regular physical breast examinations and mammographic screenings, making the current study less likely to be influenced by detection bias.

There are several limitations affecting our study. Although STAR and P-1 were large randomized clinical trials with more than 19,000 and 13,000 participants, respectively, the numbers of cases of breast cancer in each population were limited. It would be advantageous to have even larger populations with more cases to adequately explore the relationship between BMI and breast cancer risk by menopausal status, treatment, and ER status. Because most of our participants were treated with tamoxifen or raloxifene, another possible concern is a difference in treatment adherence according to BMI. However, a prior investigation of the P-1 data found no association between BMI and adherence to SERMs[122]. Another limitation may be that we did not require blood tests to verify menopausal status in P-1; therefore, we did not know definitively the menopausal status for everyone, and perimenopausal women could have been classified as premenopausal. Because of this limitation, we excluded 964 (7.3%) P-1 participants for whom menopausal status could not be determined (i.e., 50-59 year olds with a prior hysterectomy). Since these women were not missing at random, we compared their BMI and Gail scores to those of the same age group from P-1. The distribution of BMI shifted only slightly with medians of 26.6 and 27.0 for those included and excluded, respectively. Furthermore, the breast cancer risks in these two groups were no different with median Gail scores of 2.66 for those included and 2.72 for those excluded from the analysis. Therefore, it is not likely that the exclusion of these women impacted the results to a meaningful degree.

Another potential criticism may be that we did not control for levels of physical activity, which is related to both obesity and breast cancer[15,20]. Physical activity levels were not collected in STAR, but were collected in P-1. A previous investigation by Land et al. using P-1 data found no association between physical activity and invasive breast cancer[19]. Finally, although BMI≥30 is a common measure of obesity and is satisfactory for clinical and epidemiological purposes[32], it is unclear whether it is the most ideal marker of obesity for breast cancer prediction. BMI is a measure of general obesity, which has been linked to increased levels of estrogen in postmenopausal women. However, waist circumference and waist-to-hip ratio are better measures of central obesity, which is related to metabolic changes and insulin resistance[47,123]. Information about waist and hip circumference was not collected in STAR, but we were able to explore the relationship between these measurements and invasive breast cancer in P-1 and found no association in the pre- or postmenopausal populations (data not shown). However, more studies with multiple anthropometric measurements are needed to determine which ones may be more accurate markers for breast cancer prediction. Furthermore, we only had measures of BMI at study entry, which may or may not be a true estimate of long-term obesity. Some studies have suggested that BMI at age 18 reflects long-term obesity and thus may be a better marker for breast cancer risk[38,42]. Despite the potential limitations of using BMI as a marker for obesity, the measurements of height and weight used in STAR and P-1 may provide more accuracy than studies that rely on self-reported data.

In our population of high-risk women participating in chemoprevention clinical trials, we found no significant association between breast cancer risk and overweight and obesity among postmenopausal women, and a significant positive association among premenopausal women age 35 and older. These results are inconsistent with previous findings reported in the literature,

suggesting that the BMI/breast cancer association may not be the same for all women. To our knowledge, this is the first study to explore the relationship between BMI and invasive breast cancer incidence in a randomized clinical trial population of high risk women who are being routinely screened for breast cancer development. Due to the selective population and the small number of premenopausal breast cancer cases, more studies are needed to clarify the relationship between BMI and menopausal status and the risk of invasive breast cancer. However, our results suggest that overweight and obesity are not protective among premenopausal women in this population and that maintaining a healthy weight is likely beneficial for all women at high risk for developing breast cancer.

4.6 TABLES AND FIGURES

Table 4-1. Participant characteristics at entry and tumor characteristics for women included in the analyses by BMI

	STAR Postmenopausal (N=19,488)			P-1 Postmenopausal (N=6,379)			P-1 Premenopausal (N=5,864)		
	Body Mass Index			Body Mass Index			Body Mass Index		
	< 25.0	25.0–29.9	≥ 30.0	< 25.0	25.0–29.9	≥ 30.0	< 25.0	25.0–29.9	≥ 30.0
Participant Characteristic (%)									
Total number of participants	5870	6703	6915	2204	2188	1987	2596	1785	1483
Age (years)									
≤ 49	9.4	7.7	10.0	7.6	7.2	9.4	81.7	77.8	78.9
50-59	51.0	48.9	49.8	31.1	29.5	31.1	17.6	21.6	20.6
≥ 60	39.6	43.4	40.2	61.3	63.3	59.6	0.7	0.7	0.5
Treatment									
Placebo	n/a	n/a	n/a	49.2	51.7	50.0	50.2	50.1	50.4
Tamoxifen	50.5	49.8	49.7	50.8	48.3	50.0	49.8	49.9	49.6
Raloxifene	49.5	50.2	50.3	n/a	n/a	n/a	n/a	n/a	n/a
5-year predicted breast cancer risk[a]									
≤ 2.00	11.3	10.8	11.1	20.9	23.0	22.5	27.3	30.3	33.6
2.01-3.00	28.7	29.7	32.0	27.7	26.8	29.0	32.5	32.7	32.8
3.01-5.00	32.6	31.5	30.4	30.2	29.5	28.7	26.0	23.1	22.3
≥ 5.01	27.4	28.1	26.4	21.2	20.7	19.8	14.1	13.9	11.3
History of diabetes									
No	98.2	95.7	89.2	98.0	95.5	89.9	98.6	97.7	94.1
Yes	1.8	4.3	10.8	2.0	4.5	10.1	1.4	2.3	5.9
History of estrogen use									
No	25.6	26.5	30.6	45.6	45.7	51.0	89.6	86.9	88.4
Yes	74.4	73.5	69.4	54.4	54.3	49.0	10.4	13.1	11.6
History of oral contraceptive use									
No	31.8	31.9	33.8	56.2	59.5	56.8	18.5	20.6	23.3
Yes	68.2	68.1	66.2	43.8	40.5	43.2	81.5	79.4	76.7
History of smoking (years)									
None	55.5	55.2	55.7	53.8	56.8	57.0	53.9	51.6	56.3
< 15	14.1	12.5	11.9	10.0	8.9	8.6	17.7	15.4	14.8
15-34	19.4	21.5	21.8	21.1	21.2	21.4	27.4	31.3	27.4
≥ 35	10.3	10.1	9.9	14.7	12.9	12.6	0.8	1.5	1.3
Unknown	0.7	0.7	0.7	0.5	0.3	0.5	0.2	0.3	0.2
Tumor Characteristic (%)									
Total number of cases	159	191	207	42	48	37	43	45	38
Tumor size									
≤ 1.0	35.8	39.3	31.9	35.7	47.9	51.4	39.5	22.2	23.7
1.1-3.0	56.0	49.7	54.6	47.6	47.9	45.9	41.9	62.2	60.5
≥ 3.1	5.0	9.4	8.7	14.3	4.2	2.7	18.6	15.6	15.8
Unknown	3.1	1.6	4.8	2.4	0	0	0	0	0
Nodal status									
Negative	74.2	73.3	71.5	69.0	70.8	81.1	65.1	57.8	60.5
Positive	21.4	21.5	24.6	23.8	22.9	13.5	32.6	37.8	31.6
Unknown	4.4	5.2	3.9	7.1	6.3	5.4	2.3	4.4	7.9
Estrogen receptor status									
Negative	25.8	25.1	23.2	21.4	16.7	21.6	25.6	40.0	26.3
Positive	68.6	73.3	74.4	71.4	72.9	73.0	62.8	55.6	65.8
Unknown	5.7	1.6	2.4	7.1	10.4	5.4	11.6	4.4	7.9

[a] Determined by the Gail model.
Abbreviations: n/a – not applicable.

Table 4-2. BMI and incidence of invasive breast cancer among postmenopausal women

Form of Cox Regression Model	BMI	STAR Postmenopausal			P-1 Postmenopausal			STAR/P-1 Postmenopausal[a]		
		N	No. of Events	HR (95% CI)	N	No. of Events	HR (95% CI)	N	No. of Events	HR (95% CI)
Univariable assessment	< 25.0	5870	159	1.00	2204	42	1.00	7883	194	1.00
	25.0–29.9	6703	191	1.06 (0.86 – 1.30)	2188	48	1.21 (0.80 – 1.84)	8641	228	1.08 (0.89 – 1.30)
	≥ 30.0	6915	207	1.14 (0.93 – 1.40)	1987	37	1.07 (0.69 – 1.66)	8633	231	1.11 (0.92 – 1.34)
	P_{trend}			*0.22*			*0.74*			*0.29*
Full multivariable assessment[b]	< 25.0	5829	159	1.00	2194	42	1.00	7833	194	1.00
	25.0–29.9	6658	190	1.03 (0.83 – 1.27)	2182	48	1.23 (0.81 – 1.86)	8591	227	1.06 (0.87 – 1.28)
	≥ 30.0	6870	206	1.13 (0.92 – 1.40)	1978	36	1.07 (0.68 – 1.67)	8581	229	1.12 (0.92 – 1.36)
	P_{trend}			*0.24*			*0.73*			*0.25*
Final multivariable assessment[c]	< 25.0	5870	159	1.00	2204	42	1.00	7883	194	1.00
	25.0–29.9	6703	191	1.04 (0.85 – 1.29)	2188	48	1.22 (0.81 – 1.85)	8641	228	1.07 (0.88 – 1.30)
	≥ 30.0	6915	207	1.16 (0.94 – 1.42)	1987	37	1.09 (0.70 – 1.69)	8633	231	1.14 (0.94 – 1.38)
	P_{trend}			*0.16*			*0.68*			*0.17*

[a] For participants in both P-1 and STAR, only their P-1 data were included.
[b] Adjusted for treatment, Gail score, age, history of diabetes, history of oral contraceptive use, history of estrogen use, and years of cigarette smoking; STAR/P-1 combined also adjusted for trial. Those with unknown smoking status were excluded from analyses.
[c] Adjusted for treatment, Gail score and age in STAR and STAR/P-1 combined; and treatment and Gail score in P-1.
Abbreviations: HR-hazard ratio, CI-confidence interval.

Table 4-3. BMI and incidence of invasive breast cancer among premenopausal women

Form of Cox Regression Model	BMI	P-1 Premenopausal N	No. of Events	HR (95% CI)
Univariable assessment	< 25.0	2596	43	1.00
	25.0–29.9	1785	45	1.57 (1.04 – 2.39)
	≥ 30.0	1483	38	1.63 (1.06 – 2.53)
	P_{trend}			*0.02*
Full multivariable assessment[a]	< 25.0	2590	43	1.00
	25.0–29.9	1780	45	1.55 (1.02 – 2.36)
	≥ 30.0	1480	38	1.66 (1.06 – 2.58)
	P_{trend}			*0.02*
Final multivariable assessment[b]	< 25.0	2596	43	1.00
	25.0–29.9	1785	45	1.59 (1.05 – 2.42)
	≥ 30.0	1483	38	1.70 (1.10 – 2.63)
	P_{trend}			*0.01*

[a] Adjusted for treatment, Gail score, age, history of diabetes, history of oral contraceptive use, history of estrogen use, and years of cigarette smoking. Those with unknown smoking status were excluded from analyses.
[b] Adjusted for treatment and Gail score.
Abbreviations: HR-hazard ratio, CI-confidence interval.

Table 4-4. BMI and incidence of invasive breast cancer by treatment group

	BMI	Raloxifene			Tamoxifen			Placebo		
		N	No. of Events	HR (95% CI)	N	No. of Events	HR (95% CI)	N	No. of Events	HR (95% CI)
STAR/P-1 Postmenopausal[a]	< 25.0	2808	90	1.00	3990	81	1.00	1085	23	1.00
	25.0–29.9	3256	95	0.92 (0.69 – 1.22)	4254	95	1.07 (0.80 – 1.44)	1131	38	1.77 (1.05 – 2.97)
	≥ 30.0	3342	108	1.07 (0.81 – 1.42)	4298	100	1.18 (0.88 – 1.58)	993	23	1.28 (0.72 – 2.28)
	P_{trend}			*0.61*			*0.26*			*0.36*
P-1 Premenopausal[b]	< 25.0				1292	13	1.00	1304	30	1.00
	25.0–29.9				891	15	1.79 (0.85 – 3.76)	894	30	1.51 (0.91 – 2.50)
	≥ 30.0				736	15	2.33 (1.10 – 4.90)	747	23	1.41 (0.82 – 2.43)
	P_{trend}						*0.02*			*0.17*

[a] Adjusted for Gail score and age.
[b] Adjusted for Gail score.
Abbreviations: HR-hazard ratio, CI-confidence interval.

Table 4-5. BMI and incidence of ER-positive and ER-negative invasive breast cancer

	BMI	ER-Positive Cancer			ER-Negative Cancer		
		N	No. of Events	HR (95% CI)	N	No. of Events	HR (95% CI)
STAR/P-1 Postmenopausal[a]	< 25.0	7883	134	1.00	7883	48	1.00
	25.0–29.9	8641	167	1.14 (0.91 – 1.43)	8641	53	1.00 (0.68 – 1.48)
	≥ 30.0	8633	171	1.23 (0.98 – 1.55)	8633	53	1.03 (0.70 – 1.52)
	P_{trend}			*0.07*			*0.88*
P-1 Premenopausal[b]	< 25.0	2596	27	1.00	2596	11	1.00
	25.0–29.9	1785	25	1.41 (0.82 – 2.43)	1785	18	2.52 (1.19 – 5.33)
	≥ 30.0	1483	25	1.78 (1.03 – 3.07)	1483	10	1.79 (0.76 – 4.22)
	P_{trend}			*0.04*			*0.12*

[a] Adjusted for treatment, Gail score and age.
[b] Adjusted for treatment and Gail score.
Abbreviations: ER-estrogen receptor, HR-hazard ratio, CI-confidence interval.

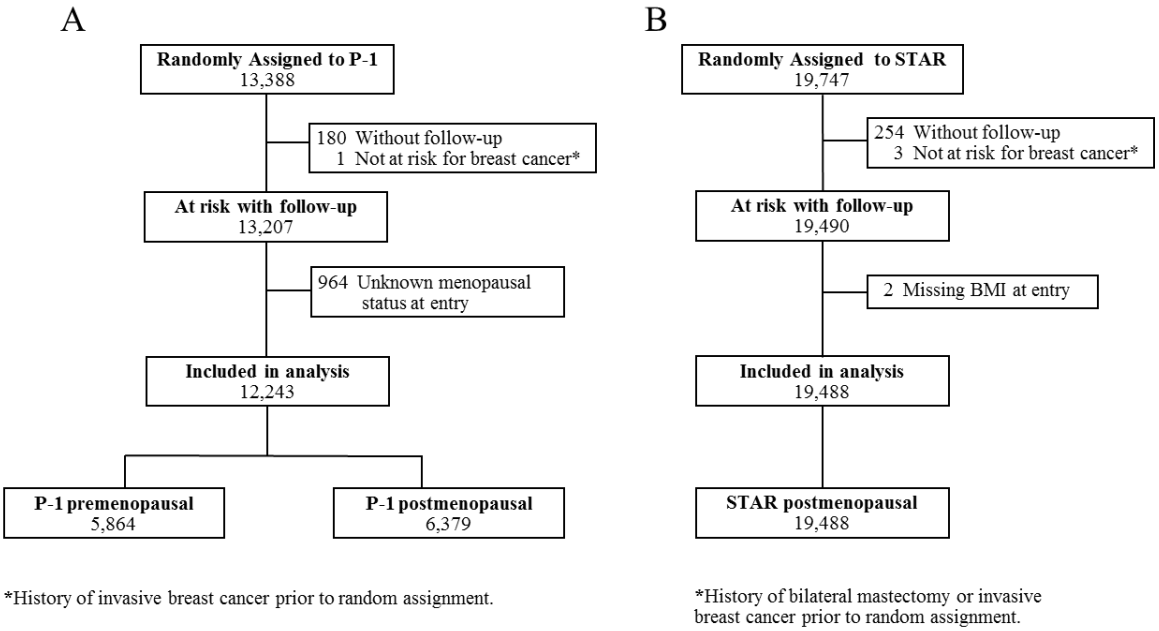

Figure 4-1. CONSORT diagrams of P-1 (A) and STAR (B)

5.0 BASELINE MAMMOGRAPHIC BREAST DENSITY AND THE RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN PARTICIPATING IN THE NSABP STUDY OF TAMOXIFEN AND RALOXIFENE (STAR)

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***This study was supported by*:** Public Health Service grants (U10-CA-12027, U10-CA-69651, U10-CA-37377, and U10-CA-69974) from the National Cancer Institute, Department of Health and Human Services; and by AstraZeneca Pharmaceuticals and Eli Lilly and Company.

***Trial registration*:** ClinTrials.gov: NCT00003906

Manuscript in Preparation

5.1 ABSTRACT

Mammographic breast density is an established risk factor for breast cancer. However, results are inconclusive regarding its use in risk prediction models. The current study evaluated 13,409 postmenopausal participants of the NSABP Study of Tamoxifen and Raloxifene. A measure of breast density as reported on the entry mammogram report was extracted and categorized according to The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) classifications. An increased risk of invasive breast cancer was associated with higher mammographic breast density (P=0.001). The association remained significant after adjusting for age, treatment, and smoking history (HR 1.32, 95%CI 1.16–1.58), as well as when added to a model including the Gail score (HR 1.33, 95%CI 1.14–1.55). At five years after random assignment, time-dependent AUC improved from 0.63 for a model with Gail score alone to 0.64 when considering breast density and Gail score. Breast density was also significant when added to an abbreviated model tailored for estrogen receptor positive breast cancers (P=0.02). In this study, high BI-RADS breast density was significantly associated with increased breast cancer risk when considered in conjunction with Gail score, but provided only slight improvement to the Gail score for predicting the incidence of invasive breast cancer. The BI-RADS classification system is a quick and readily available method for assessing breast density for risk prediction evaluations; however, its addition to the Gail model does not appear to provide substantial predictability improvements in this population of postmenopausal healthy women at increased risk for breast cancer.

5.2 INTRODUCTION

Breast cancer is the most frequently diagnosed cancer among women worldwide[5]. Therefore, accurately identifying women who have an increased risk for developing breast cancer so they may be targeted for increased screening or preventive interventions remains a high priority. The primary method for assessing non-genetic breast cancer risk is currently based on the Gail model[62,63,68-70,73]. It is a validated statistical model that has been widely accepted for breast cancer prediction. The Gail model does not currently include a measure of breast density, which has been associated with a three- to five-fold increased risk of breast cancer for women with dense tissue occupying more than half of their breast[28-30]. Some studies have suggested that adding a measure of breast density to the Gail model may improve its predictive capabilities[29,77-79]; however, it is not clear whether this is true in all populations or if the gain in predictability is of sufficient magnitude to warrant the addition of breast density to the model.

Breast density is most commonly measured through mammography. On a mammogram, fat appears dark since it is radiologically lucent; but connective and epithelial tissue are radiologically dense. Thus, mammographic breast density is a measure of the area of the breast that appears white on a mammogram. There are various methods for classifying mammographic breast density. Due to convenience and cost, the most widely used is based on The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS)[54]. This method instructs radiologists to include a qualitative classification of breast density in each mammogram report they generate. The classification system has four categories: almost entirely fat (<25% glandular), scattered fibroglandular densities (25-50% glandular), heterogeneously dense (51-75% glandular), or extremely dense (>75% glandular). The BI-RADS classifications have been

found to have only moderate inter-observer agreement. However, these guidelines are routinely followed in clinical practice in the United States for reporting mammographic breast density, making them readily available for possible use in risk prediction tools[55,61].

The Gail model predicts a woman's five-year and lifetime risk for developing breast cancer based on her reproductive, medical, and family history. The individual risk factors that are currently included in the model are age at assessment, race, the number of previous breast biopsies, history of atypical hyperplasia in the breast, age of menarche, parity, age at the first live birth of a child, and history of breast cancer in a first degree female relative (i.e., mother, sister, daughter). Any woman with a five-year risk of invasive breast cancer of 1.66% or greater is considered to be at high risk and should be evaluated further. Although some simple lifestyle modifications can help to reduce risk, other more complex prophylactic techniques may be considered. One's risk for breast cancer can be reduced by bilateral mastectomy (90%), or chemopreventive therapies such as tamoxifen or raloxifene (50%). However, these interventions are not without risk for other complications or side effects[80,93,124]. The Gail model has good calibration which indicates accuracy in predicting incidence of breast cancer in subgroups of women. However, as is common with most risk prediction models for relatively rare diseases[74], the Gail model has low discrimination (c-statistics ranging from 0.58–0.62) and therefore only modestly distinguishes at the individual level who will and will not develop breast cancer.

Researchers have suggested that different risk prediction models might perform better for different subgroups of women (i.e., premenopausal vs. postmenopausal) or for different types of breast cancer (i.e., estrogen receptor [ER]-positive vs. ER-negative)[75]. Using data from the Women's Health Initiative (WHI), Chlebowski and colleagues attempted to find improved risk prediction models when considering ER-status among postmenopausal women[75,76]. They

determined that adding additional risk factors to the Gail model did not provide significant improvement. However, they also found that for ER-positive breast cancer in postmenopausal women, a more parsimonious model performed nearly as well as the Gail model with similar discriminatory accuracy. The simpler model included age, family history of breast cancer, and a history of a previous breast biopsy. Chlebowski and colleagues assessed a number of personal characteristics but did not have the ability to assess breast density. Improving risk prediction models by including mammographic breast density has been supported in existing literature[29,77-79]; however, this needs to be studied in multiple independent populations before being put into clinical use.

In this report, we used data collected through the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR) to investigate the relationship between baseline mammographic breast density and the risk of invasive breast cancer. STAR was a randomized clinical trial that compared the relative effects of raloxifene to tamoxifen on breast cancer risk. We used data from this large breast cancer prevention trial to investigate whether a routine assessment of mammographic breast density improves the predictability of the Gail model and helps to more accurately identify women who might benefit from preventive therapies.

5.3 METHODS

5.3.1 Description of STAR

Between July 1, 1999 and November 4, 2004, a total of 19,747 participants at nearly 200 clinical centers throughout North America were enrolled and randomly assigned to receive either tamoxifen or raloxifene. Each clinical center obtained approval from institutional review boards, and all participants provided written informed consent. In April 2006, initial trial results showed that raloxifene was as effective as tamoxifen in preventing invasive breast cancer and was less toxic[93]. An update of the findings in 2010 indicated that raloxifene continued to have fewer side effects, and maintained 76% of the effectiveness of tamoxifen in preventing invasive breast cancer[94].

STAR participants were postmenopausal with no prior history of invasive breast cancer. Upon entry, each participant was assessed for all risk factors included in the Gail model, and only those considered to be at high risk for developing breast cancer, defined by a Gail score ≥1.66% or having a history of lobular carcinoma *in situ*, were eligible for the study. Participants were also required to have a baseline mammogram indicating absence of disease, and were required to submit documentation of this mammogram to the NSABP Biostatistical Center. Women were excluded from STAR if they had a prior bilateral or unilateral prophylactic mastectomy, a prior history of invasive breast cancer, or invasive cancer of any other type less than five years before random assignment with the exception of basal or squamous cell carcinoma of the skin. Other inclusion and exclusion criteria, along with additional details regarding the design and recruitment of STAR have been previously published[93].

Follow-up for STAR participants occurred every six months for the first five years of the study and annually thereafter. Each participant received an annual bilateral mammogram and a physical breast examination at each follow-up appointment. Participants were also assessed at each follow-up visit for information regarding all other events of interest including the diagnosis of other invasive cancers, cardiovascular disease, thromboembolic disease, and fractures. Staff members at each clinical center collected documentation for all reported events and submitted the documentation to the NSABP. Diagnosis of each event was then centrally reviewed and confirmed by trained medical professionals.

5.3.2 Study Design

The current study included all STAR participants with follow-up for whom breast density information could be abstracted from the baseline mammogram report. Follow-up was based on data used in the most recent update of the trial (March 31, 2009), representing an average of 6.3 years. The flow of participants included in the current study is shown in Figure 1. Three women were excluded from the analyses because they were not at risk for invasive breast cancer due to a previous bilateral mastectomy or diagnosis of breast cancer.

We used the entry mammogram reports to determine each woman's BI-RADS category of breast density. Of the 19,490 eligible STAR participants with follow-up data, entry mammogram reports were reviewed for 18,544 women (95%). We did not include women with non-English mammogram reports (mostly from French-Canadian clinical sites), as well as those for whom we did not have an entry mammogram report available. An independent reviewer trained in radiology examined each available mammogram report and completed a breast density

form based on the reported findings. Specifically, the reviewer searched each report for a qualitative description and/or a quantitative percentage of breast density. At least one measure of breast density was described in the report for 13,409 participants, with most reporting only a qualitative description (99%). There were four mammogram reports that contained only percent breast density, and these were categorized into one of the four BI-RADS groups based on the coinciding recommended percentage ranges by the American College of Radiology. There were also 100 reports that included both measures, and of those, 93 contained a percent breast density that agreed with those recommended in the BI-RADS classifications. For the remaining seven that did not agree, the breast density category was assigned based on the percent density information since it has been shown to be more accurate than the qualitative categories[55,125].

The Gail scores were centrally calculated at the NSABP Biostatistical Center using information about all risk factors included in the Gail model collected from participants during eligibility assessments for STAR. Each participant's height and weight were measured at entry by clinical staff members at each participating clinical center and these measurements were used to calculate body mass index (BMI). Other variables, including smoking history and history of diabetes were assessed via questionnaires that had been administered upon entry.

5.3.3 Statistical Analysis

We used the chi-square test to compare the distributions of participant characteristics at entry according to BI-RADS categories of breast density. Cox proportional hazards regression was used to determine whether mammographic breast density at entry was associated with invasive breast cancer. Breast density was first explored as a 4-class variable, but based on the

appearance of an approximately linear increase in the hazards of invasive breast cancer; we decided to include breast density as a single ordinal term (with values 0, 1, 2, and 3 representing the four BI-RADS categories) in the model. We adjusted for possible explanatory variables including age, treatment group, BMI, years of cigarette smoking, and history of diabetes upon entry by including them in the model with breast density. The majority of the participants were white (93%) and there were only 19 cases of breast cancer diagnosed among non-white participants, so we did not include race/ethnicity as a potential factor. We used backward elimination to drop out all of the potential variables that did not reach a statistically significant level of $P<0.05$. Because treatment with tamoxifen or raloxifene may differentially affect breast density, we tested for an interaction between breast density and treatment. We then added breast density to a model with the Gail score and subsequently to a model including Gail score and the significant explanatory variables. We calculated the time to invasive breast cancer as the time from random assignment to the date of diagnosis of invasive breast cancer. If the participant did not experience invasive breast cancer, her time was censored on the first of three possible occurrences including bilateral mastectomy, date of death, or date of last follow-up.

A secondary analysis investigated an abbreviated model developed by Chlebowski and colleagues[75] that was tailored for ER-positive breast cancer. Chlebowski's abbreviated model included only age, number of first-degree relatives with breast cancer, and number of previous breast biopsies. Our measure of breast density was added to this model to determine whether it significantly improved the predictability for this specific type of breast cancer. The variables for number or relatives and biopsies were coded in the same way that was reported by Chlebowski et al. (0 or ≥1 for number of relatives and 0, 1, or >1 for number of biopsies) and time to diagnosis was censored for ER-negative invasive breast cancers and those for whom ER status was

unknown. *P* values used to assess the statistical significance of variables in all modeling were determined using the likelihood ratio test, and all tests were evaluated using a 2-sided *P* value of 0.05. Analyses were performed using SAS version 9.2 software (SAS Institute, Inc).

We assessed the discriminatory accuracy of the models through the use of time-dependent receiver operator characteristic (ROC) curves and the corresponding area under the curve (AUC)[126]. ROC curves plot the true-positive rate (sensitivity) versus the false-positive rate (1-specificity) for all possible threshold values for the probability of an outcome at a specific time, *t*. The corresponding AUC(*t*) represents the probability that a person with onset of disease by time *t* has a higher risk score than a person with no event by time *t*. An ROC curve representing a non-predictive model would connect the coordinates (0,0) and (0,1) and have a corresponding AUC(*t*) of 0.50 indicating that the model predicts no better than chance. Conversely, an AUC(*t*) of 1.0 would indicate perfect discrimination between women who develop breast cancer by time *t* and those who do not. The c-statistic, which is a measure of the AUC, provides a global assessment of model performance over a given time frame. In addition to time-specific ROC curves and AUCs, modified overall c-statistics were calculated for each model as estimates of concordance measures that are free of censoring and to provide inference regarding the difference between the models[127]. ROC analyses and the global c-statistics were computed using R (version 2.13.2) packages written specifically for time-dependent outcomes with censored data[126-128].

5.4 RESULTS

The distributions of participant characteristics at entry by BI-RADS levels of breast density are presented in Table 1. Women with high breast density were younger than those with less dense breasts. The mean age in the highest breast density category was 57.0 years compared to 59.5 years in the lowest density category. Women with more dense breasts had a higher five-year predicted breast cancer risk (Gail score), but had a lower BMI. The mean BMI decreased from 33.0 in the lowest breast density category to 25.7 in the highest breast density category. Women with dense breasts were also less likely to have a history of diabetes than those with less dense breasts.

There were a total of 349 cases of invasive breast cancer diagnosed. Table 2 presents the distribution of cases by BI-RADS categories of breast density and ER-status. The results of univariable and multivariable analyses are shown in Table 3 (top portion). Baseline breast density was significantly associated with risk of invasive breast cancer. When assessed univariably, the hazard ratio (HR) per increase of BI-RADS breast density category was 1.30 with a 95% confidence interval (CI) of 1.12 to 1.51 ($P<0.001$). Of all the possible explanatory variables assessed, only age, treatment, and years of smoking remained significant. The HR for breast density after adjustment for the significant explanatory variables was 1.35 with a 95% CI of 1.16 to 1.58 ($P<0.001$). The interaction between breast density and treatment was not significant ($P=0.33$, data not shown).

When breast density was added to a model with Gail score, both Gail score and breast density were significant (Table 3, bottom portion). As the Gail score increased in increments of one percent, the HR was 1.13 (95% CI, 1.09–1.17; $P<0.001$). The HR for breast density was

1.29 (95% CI, 1.11–1.50; $P<0.001$) per increase of BI-RADS density category. Adjustment for the significant explanatory variables had negligible effects on the results for Gail score and breast density. The resulting HR for Gail score was 1.11 ($P<0.001$) and the HR for breast density was 1.33 ($P<0.001$). Figure 2 shows the time-specific ROC curves at year five for the models with breast density only, Gail score only, and Gail score and breast density. The AUC for the model with breast density only was 0.55 indicating low discriminatory accuracy not much better than chance. When considering the other two models, the AUC improved from 0.63 for the model with Gail score only to 0.64 when considering Gail score and breast density. The overall c-statistic throughout the first five years of follow-up was 0.627 for the model with Gail score only and 0.633 when breast density was added. The difference of 0.005 was not statistically significant (95% CI, -0.016–0.027).

There were 255 cases of ER-positive breast cancer. Based on Chlebowski's abbreviated model, we ran a proportional hazards model for ER-positive invasive breast cancer with the variables of age, number of relatives, and number of breast biopsies (Table 4). Breast density significantly added to this abbreviated model ($P=0.02$). The HR for breast density was 1.24 with a 95% CI of 1.03 to 1.49. Among our data, the number of relatives was not significant in this model. We therefore ran a model excluding this variable, but the effects on breast density were negligible (HR, 1.24; 95% CI, 1.04–1.49; $P=0.02$). Breast density had very little effect on the discriminatory accuracy of the Chlebowski model with a time-specific AUC at year five of 0.60 for both the original model and the Chlebowski model plus breast density (data not shown).

5.5 DISCUSSION

In this study of postmenopausal participants of a chemoprevention clinical trial with an increased risk for developing breast cancer, we found that the BI-RADS classification of breast density at entry was directly and significantly associated with the risk of invasive breast cancer. This association persisted when adjusting for important explanatory variables and when accounting for the calculated probability of developing breast cancer in the next five years based on the Gail model. Despite this significance, we found that the BI-RADS classification of breast density did not appear to predict breast cancer risk much better than chance, and considering breast density in conjunction with the Gail score only slightly improved model discrimination.

The Gail model has been validated and performs well in predicting the incidence of breast cancer in the population as a whole. However, its modest discrimination indicates that it is not as good at predicting whether any given individual will develop breast cancer and should not be considered a tool of diagnostic screening. Thus the Gail model is limited to the extent to which it identifies a meaningfully frequent category of high risk women who might uniquely benefit from one the preventive interventions currently available. Identifying new risk factors and improving risk prediction models remains a high priority in breast cancer prevention and risk reduction. Previous research has found promising results regarding the inclusion of breast density in risk prediction models. Using data from the Breast Cancer Detection Demonstration Project, Chen and colleagues[77] added a continuous measure of breast density to a model with weight, age of first live birth, number of affected relatives, and number of breast biopsies. They reported improved risk discrimination with this new model when compared to the Gail model with increases in concordance ranging from 0.01 to 0.09 across the seven 5-year age groups that

they studied. Three other studies[29,78,79] used data from over one million women from seven mammography registries of the Breast Cancer Surveillance Consortium (BCSC). All three reported modest improvement in predictive accuracy after adding breast density to the models with increases in c-statistics ranging from 0.01 to 0.03.

Although breast density was significantly related to breast cancer risk, the HRs in our study were smaller than in previous studies. When comparing the highest breast density group to the lowest group the HR was 2.15 (data not shown) compared to a three to five-fold increased risk of breast cancer as previously reported[28-30]. One reason for our findings may be that our population consists only of high-risk women. It could be that breast density does not provide as much of an improvement in risk prediction for those already at an increased risk based on other risk factors. Also, our population received chemopreventive therapy for five years, which substantially reduced the risk of breast cancer, and may also have affected breast density. Prior studies have reported a decrease in breast density over time with the use of tamoxifen[129-132]. We did not have the ability to assess breast density over time because submitted copies of the mammogram reports were not required for all participants during follow-up. Nevertheless, underlying changes in breast density due to treatment could have changed individual risk over time in a way that we could not measure. The current study found only a slight increase in predictive accuracy when considering breast density in conjunction with the Gail score. The modest improvements, however, are not surprising. Although a two-fold increased risk with breast density is substantial, modeling has shown that risk factors with relative risks of at least 20 may be needed to show significant improvements in predictive accuracy[79,133,134].

The current study has some limitations. First, the only measure of breast density available was the BI-RADS category assigned by radiologists at each clinical site, and therefore

was not assigned on the basis of a standardized procedure. The breast density categories may have been more accurate if we were able to collect the actual mammographic films and have an independent radiologist evaluate each film. Furthermore, computer-aids that quantitatively calculate the percent of dense breast tissue in relation to the whole area of the breast, or those that take the thickness of the breast into account to calculate volumetric breast density are believed to be more precise and reproducible methods for measuring breast density[28,52,56]. However, these methods can be costly and perhaps not appropriate for widespread use. Another criticism may involve the relationship between breast density and BMI. Since BMI is positively related to total breast area, which is the denominator for percent breast density, women with high BMI are more likely to have a low percent breast density[57]. Therefore, since a high BMI may increase breast cancer risk, it is believed that the effect of percent breast density on risk will tend to be underestimated when not adjusted for BMI[58]. However, in our study, BMI was not associated with an increased risk for breast cancer and furthermore, adjusting for BMI had negligible effects on our HR estimate for breast density. Another concern when studying breast density is the possibility of masking bias because prevalent cancers at the time of an initial mammogram could remain undetected in women with very dense breasts. However, prior studies have shown that the bias effect is only small and short-lived[28,52]. Particularly, one study looked at the site of dense tissue compared to the site of subsequent breast cancer and found that density in the cancer region of the breast was not a significant risk factor, thereby providing suggestive evidence that masking bias is not responsible for the density/breast cancer relationship[53].

This study provides further evidence that mammographic breast density is significantly associated with invasive breast cancer by evaluating the relationship among high-risk

postmenopausal participants in a clinical trial with clearly defined and accurately measured exposures and endpoints. BI-RADS breast density was significant when considered in conjunction with the Gail score, but provided only slight improvement in discrimination for predicting the incidence of invasive breast cancer. It also added significantly to Chlebowski's abbreviated model for predicting ER-positive invasive breast cancer. The BI-RADS classification system is a quick and readily available method for assessing breast density for risk prediction evaluations; however, future studies should focus on more accurate techniques for measuring breast density which may provide greater magnitudes of model improvement that could justify the inclusion of breast density in existing breast cancer risk prediction models.

5.6 TABLES AND FIGURES

Table 5-1. Participant characteristics upon entry to the NSABP STAR trial for women included in the analyses

Participant Characteristic	BI-RADS Breast Density				*P* value
	Fatty No. (%)	Scattered No. (%)	Heterogeneously No. (%)	Extremely No. (%)	
Age					
< 50	106 (9.9)	263 (8.2)	801 (9.9)	123 (11.7)	<.001
50-59	439 (41.1)	1,507 (47.2)	4,194 (51.8)	607 (57.9)	
≥ 60	522 (48.9)	1,421 (44.5)	3,108 (38.4)	318 (30.3)	
Treatment					
Tamoxifen	534 (50.0)	1,630 (51.1)	4,001 (49.4)	510 (48.7)	0.36
Raloxifene	533 (50.0)	1,561 (48.9)	4,102 (50.6)	538 (51.3)	
No. 1° relatives with BC					
0	222 (20.8)	827 (25.9)	2,447 (30.2)	379 (36.2)	<.001
≥ 1	845 (79.2)	2,364 (74.1)	5,656 (69.8)	669 (63.8)	
No. previous breast biopsies					
0	566 (53.0)	1,315 (41.2)	2,662 (32.9)	244 (23.3)	<.001
1	284 (26.6)	958 (30.0)	2,547 (31.4)	311 (29.7)	
> 1	203 (19.0)	879 (27.5)	2,811 (34.7)	476 (45.4)	
Unknown	14 (1.3)	39 (1.2)	83 (1.0)	17 (1.6)	
5-year predicted BC risk (%)[b]					
≤ 2.00	153 (14.3)	382 (12.0)	891 (11.0)	102 (9.7)	<.001
2.01-3.00	375 (35.1)	992 (31.1)	2,431 (30.0)	277 (26.4)	
3.01-5.00	298 (27.9)	1,031 (32.3)	2,546 (31.4)	359 (34.3)	
≥ 5.01	241 (22.6)	786 (24.6)	2,235 (27.6)	310 (29.6)	
Body Mass Index (kg/m^2) [a]					
< 25.0	109 (10.2)	687 (21.5)	2,784 (34.4)	559 (53.4)	<.001
25.0–29.9	305 (28.6)	1,087 (34.1)	2,866 (35.4)	303 (28.9)	
≥ 30.0	653 (61.2)	1,417 (44.4)	2,453 (30.3)	185 (17.7)	
History of Diabetes					
No	965 (90.4)	2,972 (93.1)	7,670 (94.7)	1,014 (96.8)	<.001
Yes	102 (9.6)	219 (6.9)	433 (5.3)	34 (3.2)	
History of Smoking (years)					
None	601 (56.3)	1,740 (54.5)	4,565 (56.3)	596 (56.9)	0.002
< 15	103 (9.7)	417 (13.1)	1,060 (13.1)	133 (12.7)	
15-34	217 (20.3)	680 (21.3)	1,663 (20.5)	226 (21.6)	
≥ 35	138 (12.9)	330 (10.3)	759 (9.4)	88 (8.4)	
Unknown	8 (0.7)	24 (0.8)	56 (0.7)	5 (0.5)	
Total	1,067	3,191	8,103	1,048	

[a] There was one participant for whom BMI was unknown.
[b] Determined by the Gail model.
Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; BC, breast cancer.

Table 5-2. Distribution of invasive breast cancer cases by breast density category and ER-status

BI-RADS Breast Density	ER-Status			Total
	Negative	Positive	Unknown	
Almost entirely fatty (<25% dense)	5	14	0	19
Scattered fibroglandular densities (25-50% dense)	16	47	4	67
Heterogeneously dense (50-75% dense)	51	169	4	224
Extremely dense (>75% dense)	11	25	3	39
Total	83	255	11	349

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; ER, estrogen receptor.

Table 5-3. Breast density and incidence of invasive breast cancer

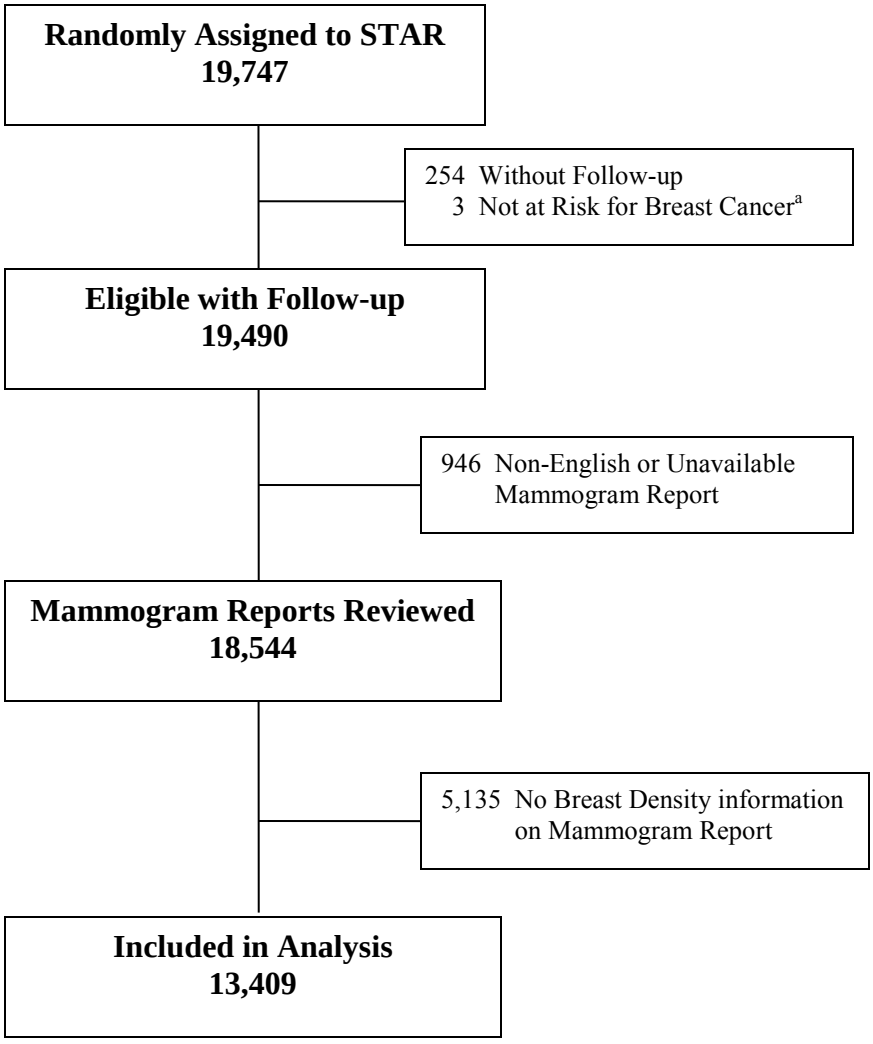
Breast Density			
	HR[a]	95% CI	*P* value
Model 1			
Breast density	1.30	1.12 – 1.51	<.001
Model 2[b]			
Breast density	1.35	1.16 – 1.58	<.001
Gail Score + Breast Density			
	HR[a]	95% CI	*P* value
Model 3			
Breast density	1.29	1.11 – 1.50	<.001
Model 4[b]			
Breast density	1.33	1.14 – 1.55	<.001

[a] Reference group for breast density was "Almost entirely fatty"
[b] Adjusted for age (continuous), treatment (tamoxifen, raloxifene), and years of cigarette smoking (none, <15, 15-34, 35+ yrs). Those with unknown smoking status were excluded from analyses.
Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 5-4. Breast density and Chlebowski's abbreviated model for ER-positive invasive breast cancer

Variables	HR[a]	95% CI	*P* value
Age	1.03	1.02 – 1.05	<.001
No. 1° relatives with breast cancer	0.82	0.62 – 1.08	0.17
No. previous breast biopsies [b]	1.27	1.08 – 1.50	0.004
Breast density	1.24	1.03 – 1.49	0.02

[a] HR for age is per one year increase; reference groups for number of relatives and breast biopsies were "0"; reference group for breast density was "Almost entirely fatty"
[b] Those with unknown biopsy data were excluded from analyses.
Abbreviations: HR, hazard ratio; CI, confidence interval; ER, estrogen receptor.



[a] History of bilateral mastectomy or invasive breast cancer prior to randomization.

Figure 5-1. CONSORT diagram

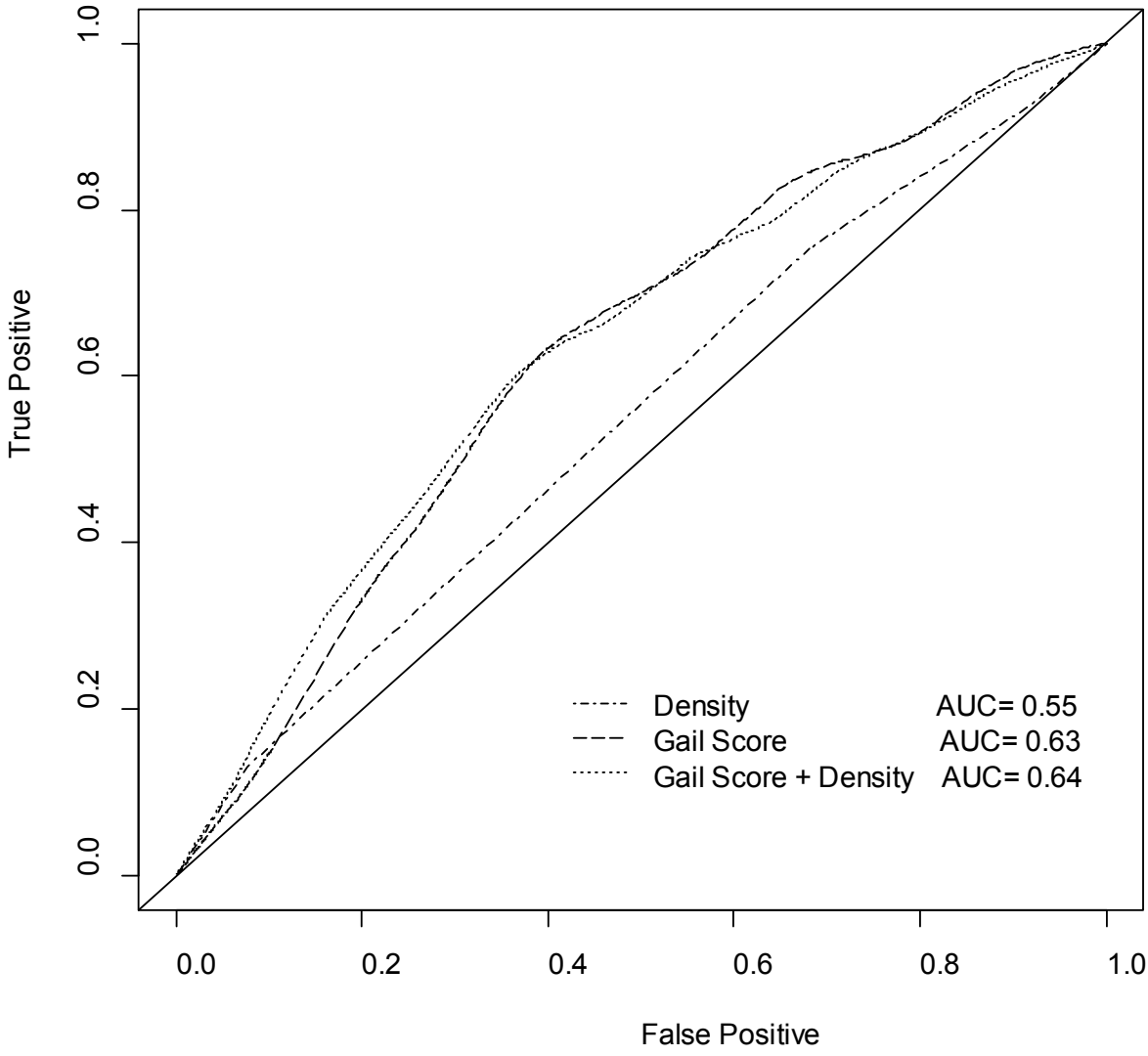


Figure 5-2. Estimated ROC curves and corresponding AUC at year 5 for models with BI-RADS breast density only, Gail score only, and Gail score and BI-RADS breast density

6.0 EFFECTS OF TAMOXIFEN ON FRACTURE RISK IN WOMEN PARTICIPATING IN THE NSABP P-1 BREAST CANCER PREVENTION TRIAL

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***These studies were supported by*:** Public Health Service grants (U10-CA-37377 and U10-CA-69974) from the National Cancer Institute, Department of Health and Human Services.

***Trial registration*:** PDQ: NSABP-P-1;

Manuscript in Preparation

6.1 ABSTRACT

Results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (P-1) demonstrated a 49% reduction in invasive breast cancer incidence with tamoxifen use compared to placebo. In addition, results indicated a statistically significant reduction in total osteoporotic fractures including those of the hip, spine, and Colles. The current study assessed whether the effect of tamoxifen on fracture incidence was consistent across different categories of fracture risk for both osteoporotic and all clinical fractures. The analysis included 13,207 women randomly assigned to 20 mg per day of tamoxifen or placebo for five years. There was no evidence of an overall reduction in clinical fractures with tamoxifen therapy compared to placebo. However, a differential benefit from tamoxifen was identified for women with and without a history of osteoporosis ($P_{interaction}$=0.04). Tamoxifen reduced the incidence of clinical fractures by 35% among those with a history of osteoporosis (HR, 0.65; 95% CI, 0.45-0.93), but had no effect among those without a history of osteoporosis. When considering osteoporotic fractures, there was a reduction with tamoxifen in all subgroups examined. However, the only differential benefit from tamoxifen was based on a history of bone fractures ($P_{interaction}$=0.03), with a significant reduction occurring among those with no history of fracture (HR, 0.49; 95% CI, 0.31-0.75). Women at high risk for developing breast cancer who are considering tamoxifen use for breast cancer risk reduction will gain the added benefit of fracture risk reduction, especially those who have a history of osteoporosis or no prior fracture.

6.2 INTRODUCTION

Each year in the United States, approximately 1.5 million older people experience fractures because their bones have become weak, mostly due to osteoporosis[135]. The risk for osteoporosis is highest among women and increases with age. The risk for developing breast cancer among women also increases with age. Therefore, multifactorial approaches to prevention in which multiple endpoints are considered when assessing an individual's risk to benefit balance are desirable[136]. Selective estrogen receptor modulators (SERMs) have been developed in an effort to reduce the risk of multiple conditions affecting aging women, including breast cancer, cardiovascular disease, and vertebral and nonvertebral fractures.

Tamoxifen is a SERM that binds to the estrogen receptor and inhibits estrogen like activity in the breast. In 1998, results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT, P-1) were released indicating a 49% reduction in the incidence of invasive breast cancer with tamoxifen compared to placebo. In 2005, updated results indicated that the effect persisted through seven years of follow-up[80,87]. Tamoxifen was the first of two drugs to be approved by the US Food and Drug Administration as a preventive therapy for breast cancer for high risk women, and remains the only drug approved for use in premenopausal women. Although tamoxifen had unfavorable toxicity results regarding endometrial cancer and thromboembolic events, results of P-1 also indicated a reduction in total osteoporotic fractures including those of the hip, spine, and Colles. The current study evaluated this relationship further to determine whether the effect of tamoxifen on fractures was consistent across different categories of fracture risk for both osteoporotic and all clinical fractures.

6.3 METHODS

6.3.1 Overview

P-1 was a multicenter, double-blinded, placebo-controlled, randomized clinical trial. The primary aim of P-1 was to determine whether 20 mg per day of tamoxifen administered for five years reduced the incidence of invasive breast cancer. Secondary endpoints included the incidence of noninvasive breast cancer, other invasive cancer, cardiovascular disease, stroke, deep vein thrombosis, pulmonary embolus, and bone fractures. Institutional review boards at each clinical center approved the protocol, and all participants provided written informed consent.

Between June 1, 1992 and September 30, 1997, 13,388 women were enrolled in P-1 at 131 clinical centers throughout North America. Each woman was randomly assigned to receive either placebo or tamoxifen for five years. To evaluate eligibility, participants were required to complete a risk assessment form that gathered information regarding current age, race, age at menarche, age at first live birth, number of previous breast biopsies, presence of atypical hyperplasia, and number of first-degree relatives with a history of breast cancer. Using these responses, the 5-year predicted breast cancer risk (Gail score) was centrally calculated by the NSABP Biostatistical Center[62,64]. Eligible women had to be at least 35 years of age with no history of invasive breast cancer. Women were also required to have a high risk for developing breast cancer, defined as having a history of lobular carcinoma *in situ*, being age 60 years or older, or having a minimum Gail score of at least 1.66%. Women were excluded from P-1 if they had previously undergone a bilateral or unilateral prophylactic mastectomy. Women were

also required to discontinue all use of estrogen or progesterone replacement therapy, oral contraceptives, or androgens for at least three months before random assignment. Further details regarding accrual, study design, other inclusion and exclusion criteria, and main results of P-1 have been published elsewhere[80,87].

6.3.2 Assessment of risk factors for osteoporosis

Information about medical and behavioral history was collected at baseline. Participants completed questionnaires upon entry into the trial that assessed their history of medical conditions (e.g., bone fractures, osteoporosis, and diabetes) and medication use (e.g., estrogen, oral contraceptives, thyroid replacement medication, cholesterol lowering agents, and calcium supplements). They also completed a series of questions that assessed smoking status, alcohol use, leisure time physical activity levels, and menopausal status. Alcohol use was calculated as the average number of drinks per day by combining information reported separately regarding the amount and frequency of beer, wine, and liquor consumption. Menopausal status was inferred from questions about menstrual history. A woman was considered postmenopausal if she reported that her menstrual periods had stopped for at least 12 months or that both of her ovaries had been removed. For women with missing information or those who underwent a hysterectomy before entry but had at least one intact ovary and were menstruating at the time of the hysterectomy, menopausal status was classified on the basis of age at entry. Women younger than age 50 were classified as premenopausal, and women age 60 or older were considered postmenopausal. We could not confidently make assumptions based on age for women 50-59 years and consequently, their menopausal status at entry was considered unknown for this

evaluation. Each participant's height and weight were measured and recorded by clinical staff members at each participating clinical center during a baseline clinical examination. These measurements were used to calculate body mass index (BMI; kg/m^2).

6.3.3 Fracture outcomes

Participants were followed every six months for the first five years and annually thereafter. Staff members from participating clinical centers were responsible for performing participant follow-up and were required to submit documentation, including a case report form as well as a confirmatory radiology report, for all bone fractures experienced during follow-up. The documentation was reviewed centrally by trained medical professionals at the NSABP to confirm each fracture. Although, information for all bone fractures was collected, it was decided *a priori* that fractures of the hip, spine and radius (Colles) would be studied as the primary fracture endpoints associated with osteoporosis. The current study focuses on two primary endpoints: clinical fracture which includes all reported fractures except those of the skull, and osteoporotic fracture which only includes those of the hip, spine and Colles. For women who experienced more than one fracture, only the first reported fracture was considered for these endpoints.

6.3.4 Statistical analyses

Data for the current study is based on the most recent update of the trial and comprises all data received and processed as of March 31, 2005. Because follow-up was not required beyond seven years for the placebo arm, data is censored at seven years after the date of random assignment.

All analyses followed the intention-to-treat principle, and included all women for whom follow-up data were available. The flow of participants included in the current study is shown in Figure 1. A total of 13,207 women were included in the analysis; 6,610 assigned to placebo and 6,597 assigned to tamoxifen.

Cox proportional hazards regression was used to estimate hazards ratios (HR) and 95% confidence intervals (CI) for tamoxifen versus placebo for all clinical fractures, all osteoporotic fractures, and hip, spine, and Colles fractures individually. Cumulative incidence rates were also determined for each fracture outcome accounting for competing risk due to death, and differences between the cumulative incidence curves for each treatment group were assessed by the method of Pepe and Mori[137,138]. Time to fracture for each fracture outcome was calculated as the time from random assignment to the date of first reported fracture. If the participant did not experience the fracture outcome of interest, her time was censored on the date of death, date of last follow-up, or seven years after the date of random assignment based on which occurred first.

For all clinical fractures and all osteoporotic fractures, we assessed whether the effect of tamoxifen differed by potential fracture risk factors with tests of interaction between the potential risk factor and treatment assignment. We also computed the HR and 95% CI for tamoxifen versus placebo for each risk factor subgroup. The subgroups were defined by age (35-49, 50-59, ≥60 years), Gail score (≤2.00, 2.01-3.00, 3.01-5.00, ≥5.01), BMI (<25, 25-29.9, ≥30), menopausal status, smoking status (never or previously, current), alcohol use (none, 0-1 drinks per day, >1 drinks per day), leisure time physical activity (moderate to heavy, none to light), history of diabetes, history of bone fracture, history of osteoporosis, prior estrogen use, prior oral contraceptive use, use of thyroid replacement medication, use of cholesterol lowering agents, calcium supplement use, and summary fracture risk score (low, moderate, high).

Summary fracture risk scores were calculated as a measure of osteoporotic fracture risk in this population, and were developed in the placebo group using logistic regression and previously published methods[113,139,140]. Age, smoking status, physical activity, alcohol use, BMI, history of bone fractures, history of diabetes, history of osteoporosis, and prior use of estrogen, oral contraceptives, thyroid replacement medication, cholesterol lowering agents, and calcium supplements were assessed for inclusion in the risk factor set. A backward elimination selection method was used based on a significance level of 0.05. The final model included age, BMI, history of bone fractures, and history of osteoporosis. A summary fracture risk score was then calculated using the coefficients from the final model and applying it to all participants from both treatment groups. The area under the receiver operating characteristic curve (AUC) was 0.76 (95% CI, 0.72-0.79) for osteoporotic fractures. Based on summary fracture risk score, the participants were stratified into tertiles of low, moderate, and high risk for osteoporotic fracture. *P* values for all analyses were 2-sided using $P<0.05$ to determine statistical significance and all analyses were performed using SAS version 9.2 software (SAS Institute, Inc).

6.4 RESULTS

The mean age of participants included in this analysis was 53.9 years and 96% of the participants were white. The majority were non-smokers (87% never smoked or quit smoking) and moderate drinkers (87% reported <1 alcoholic drink per day), and only 4.1% reported a history of diabetes. About 31% of participants reported a history of bone fractures whereas only 4.5% reported a history of osteoporosis. Participant characteristics at entry were similar between those randomly

assigned to receive tamoxifen and those assigned to the placebo group (data not shown). Table 1 presents the distribution of participants by entry characteristics for women who experienced a clinical or osteoporotic fracture and those who did not. Generally, women who experienced any clinical or osteoporotic fracture were older, more likely to have had a history of bone fracture and osteoporosis, and more likely to have used estrogen, thyroid replacement medication, cholesterol lowering agents, and calcium supplements. They were also less likely to have used oral contraceptives. Women who experienced an osteoporotic fracture during the study were less likely to have consumed more than one alcoholic drink per day and had a lower BMI. The mean time of follow-up for all participants included in the analysis was 6.2 years.

6.4.1 Clinical Fractures

There was no evidence of an overall reduction in clinical fracture incidence with tamoxifen therapy. A total of 747 (11.3%) women in the placebo group and 695 (10.5%) women in the tamoxifen group experienced a clinical fracture. The HR comparing the tamoxifen group to the placebo group was 0.92 (95% CI, 0.83-1.03). The cumulative incidence curves for clinical fractures by treatment group were similar (P=0.29, Figure 2). The cumulative rate of clinical fracture at seven years was 126.9 per 1000 in the placebo group and 117.5 per 1000 in the tamoxifen group.

The hazard ratios and confidence intervals for comparing tamoxifen to placebo by the different risk factor subgroups for clinical fractures are presented in Table 2. The interaction between treatment group and history of osteoporosis was the only interaction that reached statistical significance (P=0.04). Tamoxifen reduced the incidence of clinical fractures by 35%

compared to placebo among those with a history of osteoporosis (HR, 0.65; 95% CI, 0.45-0.93), but had no effect among those without a history of osteoporosis (HR, 0.95; 95% CI, 0.86-1.06). Tamoxifen also appeared to have reduced the risk of clinical fractures compared to placebo for women who were age 60 years or older, postmenopausal, maintained moderate to heavy leisure time physical activity, previously used estrogen, did not ever use oral contraceptives, and had a high summary fracture risk score; but none of the interactions with treatment for these factors were statistically significant.

6.4.2 Osteoporotic Fractures

As previously reported in the update of the primary findings of P-1, tamoxifen was significantly associated with a reduction in total osteoporotic fractures compared to placebo[87]. There were 116 (1.8%) women with fractures of the hip, spine, and Colles in the placebo group and 80 (1.2%) in the tamoxifen group (HR, 0.68; 95% CI 0.51-0.91). There was a 32% reduction in fractures of the hip (HR, 0.68; 95% CI 0.41-1.15), a 25% reduction in fractures of the spine (HR, 0.75; 95% CI 0.50-1.13), and a 31% reduction in Colles fractures (HR, 0.69; 95% CI 0.39-1.22). The cumulative incidence curves for all osteoporotic fractures combined and for hip, spine, and Colles fractures individually are shown in Figure 3. The cumulative incidence for osteoporotic fractures was significantly lower for the tamoxifen group compared to placebo (P=0.002). The cumulative rate of osteoporotic fracture at seven years was 19.8 per 1000 in the placebo group and 13.8 per 1000 in the tamoxifen group. When examining the individual sites of osteoporotic fracture, the cumulative rate of fracture was consistently lower in the tamoxifen group than the

placebo group for all three sites; however, hip fracture was the only site for which the difference between cumulative incidence reached statistical significance (P=0.04).

Table 3 presents the results when examining osteoporotic fractures by risk factor subgroups. The majority of these fractures occurred in women age 60 and older. There was a reduction in osteoporotic fractures with tamoxifen compared to placebo in all subgroups examined; however, the only significant interaction was between treatment and history of bone fracture. Tamoxifen reduced the incidence of osteoporotic fractures by 51% among those with a no history of bone fracture (HR, 0.49; 95% CI, 0.31-0.75), and by 9% among those with a history of bone fracture (HR, 0.91; 95% CI, 0.62-1.34).

6.5 DISCUSSION

In this population of healthy women at high risk for developing breast cancer, tamoxifen therapy significantly reduced the risk of osteoporotic fractures. The results were consistent regardless of whether most risk factors were present or absent, with the exception of a history of bone fractures. There was a slight but nonsignificant reduction in all clinical fractures with tamoxifen, and this effect was modified when considering a history of osteoporosis.

The relationship between tamoxifen and bone mineral density (BMD) has been extensively studied in the literature[106]. Because of the estrogen-agonist effects on the bone, tamoxifen has been found to increase BMD and prevent bone loss among postmenopausal women with breast cancer receiving adjuvant treatment with tamoxifen. However, since using fractures as an endpoint requires longer follow-up time and larger sample sizes than studies of

BMD, the subsequent effect of tamoxifen on fractures has not been studied as extensively. The current study is the first to our knowledge to compare the relative effects of tamoxifen to placebo on fracture risk by subgroups of healthy women defined by potential fracture risk factors.

Although tamoxifen has been shown to prevent bone loss in postmenopausal women, studies have found significant bone loss in patients who have remained premenopausal following preventive or adjuvant tamoxifen therapy for breast cancer[107-109]. The different effects of tamoxifen by menopausal status have been attributed to the differing levels of endogenous estrogen before and after menopause. Specifically, high premenopausal levels of estrogen may be modifying the sensitivity of the estrogen receptors in osteoblasts causing tamoxifen to have an antagonist effect before menopause compared to an agonist effect after menopause. In our study, the data suggest that tamoxifen may reduce the incidence of clinical fractures among postmenopausal women only, but the interaction between treatment and menopausal status was not significant and so we cannot draw any definitive conclusions. Furthermore, when considering osteoporotic fractures, we found no difference in the effect of tamoxifen by menopausal subgroups, and tamoxifen reduced the incidence of fractures in both pre- and postmenopausal women.

When considering all clinical fractures, there was a significant reduction in risk with tamoxifen use among those with a history of osteoporosis and no effect among those without a history of osteoporosis. When considering osteoporotic fractures, the hazards ratios showed a similar effect even though the interaction term was not significant. Because a history of osteoporosis is often an indicator of increased risk of bone fracture, one would expect similar results among subgroups defined by history of bone fracture. However, there was no difference in treatment effect for clinical fractures irrespective of bone fracture history, and the results for

osteoporotic fractures were different than one would expect with a greater reduction seen among those with no history of bone fracture. A possible explanation for these results could be that the general question pertaining to a lifetime history of bone fractures may have captured other characteristics that affect a woman's fracture risk (e.g., risk-taking personalities, athleticism, or clumsiness) that are different than osteoporosis-related factors. Furthermore, when considering the summary fracture risk score which had good AUC, there was a significant reduction with tamoxifen in the highest fracture risk group. This was inconsistent with the history of bone fracture findings and thus the significant association between no history of bone fracture and osteoporotic fractures may have been due to chance.

There has been substantial interest in the development and implementation of risk tools designed to identify women who may be at greater risk for developing osteoporosis and fractures[139,141-143]. Because P-1 was a breast cancer prevention trial and fractures were not the primary endpoint, we did not collect all of the variables typically included in the available risk tools. However, we were able to calculate a summary fracture risk score for this analysis as a way to classify our population into groups of low, moderate, and high risk for experiencing an osteoporotic fracture. Based on multiple risk factors that we had available, we were able to investigate whether those at high risk might benefit more from treatment with tamoxifen than those at lower risk. However, the effect of tamoxifen on both clinical fracture risk and osteoporotic fracture risk was not significantly different between the risk groups.

The study design of the P1-trial is strong. It was a randomized clinical trial conducted in a large population of healthy women, and all fracture endpoints were centrally reviewed and confirmed. However, the primary study objective was the assessment of breast cancer risk and the study population was women at high risk for breast cancer development. When used to

assess the risk of fractures, the P-1 trial is not without limitation. Although the total number of clinical fractures was substantial, the numbers of fractures experienced within some of the risk factor subgroups were small and the numbers of individual fractures of interest (hip, spine, and Colles) were limited. These limited numbers did not allow us to explore subgroup analyses by the individual types of osteoporotic fractures. Additionally, when the initial results of P-1 were released and the trial was unblinded, about 32% of participants assigned to placebo crossed over to active treatment with tamoxifen. Thus, the true effect of tamoxifen may be underestimated in this analysis. Our results were also limited by the general definition that was used to define a clinical fracture event. All clinical fractures other than those of the skull were considered, regardless of the cause of their occurrence; thus, we were unable to determine which fractures occurred due to an accident and which were likely due to weakened bones. Another limitation is that our population consisted mostly of white women, and all participants were at high-risk for breast cancer. Therefore our results may not be generalizable to other populations of women. Furthermore, we know that an increase in BMD is associated with an increased risk for breast cancer[27]. We did not collect information on BMD in P-1, but since all women had an increased risk for breast cancer, they may also have had higher BMD than the general population.

This study elaborated on fracture findings from P-1, and showed that tamoxifen use significantly reduced osteoporotic fracture risk among healthy women at risk for developing breast cancer. Subgroup analyses showed that the reduction was similar for both premenopausal and postmenopausal women, as well as most other subgroups of women based on potential fracture risk factors, except a history of bone fracture. Our results also indicated the potential for a reduction in all clinical fractures with tamoxifen for women with a history of osteoporosis. We know from current literature that tamoxifen is associated with increased BMD in postmenopausal

women, and this study supports the concept that this transfers into a reduction of osteoporotic fractures regardless of menopausal status. Women at high risk for developing breast cancer, who are contemplating tamoxifen use for breast cancer risk reduction, will gain the added benefit of fracture risk reduction, especially those who have a history of osteoporosis or no prior fractures.

6.6 TABLES AND FIGURES

Table 6-1. Percent distribution of participants by baseline characteristics for women with and without fractures

Participant Characteristic[b]	All Clinical Fractures		Osteoporotic Fractures[a]	
	No Fracture *(n = 11,765)*	Fracture *(n = 1,442)*	No Fracture *(n = 13,011)*	Fracture *(n = 196)*
Tamoxifen group	50.2	48.2	50.1	40.8
White race	96.3	97.7	96.4	96.9
Postmenopausal	50.7	63.3	51.6	84.2
Current smoker	12.8	10.4	12.5	14.3
>1 alcoholic drinks per day	13.0	11.9	12.9	10.2
None to light leisure time physical activity	54.1	54.8	54.3	50.0
History of diabetes	4.0	4.6	4.0	6.1
History of bone fracture	29.2	42.4	30.3	53.6
History of osteoporosis	4.0	8.3	4.3	15.3
History of estrogen use	33.4	40.5	33.9	52.0
History of oral contraceptive use	61.4	54.4	61.0	38.8
History of thyroid replacement medication	15.9	18.2	16.1	20.9
History of cholesterol lowering agents	7.8	10.8	8.1	12.2
History of calcium supplements	37.9	46.3	38.6	53.6
Age (years)				
35-49	40.5	29.2	39.7	11.2
50-59 years	30.8	30.4	30.9	21.9
≥ 60 years	28.7	40.4	29.4	66.8
BMI (kg/m^2)				
< 25.0	38.9	37.0	38.6	45.9
25.0-29.9	32.9	33.5	32.9	34.2
≥ 30.0	28.2	29.5	28.5	19.9
5-year predicted breast cancer risk (%)				
≤ 2.00	25.2	23.2	25.0	23.0
2.01-3.00	31.2	29.9	31.1	30.1
3.01-5.00	26.4	28.2	26.6	28.1
≥ 5.01	17.2	18.8	17.3	18.9
Summary fracture risk score				
Low	32.7	22.0	31.9	8.7
Moderate	34.8	32.2	34.8	19.4
High	32.5	45.8	33.4	71.9

[a] Includes unduplicated count of hip, spine, and Colles fractures.
[b] Denominators for percentages differ because of missing data.

Table 6-2. Number of clinical fractures and hazard ratios by treatment and risk subgroup

Participant Characteristic at Baseline	Placebo *(n = 6,610)* No. (%)	Tamoxifen *(n=6,597)* No. (%)	Hazard Ratio[a]	95% CI	*P* for interaction
All participants	747 (11.3)	695 (10.5)	0.92	0.83 – 1.03	
Age (years)					
35-49	211 (8.1)	210 (8.1)	1.00	0.83 – 1.21	0.27
50-59	219 (10.8)	219 (10.8)	0.98	0.81 – 1.18	
60+	317 (15.9)	266 (13.5)	0.83	0.71 – 0.98	
5-year predicted breast cancer risk (%)					
≤ 2.00	171 (10.3)	163 (9.9)	0.96	0.78 – 1.19	0.80
2.01-3.00	219 (10.8)	212 (10.3)	0.94	0.77 – 1.13	
3.01-5.00	213 (11.9)	193 (11.2)	0.95	0.78 – 1.15	
≥ 5.01	144 (12.9)	127 (10.8)	0.83	0.65 – 1.05	
BMI					
< 25.0	276 (10.9)	258 (10.0)	0.91	0.77 – 1.08	0.97
25.0-29.9	254 (11.5)	229 (10.7)	0.93	0.78 – 1.11	
≥ 30.0	217 (11.6)	208 (11.0)	0.94	0.78 – 1.14	
Menopausal status					
Premenopausal	242 (8.2)	246 (8.4)	1.02	0.86 – 1.22	0.15
Postmenopausal	450 (14.0)	390 (12.3)	0.87	0.76 – 0.99	
Smoking status					
Never or previously smoked	668 (11.6)	624 (10.9)	0.93	0.83 – 1.04	0.78
Current smoker	79 (9.7)	71 (8.5)	0.89	0.64 – 1.22	
Alcohol Use					
None	166 (11.9)	142 (10.5)	0.88	0.71 – 1.11	0.91
0-1 drinks per day	491 (11.3)	472 (10.7)	0.94	0.83 – 1.06	
>1 drinks per day	90 (10.4)	81 (9.7)	0.93	0.69 – 1.25	
Leisure Time Physical Activity					
Moderate to heavy	352 (11.7)	300 (9.9)	0.83	0.71 – 0.97	0.06
None to light	395 (11.0)	395 (11.1)	1.01	0.88 – 1.16	
History of diabetes					
No	716 (11.3)	660 (10.4)	0.92	0.83 – 1.02	0.62
Yes	31 (11.9)	35 (12.6)	1.04	0.64 – 1.69	
History of bone fracture					
No	431 (9.4)	400 (8.7)	0.92	0.80 – 1.05	0.84
Yes	316 (15.6)	295 (14.6)	0.94	0.80 – 1.10	
History of osteoporosis					
No	676 (10.7)	647 (10.3)	0.95	0.86 – 1.06	0.04
Yes	71 (24.2)	48 (16.2)	0.65	0.45 – 0.93	
History of estrogen use					
No	434 (9.9)	424 (9.8)	0.99	0.86 – 1.13	0.12
Yes	313 (14.0)	271 (11.9)	0.83	0.71 – 0.98	
History of oral contraceptive use					
No	353 (13.5)	304 (11.8)	0.85	0.73 – 0.99	0.15
Yes	394 (9.9)	391 (9.7)	0.99	0.86 – 1.14	
History of thyroid replacement medication					
No	603 (10.9)	577 (10.4)	0.94	0.84 – 1.06	0.40
Yes	144 (13.1)	118 (11.4)	0.84	0.66 – 1.07	
History of cholesterol lowering agents					
No	672 (11.1)	614 (10.1)	0.90	0.81 – 1.01	0.21
Yes	75 (13.7)	81 (15.3)	1.12	0.82 – 1.53	
History of calcium supplements					
No	392 (9.7)	382 (9.5)	0.97	0.85 – 1.12	0.28
Yes	355 (13.8)	313 (12.2)	0.87	0.75 – 1.01	
Summary fracture risk score					
Low	156 (7.5)	161 (7.7)	1.01	0.81 – 1.26	0.21
Moderate	233 (10.2)	232 (10.2)	1.01	0.84 – 1.21	
High	358 (15.9)	302 (13.5)	0.84	0.72 – 0.97	

[a] Hazard ratios for women in the tamoxifen group compared to women in the placebo group.

Table 6-3. Number of osteoporotic fractures and hazard ratios by treatment and risk subgroup

Participant Characteristic at Baseline	Placebo *(n = 6,610)* No. (%)	Tamoxifen *(n=6,597)* No. (%)	Hazard Ratio[a]	95% CI	*P* for interaction
All participants	116 (1.8)	80 (1.2)	0.68	0.51 – 0.91	
Age (years)					
35-49	15 (0.6)	7 (0.3)	0.47	0.19 – 1.15	0.40
50-59	22 (1.1)	21 (1.0)	0.93	0.51 – 1.70	
60+	79 (4.0)	52 (2.6)	0.65	0.46 – 0.93	
5-year predicted breast cancer risk (%)					
≤ 2.00	23 (1.4)	22 (1.3)	0.97	0.54 – 1.73	0.14
2.01-3.00	39 (1.9)	20 (1.0)	0.49	0.29 – 0.85	
3.01-5.00	29 (1.6)	26 (1.5)	0.93	0.55 – 1.58	
≥ 5.01	25 (2.2)	12 (1.0)	0.46	0.23 – 0.91	
BMI					
< 25.0	55 (2.2)	35 (1.4)	0.62	0.40 – 0.94	0.54
25.0-29.9	41 (1.9)	26 (1.2)	0.65	0.40 – 1.06	
≥ 30.0	20 (1.1)	19 (1.0)	0.94	0.50 – 1.76	
Menopausal status					
Premenopausal	18 (0.6)	11 (0.4)	0.61	0.29 – 1.29	0.76
Postmenopausal	91 (2.8)	63 (2.0)	0.69	0.50 – 0.96	
Smoking status					
Never or previously smoked	100 (1.7)	68 (1.2)	0.68	0.50 – 0.92	0.82
Current smoker	16 (2.0)	12 (1.4)	0.74	0.35 – 1.56	
Alcohol Use					
None	32 (2.3)	23 (1.7)	0.75	0.44 – 1.27	0.80
0-1 drinks per day	73 (1.7)	48 (1.1)	0.64	0.44 – 0.92	
>1 drinks per day	11 (1.3)	9 (1.1)	0.84	0.35 – 2.04	
Leisure Time Physical Activity					
Moderate to heavy	56 (1.9)	42 (1.4)	0.73	0.49 – 1.10	0.62
None to light	60 (1.7)	38 (1.1)	0.64	0.42 – 0.95	
History of diabetes					
No	110 (1.7)	74 (1.2)	0.67	0.50 – 0.90	0.60
Yes	6 (2.3)	6 (2.2)	0.92	0.30 – 2.86	
History of bone fracture					
No	61 (1.3)	30 (0.7)	0.49	0.31 – 0.75	0.03
Yes	55 (2.7)	50 (2.5)	0.91	0.62 – 1.34	
History of osteoporosis					
No	96 (1.5)	70 (1.1)	0.72	0.53 – 0.98	0.33
Yes	20 (6.8)	10 (3.4)	0.49	0.23 – 1.05	
History of estrogen use					
No	58 (1.3)	36 (0.8)	0.62	0.41 – 0.94	0.58
Yes	58 (2.6)	44 (1.9)	0.73	0.50 – 1.09	
History of oral contraceptive use					
No	73 (2.8)	47 (1.8)	0.64	0.44 – 0.92	0.55
Yes	43 (1.1)	33 (0.8)	0.76	0.48 – 1.20	
History of thyroid replacement medication					
No	93 (1.7)	62 (1.1)	0.66	0.48 – 0.90	0.55
Yes	23 (2.1)	18 (1.7)	0.81	0.44 – 1.50	
History of cholesterol lowering agents					
No	102 (1.7)	70 (1.2)	0.68	0.50 – 0.92	0.88
Yes	14 (2.6)	10 (1.9)	0.73	0.32 – 1.64	
History of calcium supplements					
No	51 (1.3)	40 (1.0)	0.78	0.52 – 1.18	0.38
Yes	65 (2.5)	40 (1.6)	0.61	0.41 – 0.90	
Summary fracture risk score					
Low	11 (0.5)	6 (0.3)	0.53	0.20 – 1.44	0.58
Moderate	20 (0.9)	18 (0.8)	0.91	0.48 – 1.72	
High	85 (3.8)	56 (2.5)	0.65	0.47 – 0.92	

[a] Hazard ratios for women in the tamoxifen group compared to women in the placebo group.

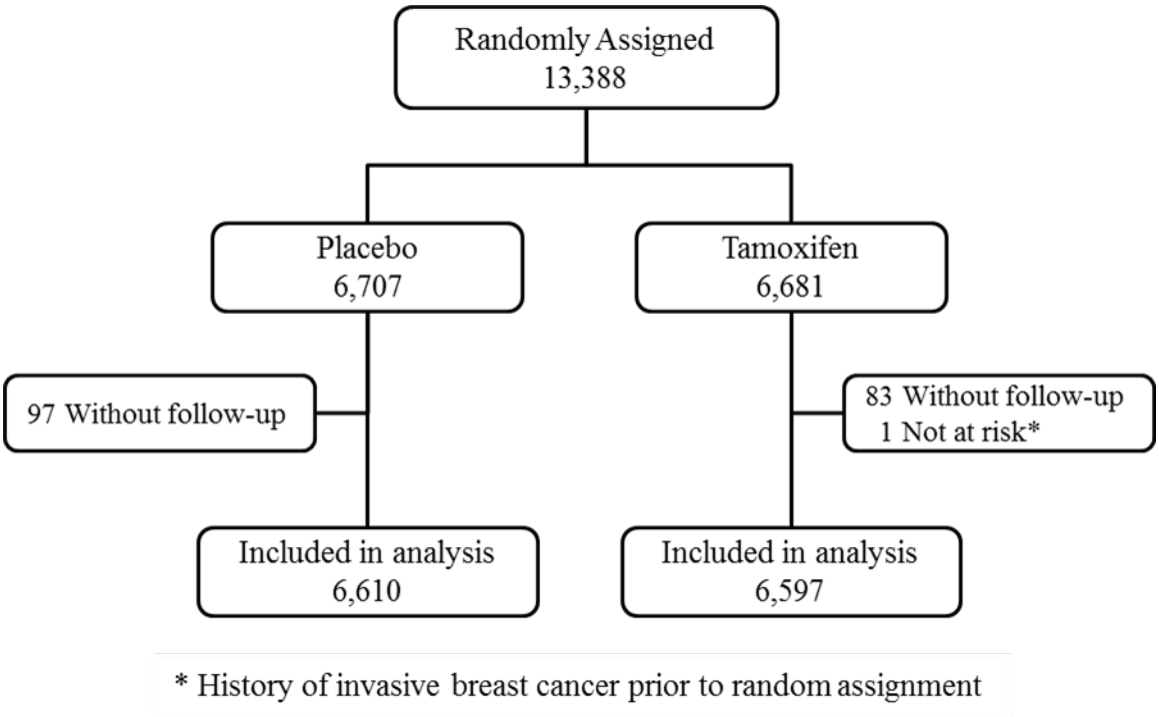
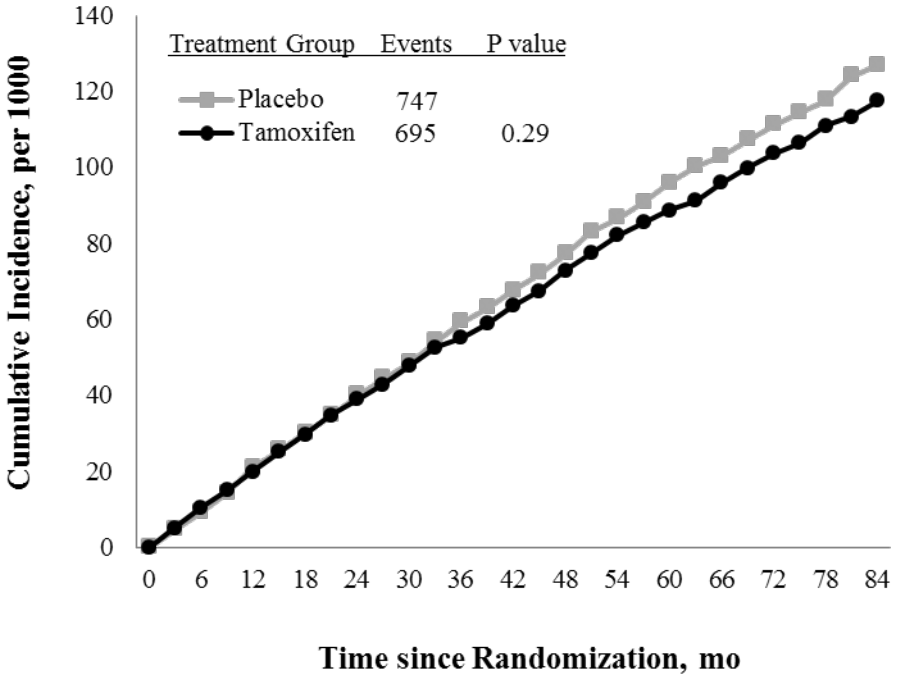


Figure 6-1. CONSORT diagram



No. at Risk

Placebo	6610	6227	5861	5566	5305	5023	4702	3832
Tamoxifen	6597	6211	5846	5587	5344	5101	4808	4340

Figure 6-2. Cumulative incidence of all clinical fractures

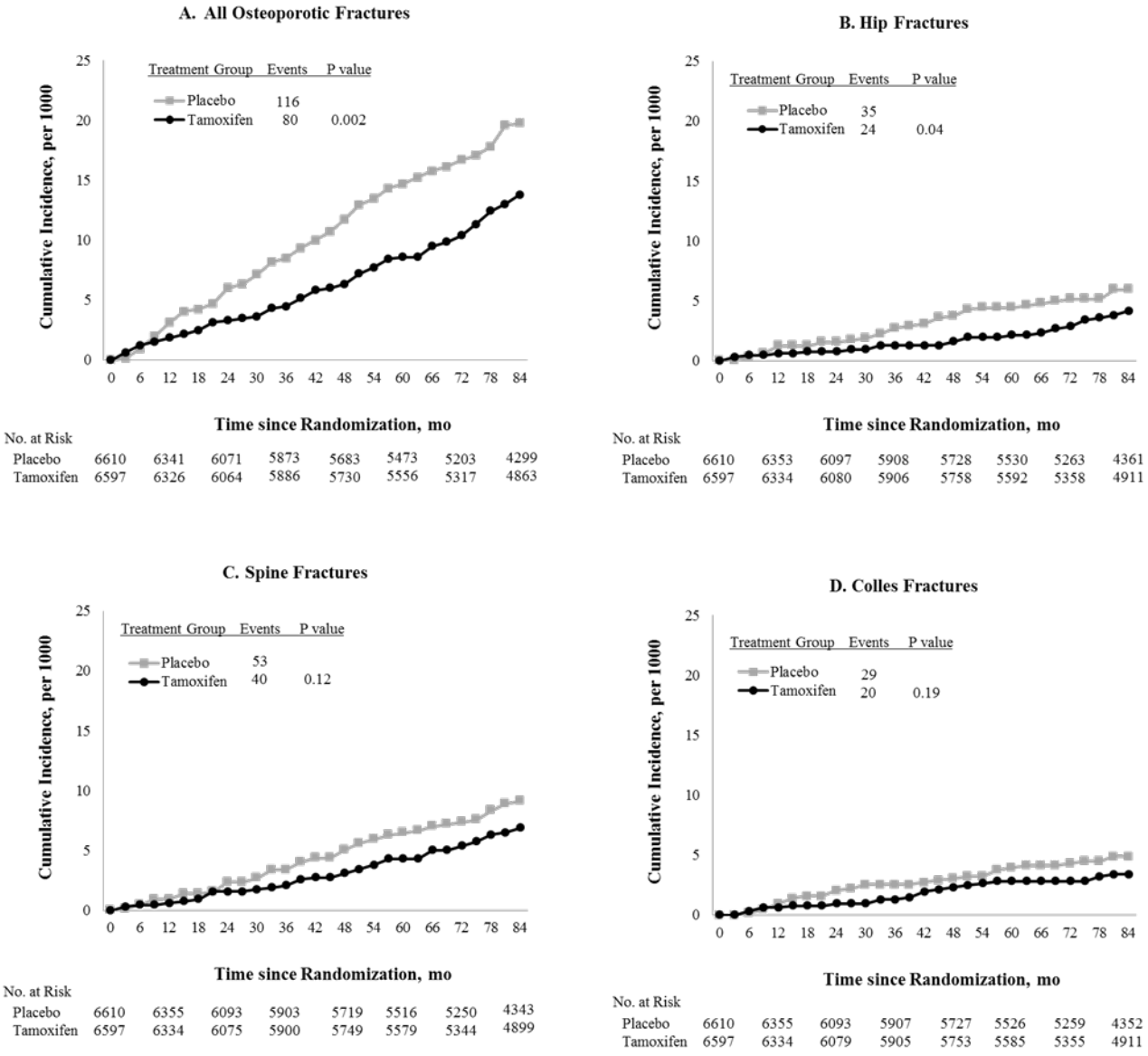


Figure 6-3. Cumulative incidence of osteoporotic fractures by site of fracture

7.0 GENERAL DISCUSSION

7.1 SUMMARY OF FINDINGS

This dissertation evaluated important issues related to breast cancer risk reduction in women participating in two breast cancer chemoprevention clinical trials (BCPT and STAR) conducted by the NSABP. Chapter 4 assessed women from both trials to determine whether BMI was related to the risk of invasive breast cancer among pre- and postmenopausal women. Chapter 5 evaluated the relationship between breast density and invasive breast cancer among STAR participants and assessed whether a common, one-time assessment of breast density would improve the predictability of the Gail model. Chapter 6 investigated the reduction in risk of bone fracture, a concomitant benefit of tamoxifen, in BCPT participants to see whether the effect of tamoxifen on osteoporotic and all clinical fractures differed by fracture risk subgroups. All participants analyzed were required to be at high-risk for developing breast cancer and were randomly assigned to receive either placebo or tamoxifen in BCPT, and tamoxifen or raloxifene in STAR.

The results presented in Chapter 4 indicated a statistically significant positive association between BMI and breast cancer risk among premenopausal women and no association among postmenopausal women. Although the interaction between BMI and treatment was not significant, our results were suggestive that SERM therapy might attenuate the BMI/breast

cancer association among postmenopausal women. We also found that BMI was more strongly associated with ER-positive cancer than with ER-negative cancer.

As shown in Chapter 5, the BI-RADS classification of breast density at entry was directly and significantly associated with the risk of invasive breast cancer when assessed in conjunction with the Gail score. However, the addition of this measure of breast density only slightly and nonsignificantly improved model discrimination. The BI-RADS classification of breast density had similar effects when added to Chlebowski's abbreviated model for predicting ER-positive invasive breast cancer only.

Lastly, as presented in Chapter 6, tamoxifen therapy significantly reduced the risk of osteoporotic fractures, regardless of whether most risk factors were absent or present, with the exception of a history of bone fracture. Women with no history of a prior bone fracture experienced a greater reduction in new osteoporotic fractures with tamoxifen use. Although the overall reduction in all clinical fractures with tamoxifen was not statistically significant, the results supported the potential for a reduction in all clinical fractures among women with a history of osteoporosis.

7.2 CONCLUSIONS AND PUBLIC HEALTH SIGNIFICANCE

The overweight and obesity epidemic in the United States is an important public health challenge. In addition to complications such as cardiovascular disease, type 2 diabetes, and osteoarthritis, excess weight has also been linked to an increased risk for breast cancer among postmenopausal women. However, the relationship has remained unclear in premenopausal

women. Our results for high-risk women participating in chemoprevention clinical trials were inconsistent with some of the previous findings reported in the literature. This inconsistency suggests that the relationship between BMI and breast cancer may not be the same for all women. More studies are needed to clarify the relationship between excess weight and the risk of invasive breast cancer by menopausal status, and future research may focus on different markers for high body weight as well as changes in weight over time. However, in this population, overweight and obesity were not protective among premenopausal women, and instead significantly increased breast cancer risk. This is important since body weight is a modifiable risk factor. Currently, overweight and obesity are only listed as risk factors among postmenopausal women, which may give the impression to premenopausal women that they do not need to be concerned about excess weight. However, our results suggest that all women at high risk for developing breast cancer should strive to achieve and maintain a healthy weight.

Mammographic breast density is an established risk factor for breast cancer. Our findings provided further evidence that mammographic breast density is significantly associated with invasive breast cancer among high-risk postmenopausal participants. However, the BI-RADS measure of breast density did not significantly improve discrimination for predicting invasive breast cancer incidence compared to the Gail score alone. There is currently debate in the clinical setting about whether breast density should be used as a marker for more extensive breast cancer screening. Although our findings do not definitively support either side of the argument, this simple one-time assessment of breast density does not appear to predict breast cancer risk much better than chance, and does not seem to provide further predictability beyond the factors already assessed in the Gail model. The BI-RADS classification system is a quick, inexpensive, and readily available method for assessing breast density for risk evaluations;

however, future studies should focus on newer, more accurate techniques for measuring breast density as well as changes in density over time. These methods may provide greater magnitudes of model improvement that could potentially justify the inclusion of breast density in existing models for breast cancer risk prediction.

According to the 2004 Surgeon General's Report on Bone Health and Osteoporosis, approximately 1.5 million older people each year experience fractures because their bones have become weak, and the medical costs for treating those broken bones is estimated at $18 billion each year. Since the risk for both osteoporosis and breast cancer among women increases with age, interest among researchers and clinicians has shifted to multifactorial approaches to prevention. We have learned from previous research that tamoxifen is associated with an increased BMD in postmenopausal women, and this study supports that tamoxifen also leads to a reduction of osteoporotic fractures regardless of menopausal status. Therefore, women with or at risk for osteoporosis who are using tamoxifen for breast cancer risk reduction will receive the additional benefit of fracture risk reduction.

Breast cancer incidence and mortality rates have been slowly declining in the US; however, breast cancer remains the most frequently diagnosed cancer and the second leading cause of cancer death among women. Therefore, breast cancer prevention remains an important area of research. We must be able to accurately identify high-risk women, and also provide safe options for lowering their risk. If modifiable risk factors such as excess body weight are present, then based on our results, all women regardless of menopausal status should be advised to maintain a healthy lifestyle through diet and exercise. On the other hand, if a woman's increased risk is based on risk factors that are not easily modifiable, such as those included in the Gail model, then more complex methods for lowering risk such as tamoxifen or raloxifene therapy

may be recommended. However, these drugs have been associated with side effects, and so we must accurately predict who is high-risk and would likely benefit from preventive therapy to the best of our ability. Mammographic breast density has been considered for inclusion in the Gail model; but, our results showed that the BI-RADS measurement was not favorable for predictive improvements. Therefore, the Gail model remains the gold standard for assessing non-genetic breast cancer risk. Despite the acceptance of the Gail model by clinicians and the success of chemopreventive therapies in lowering breast cancer risk, few high-risk women are actually choosing to use tamoxifen or raloxifene. While we are trying to determine the reasons for this reluctance and identify other agents with fewer side effects, we hope that providing more knowledge about these drugs, such as their combined benefits on the bone and the breast, may help to encourage their use.

The analyses discussed in this dissertation helped to clarify and expand information surrounding some important issues in breast cancer prevention. Advancement in breast cancer risk reduction, including the refinement of important risk factors and preventive therapies, may help to continue the decline of breast cancer incidence and mortality in the US.

BIBLIOGRAPHY

1. American Cancer Society. *Cancer Facts & Figures 2012.* Atlanta, Ga: American Cancer Society;2012.

2. American Cancer Society. *Breast Cancer Facts & Figures 2011-2012.* Atlanta: American Cancer Society, Inc.

3. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321-333.

4. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA.* 2003;289(24):3243-3253.

5. American Cancer Society. *Global Cancer Facts & Figures 2nd Edition.* Atlanta: American Cancer Society;2011.

6. American Cancer Society. *Detailed Guide: Breast Cancer.* Atlanta, Ga: American Cancer Society;2011.

7. Bharat A, Gao F, Margenthaler JA. Tumor characteristics and patient outcomes are similar between invasive lobular and mixed invasive ductal/lobular breast cancers but differ from pure invasive ductal breast cancers. *Am. J. Surg.* 2009;198(4):516-519.

8. Wasif N, Maggard MA, Ko CY, Giuliano AE. Invasive lobular vs. ductal breast cancer: a stage-matched comparison of outcomes. *Ann. Surg. Oncol.* 2010;17(7):1862-1869.

9. McGuire WL, Horwitz KB, Pearson OH, Segaloff A. Current status of estrogen and progesterone receptors in breast cancer. *Cancer.* 1977;39(6 Suppl):2934-2947.

10. Chen WY, Colditz GA. Risk factors and hormone-receptor status: epidemiology, risk-prediction models and treatment implications for breast cancer. *Nat Clin Pract Oncol.* 2007;4(7):415-423.

11. Hicks DG, Kulkarni S. HER2+ breast cancer: review of biologic relevance and optimal use of diagnostic tools. *Am. J. Clin. Pathol.* 2008;129(2):263-273.

12. Hulka BS, Moorman PG. Breast cancer: hormones and other risk factors. *Maturitas.* 2001;38(1):103-113; discussion 113-106.

13. Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br. J. Cancer.* 2002;87(11):1234-1245.

14. Key J, Hodgson S, Omar RZ, et al. Meta-analysis of studies of alcohol and breast cancer with consideration of the methodological issues. *Cancer Causes Control.* 2006;17(6):759-770.

15. Nasca PC, Pastides H. *Fundamentals of Cancer Epidemiology.* Vol Second. Canada: Jones and Bartlett Publishers; 2008.

16. Li CI, Chlebowski RT, Freiberg M, et al. Alcohol consumption and risk of postmenopausal breast cancer by subtype: the women's health initiative observational study. *J. Natl. Cancer Inst.* 2010;102(18):1422-1431.

17. Xue F, Willett WC, Rosner BA, Hankinson SE, Michels KB. Cigarette smoking and the incidence of breast cancer. *Arch. Intern. Med.* 2011;171(2):125-133.

18. Luo J, Margolis KL, Wactawski-Wende J, et al. Association of active and passive smoking with risk of breast cancer among postmenopausal women: a prospective cohort study. *BMJ.* 2011;342(Journal Article):d1016.

19. Land SR, Christian N, Wickerham DL, Costantino JP, Ganz PA. Cigarette smoking, fitness, and alcohol use as predictors of cancer outcomes among women in the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT). *J Clin Oncol (ASCO Meeting Abstracts).* 2011;29(15_suppl):1505.

20. McTiernan A, Kooperberg C, White E, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. *JAMA.* 2003;290(10):1331-1336.

21. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet.* 2002;360(9328):187-195.

22. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet.* 1997;350(9084):1047-1059.

23. Beral V, Million Women Study C. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet.* 2003;362(9382):419-427.

24. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* 2004;291(14):1701-1712.

25. Prentice RL, Chlebowski RT, Stefanick ML, et al. Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. *Am. J. Epidemiol.* 2008;167(12):1407-1415.

26. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet.* 1996;347(9017):1713-1727.

27. Cauley JA, Lucas FL, Kuller LH, Vogt MT, Browner WS, Cummings SR. Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures. Study of Osteoporotic Fractures Research Group. *JAMA.* 1996;276(17):1404-1408.

28. Boyd NF, Martin LJ, Bronskill M, Yaffe MJ, Duric N, Minkin S. Breast tissue composition and susceptibility to breast cancer. *J. Natl. Cancer Inst.* 2010;102(16):1224-1237.

29. Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Ann. Intern. Med.* 2008;148(5):337-347.

30. Kerlikowske K, Ichikawa L, Miglioretti DL, et al. Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk. *J. Natl. Cancer Inst.* 2007;99(5):386-395.

31. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The Epidemiology of Obesity. *Gastroenterology.* 2007;132(6):2087-2102.

32. Rose DP, Vona-Davis L. Interaction between menopausal status and obesity in affecting breast cancer risk. *Maturitas.* 2010;66(1):33-38.

33. Trentham-Dietz A, Newcomb PA, Storer BE, et al. Body size and risk of breast cancer. *Am. J. Epidemiol.* 1997;145(11):1011-1019.

34. Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control.* 2002;13(8):741-751.

35. Lahmann PH, Hoffmann K, Allen N, et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). *Int. J. Cancer.* 2004;111(5):762-771.

36. Vatten LJ, Kvinnsland S. Prospective study of height, body mass index and risk of breast cancer. *Acta Oncol.* 1992;31(2):195-200.

37. Hall IJ, Newman B, Millikan RC, Moorman PG. Body size and breast cancer risk in black women and white women: the Carolina Breast Cancer Study. *Am. J. Epidemiol.* 2000;151(8):754-764.

38. Michels KB, Terry KL, Willett WC. Longitudinal study on the role of body size in premenopausal breast cancer. *Arch. Intern. Med.* 2006;166(21):2395-2402.

39. Ursin G, Longnecker MP, Haile RW, Greenland S. A meta-analysis of body mass index and risk of premenopausal breast cancer. *Epidemiology.* 1995;6(2):137-141.

40. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am. J. Epidemiol.* 2000;152(6):514-527.

41. Kaaks R, Van Noord PA, Den Tonkelaar I, Peeters PH, Riboli E, Grobbee DE. Breast-cancer incidence in relation to height, weight and body-fat distribution in the Dutch "DOM" cohort. *Int. J. Cancer.* 1998;76(5):647-651.

42. Berstad P, Coates RJ, Bernstein L, et al. A Case-Control Study of Body Mass Index and Breast Cancer Risk in White and African-American Women. *Cancer Epidemiol. Biomarkers Prev.* 2010;19(6):1532-1544.

43. Pichard C, Plu-Bureau G, Neves-e Castro M, Gompel A. Insulin resistance, obesity and breast cancer risk. *Maturitas.* 2008;60(1):19-30.

44. Key TJ, Appleby PN, Reeves GK, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J. Natl. Cancer Inst.* 2003;95(16):1218-1226.

45. Cleary MP, Grossmann ME. Minireview: Obesity and breast cancer: the estrogen connection. *Endocrinology.* 2009;150(6):2537-2542.

46. Yang XR, Chang-Claude J, Goode EL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. *J. Natl. Cancer Inst.* 2011;103(3):250-263.

47. Harris HR, Willett WC, Terry KL, Michels KB. Body Fat Distribution and Risk of Premenopausal Breast Cancer in the Nurses' Health Study II. *J. Natl. Cancer Inst.* 2011;103(3):273-278.

48. Maiti B, Kundranda MN, Spiro TP, Daw HA. The association of metabolic syndrome with triple-negative breast cancer. *Breast Cancer Res. Treat.* 2010;121(2):479-483.

49. DeCensi A, Gennari A. Insulin breast cancer connection: confirmatory data set the stage for better care. *J. Clin. Oncol.* 2011;29(1):7-10.

50. Sinicrope FA, Dannenberg AJ. Obesity and breast cancer prognosis: weight of the evidence. *J. Clin. Oncol.* 2011;29(1):4-7.

51. Cui Y, Whiteman MK, Flaws JA, Langenberg P, Tkaczuk KH, Bush TL. Body mass and stage of breast cancer at diagnosis. *Int. J. Cancer.* 2002;98(2):279-283.

52. Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density: relationship with breast cancer risk. *Radiology.* 2004;230(1):29-41.

53. Vachon CM, Brandt KR, Ghosh K, et al. Mammographic breast density as a general marker of breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 2007;16(1):43-49.

54. D'Orsi CJ, Bassett LW, Berg WA, et al. BI-RADS: Mammography, 4th edition in: D'Orsi CJ, Mendelson EB, Ikeda DM, et al: Breast Imaging Reporting and Data System: ACR BI-RADS - Breast Imaging Atlas. Reston, VA: American College of Radiology; 2003.

55. Nicholson BT, LoRusso AP, Smolkin M, Bovbjerg VE, Petroni GR, Harvey JA. Accuracy of assigned BI-RADS breast density category definitions. *Acad. Radiol.* 2006;13(9):1143-1149.

56. Lokate M, Kallenberg MG, Karssemeijer N, Van den Bosch MA, Peeters PH, Van Gils CH. Volumetric breast density from full-field digital mammograms and its association with breast cancer risk factors: a comparison with a threshold method. *Cancer Epidemiol. Biomarkers Prev.* 2010;19(12):3096-3105.

57. Stone J, Warren RM, Pinney E, Warwick J, Cuzick J. Determinants of percentage and area measures of mammographic density. *Am. J. Epidemiol.* 2009;170(12):1571-1578.

58. Boyd NF, Martin LJ, Sun L, et al. Body size, mammographic density, and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 2006;15(11):2086-2092.

59. Boyd N, Martin L, Stone J, Little L, Minkin S, Yaffe M. A longitudinal study of the effects of menopause on mammographic features. *Cancer Epidemiol. Biomarkers Prev.* 2002;11(10 Pt 1):1048-1053.

60. Ginsburg OM, Martin LJ, Boyd NF. Mammographic density, lobular involution, and risk of breast cancer. *Br. J. Cancer.* 2008;99(9):1369-1374.

61. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density and breast cancer risk: current understanding and future prospects. *Breast Cancer Res.* 2011;13(6):223.

62. 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):1879-1886.

63. 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):1541-1548.

64. 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):1829-1846.

65. Gail MH, Benichou J. Validation studies on a model for breast cancer risk. *J. Natl. Cancer Inst.* 1994;86(8):573-575.

66. Spiegelman D, Colditz GA, Hunter D, Hertzmark E. Validation of the Gail et al. model for predicting individual breast cancer risk. *J. Natl. Cancer Inst.* 1994;86(8):600-607.

67. Bondy ML, Lustbader ED, Halabi S, Ross E, Vogel VG. Validation of a breast cancer risk assessment model in women with a positive family history. *J. Natl. Cancer Inst.* 1994;86(8):620-625.

68. Rockhill B, Spiegelman D, Byrne C, Hunter DJ, Colditz GA. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. *J. Natl. Cancer Inst.* 2001;93(5):358-366.

69. 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):1782-1792.

70. 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):951-961.

71. Schonfeld SJ, Pee D, Greenlee RT, et al. Effect of changing breast cancer incidence rates on the calibration of the Gail model. *J. Clin. Oncol.* 2010;28(14):2411-2417.

72. Office of Cancer Communication. Breast Cancer Risk Assessment Tool for Health Care Providers. Bethesda (MD)1998.

73. National Cancer Institute. Breast Cancer Risk Assessment Tool. Available at: http://www.cancer.gov/bcrisktool, Accessed March 20, 2012.

74. Cummings SR, Tice JA, Bauer S, et al. Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. *J. Natl. Cancer Inst.* 2009;101(6):384-398.

75. Chlebowski RT, Anderson GL, Lane DS, et al. Predicting risk of breast cancer in postmenopausal women by hormone receptor status. *J. Natl. Cancer Inst.* 2007;99(22):1695-1705.

76. Gail MH, Anderson WF, Garcia-Closas M, Sherman ME. Absolute risk models for subtypes of breast cancer. *J. Natl. Cancer Inst.* 2007;99(22):1657-1659.

77. Chen J, Pee D, Ayyagari R, et al. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. *J. Natl. Cancer Inst.* 2006;98(17):1215-1226.

78. Barlow WE, White E, Ballard-Barbash R, et al. Prospective breast cancer risk prediction model for women undergoing screening mammography. *J. Natl. Cancer Inst.* 2006;98(17):1204-1214.

79. Tice JA, Cummings SR, Ziv E, Kerlikowske K. Mammographic breast density and the Gail model for breast cancer risk prediction in a screening population. *Breast Cancer Res. Treat.* 2005;94(2):115-122.

80. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J. Natl. Cancer Inst.* 1998;90(18):1371-1388.

81. Cuzick J, Forbes J, Edwards R, et al. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. *Lancet.* 2002;360(9336):817-824.

82. Veronesi U, Maisonneuve P, Costa A, et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. *Lancet.* 1998;352(9122):93-97.

83. Veronesi U, Maisonneuve P, Rotmensz N, et al. Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. *J. Natl. Cancer Inst.* 2007;99(9):727-737.

84. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. *J. Natl. Cancer Inst.* 2007;99(4):283-290.

85. Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet.* 2003;361(9354):296-300.

86. Martino S, Costantino J, McNabb M, et al. The role of selective estrogen receptor modulators in the prevention of breast cancer: comparison of the clinical trials. *Oncologist.* 2004;9(2):116-125.

87. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J. Natl. Cancer Inst.* 2005;97(22):1652-1662.

88. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA.* 1999;281(23):2189-2197.

89. Cauley JA, Norton L, Lippman ME, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res. Treat.* 2001;65(2):125-134.

90. Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J. Natl. Cancer Inst.* 2004;96(23):1751-1761.

91. Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N. Engl. J. Med.* 2006;355(2):125-137.

92. Grady D, Cauley JA, Geiger MJ, et al. Reduced incidence of invasive breast cancer with raloxifene among women at increased coronary risk. *J. Natl. Cancer Inst.* 2008;100(12):854-861.

93. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA.* 2006;295(23):2727-2741.

94. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. *Cancer Prev Res.* 2010;3(6):696-706.

95. Visvanathan K, Chlebowski RT, 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. *J. Clin. Oncol.* 2009;27(19):3235-3258.

96. Fagerlin A, Zikmund-Fisher BJ, Nair V, et al. Women's decisions regarding tamoxifen for breast cancer prevention: responses to a tailored decision aid. *Breast Cancer Res. Treat.* 2010;119(3):613-620.

97. Waters EA, Cronin KA, Graubard BI, Han PK, Freedman AN. Prevalence of tamoxifen use for breast cancer chemoprevention among U.S. women. *Cancer Epidemiol. Biomarkers Prev.* 2010;19(2):443-446.

98. Vogel VG. Tipping the balance for the primary prevention of breast cancer. *J. Natl. Cancer Inst.* 2010;102(22):1683-1685.

99. Ravdin PM. The lack, need, and opportunities for decision-making and informational tools to educate primary-care physicians and women about breast cancer chemoprevention. *Cancer Prev Res.* 2010;3(6):686-688.

100. LaCroix AZ, Powles T, Osborne CK, et al. Breast cancer incidence in the randomized PEARL trial of lasofoxifene in postmenopausal osteoporotic women. *J. Natl. Cancer Inst.* 2010;102(22):1706-1715.

101. Cummings SR, McClung M, Reginster JY, et al. Arzoxifene for prevention of fractures and invasive breast cancer in postmenopausal women. *J. Bone Miner. Res.* 2011;26(2):397-404.

102. Richardson H, Johnston D, Pater J, Goss P. The National Cancer Institute of Canada Clinical Trials Group MAP.3 trial: an international breast cancer prevention trial. *Curr Oncol.* 2007;14(3):89-96.

103. IBIS-II: International Breast Cancer Intervention Study. Available at: http://www.ibis-trials.org, Accessed March 20, 2012.

104. Decensi A, Robertson C, Guerrieri-Gonzaga A, et al. Randomized double-blind 2 x 2 trial of low-dose tamoxifen and fenretinide for breast cancer prevention in high-risk premenopausal women. *J. Clin. Oncol.* 2009;27(23):3749-3756.

105. Osteoporosis Prevention, Diagnosis, and Therapy. *NIH Consens. Statement.*17(1):1-36. Accessed January 20, 2012.

106. Ding H, Field TS. Bone health in postmenopausal women with early breast cancer: how protective is tamoxifen? *Cancer Treat. Rev.* 2007;33(6):506-513.

107. Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. *J. Clin. Oncol.* 1996;14(1):78-84.

108. Sverrisdottir A, Fornander T, Jacobsson H, von Schoultz E, Rutqvist LE. Bone mineral density among premenopausal women with early breast cancer in a randomized trial of adjuvant endocrine therapy. *J. Clin. Oncol.* 2004;22(18):3694-3699.

109. Vehmanen L, Elomaa I, Blomqvist C, Saarto T. Tamoxifen treatment after adjuvant chemotherapy has opposite effects on bone mineral density in premenopausal patients depending on menstrual status. *J. Clin. Oncol.* 2006;24(4):675-680.

110. Cooke AL, Metge C, Lix L, Prior HJ, Leslie WD. Tamoxifen use and osteoporotic fracture risk: a population-based analysis. *J. Clin. Oncol.* 2008;26(32):5227-5232.

111. Johnell O, Cauley JA, Kulkarni PM, Wong M, Stock JL. Raloxifene reduces risk of vertebral fractures [corrected] in postmenopausal women regardless of prior hormone therapy. *J. Fam. Pract.* 2004;53(10):789-796.

112. Eng-Wong J, Reynolds JC, Venzon D, et al. Effect of raloxifene on bone mineral density in premenopausal women at increased risk of breast cancer. *J. Clin. Endocrinol. Metab.* 2006;91(10):3941-3946.

113. Ensrud KE, Stock JL, Barrett-Connor E, et al. Effects of raloxifene on fracture risk in postmenopausal women: the Raloxifene Use for the Heart Trial. *J. Bone Miner. Res.* 2008;23(1):112-120.

114. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA.* 2010;303(3):235-241.

115. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer Epidemiol. Biomarkers Prev.* 2009;18(10):2569-2578.

116. Pilie PG, Ibarra-Drendall C, Troch MM, et al. Protein Microarray Analysis of Mammary Epithelial Cells from Obese and Non-Obese Women at High Risk for Breast Cancer: Feasibility Data. *Cancer Epidemiol. Biomarkers Prev.* 2011(Journal Article).

117. Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA.* 2006;295(14):1647-1657.

118. Enger SM, Ross RK, Paganini-Hill A, Carpenter CL, Bernstein L. Body size, physical activity, and breast cancer hormone receptor status: results from two case-control studies. *Cancer Epidemiol. Biomarkers Prev.* 2000;9(7):681-687.

119. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status--a meta-analysis. *Int. J. Cancer.* 2009;124(3):698-712.

120. Peacock SL, White E, Daling JR, Voigt LF, Malone KE. Relation between obesity and breast cancer in young women. *Am. J. Epidemiol.* 1999;149(4):339-346.

121. Key TJ, Pike MC. The role of oestrogens and progestagens in the epidemiology and prevention of breast cancer. *Eur. J. Cancer Clin. Oncol.* Jan 1988;24(1):29-43.

122. Land SR, Cronin WM, Wickerham DL, et al. Cigarette smoking, obesity, physical activity, and alcohol use as predictors of chemoprevention adherence in the national surgical adjuvant breast and bowel project p-1 breast cancer prevention trial. *Cancer Prev Res.* 2011;4(9):1393-1400.

123. Harvie M, Hooper L, Howell AH. Central obesity and breast cancer risk: a systematic review. *Obesity Rev.* 2003;4(3):157-173.

124. Anderson BO. Prophylactic surgery to reduce breast cancer risk: a brief literature review. *The Breast Journal.* 2001;7(5):321-330.

125. Martin KE, Helvie MA, Zhou C, et al. Mammographic density measured with quantitative computer-aided method: comparison with radiologists' estimates and BI-RADS categories. *Radiology.* 2006;240(3):656-665.

126. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics.* 2000;56(2):337-344.

127. Uno H, Cai T, Pencina MJ, D'Agostino RB, Wei LJ. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. *Stat. Med.* 2011;30(10):1105-1117.

128. Heagerty PJ, Zheng Y. Survival model predictive accuracy and ROC curves. *Biometrics.* 2005;61(1):92-105.

129. Cuzick J, Warwick J, Pinney E, Warren RM, Duffy SW. Tamoxifen and breast density in women at increased risk of breast cancer. *J. Natl. Cancer Inst.* 2004;96(8):621-628.

130. Cuzick J, Warwick J, Pinney E, et al. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. *J. Natl. Cancer Inst.* 2011;103(9):744-752.

131. Brisson J, Brisson B, Cote G, Maunsell E, Berube S, Robert J. Tamoxifen and mammographic breast densities. *Cancer Epidemiol. Biomarkers Prev.* 2000;9(9):911-915.

132. Atkinson C, Warren R, Bingham SA, Day NE. Mammographic patterns as a predictive biomarker of breast cancer risk: effect of tamoxifen. *Cancer Epidemiol. Biomarkers Prev.* 1999;8(10):863-866.

133. Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. *Am. J. Epidemiol.* 2004;159(9):882-890.

134. Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? *BMJ.* 1999;319(7224):1562-1565.

135. *The 2004 Surgeon General's Report on Bone Health and Osteoporosis: What it Means To You.* Office of the Surgeon General: U.S. Department of Health and Human Services;2004.

136. Cuzick J, DeCensi A, Arun B, et al. Preventive therapy for breast cancer: a consensus statement. *Lancet Oncol.* 2011;12(Journal Article):496-503.

137. Korn EL, Dorey FJ. Applications of crude incidence curves. *Stat. Med.* 1992;11(6):813-829.

138. Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? *Stat. Med.* 1993;12(8):737-751.

139. Black DM, Steinbuch M, Palermo L, et al. An assessment tool for predicting fracture risk in postmenopausal women. *Osteoporos. Int.* 2001;12(7):519-528.

140. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA.* 2003;290(13):1729-1738.

141. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. *BMJ.* 2009;339(Journal Article):b4229.

142. Watts NB. The Fracture Risk Assessment Tool (FRAX(R)): applications in clinical practice. *J. Womens Health.* 2011;20(4):525-531.

143. van den Bergh JP, van Geel TA, Lems WF, Geusens PP. Assessment of individual fracture risk: FRAX and beyond. *Curr Osteoporos Rep.* 2010;8(3):131-137.