**Distribution Agreement**

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Priya Patel Date

Association of tumor receptor status and treatment-induced amenorrhea in breast cancer survivors

By

Priya Patel

MPH

Epidemiology

_____

Penelope P. Howards

Committee Chair

# Association of tumor receptor status and treatment-induced amenorrhea in breast cancer survivors

By

Priya Patel

B.S., Georgia Institute of Technology, 2014

Thesis Committee Chair: Penelope P. Howards Ph.D., M.S.

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Epidemiology

2016

**Abstract**

Association of tumor receptor status and treatment-induced amenorrhea in breast cancer survivors

By Priya Patel

As survival for breast cancer has improved, concerns about the long-term side effects that may result from treatment, including amenorrhea and impaired fertility, have increased. Examining the association between estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status and treatment-induced amenorrhea may provide information clinicians can use when counseling premenopausal breast cancer patients treated with chemotherapy about possible effects of treatment on amenorrhea and fertility. This study included participants from the FUCHSIA Women's Study, which recruited female cancer survivors in Georgia who were diagnosed between the ages of 20-35 and who survived at least 2 years after diagnosis (median = 7 years; interquartile range, 5-11). Data were obtained through interview and medical records abstraction. Eligible women for this study included breast cancer survivors who were treated with chemotherapy. Among the 249 women in the final study population, 60.2% reported experiencing amenorrhea lasting six months or longer during treatment. The frequency of amenorrhea did not vary by ER or PR receptor status, but HER2 positive women were more likely to report amenorrhea than HER2 negative women (67.1% vs. 57.4%). After adjusting for confounders and cancer treatment, a possible intermediate between receptor status and amenorrhea, ER positive women were slightly less likely than ER negative women to report treatment-induced amenorrhea (aOR = 0.74; 95% CI, 0.23, 2.34), while the association between PR status and amenorrhea was null (aOR = 1.11; 95% CI, 0.43, 2.87). HER2 positive women were less likely to report treatment-induced amenorrhea than HER2 negative women after adjustment (aOR = 0.55; 95% CI, 0.23, 1.31). Treatment with Herceptin, commonly prescribed to HER2 positive women, was associated with an increased odds of amenorrhea (aOR = 3.92; 95% CI, 1.27-12.12). The value of knowing ER and PR receptor status was unclear. However, knowing HER2 status and whether Herceptin will be prescribed may help clinicians counsel premenopausal breast cancer patients on the potential effects of chemotherapy on amenorrhea and future fertility.

# Association of tumor receptor status and treatment-induced amenorrhea in breast cancer survivors

By

Priya Patel

B.S., Georgia Institute of Technology, 2014

Thesis Committee Chair: Penelope P. Howards, Ph.D., M.S.

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Epidemiology

2016

# Chapter I: Background

1. Introduction

Breast cancer is the most common cancer in women (aside from non-melanoma skin cancer), affecting 12% of all American women (1). Though it remains the second leading cause of cancer related deaths in women, survival for women diagnosed with breast cancer has improved over time through advanced screening and treatment methods (2). With improvement in survival, however, concerns about potential long-term side effects resulting from treatment have increased. In particular, amenorrhea and infertility are of interest among reproductive age women (3).

Chemotherapy has been associated with amenorrhea following treatment (4). Treatment-induced amenorrhea may include temporary loss of a woman's menstrual period or may indicate early menopause (5). Although a woman experiencing treatment-induced amenorrhea may resume menstruating, temporary amenorrhea may be a marker for subfertility or a shortened reproductive window (6). Not all women undergoing chemotherapy experience treatment-induced amenorrhea. Some factors that have been suggested to predict a woman's susceptibility to treatment-induced amenorrhea include age at diagnosis and type of treatment (7-10). It would be useful to identify additional factors associated with treatment-induced amenorrhea because identifying women at high risk of amenorrhea may help clinicians counsel patients about their future fertility and discuss treatment options.

Breast cancer receptors, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), which lie on the surface of tumors, promote tumor growth when bound to their respective agents (11). Receptor

status determines in part the cancer treatment options for women diagnosed with breast cancer (12), which in turn affect the probability of experiencing treatment-induced amenorrhea. Thus, receptor status may affect amenorrhea indirectly through treatment, but receptor status may also be associated with treatment-induced amenorrhea even after accounting for treatment. Receptor status has been reported to be associated with factors such as parity, and therefore, it may be related to a woman's underlying fertility (13). Thus, receptor status may be a predictor of treatment-induced amenorrhea if it is a marker for underlying fertility.

Insight into the relation between receptor status and treatment-induced amenorrhea might assist physicians when counseling reproductive age patients interested in learning about the potential effects of their treatment on fertility. Therefore, this study aims to explore a relation between breast cancer receptor status (ER, PR, and HER2) and treatment-induced amenorrhea in reproductive age women diagnosed with breast cancer.

## 2. Descriptive epidemiology

Breast cancer affects 1 out of every 8 women in the United States. It is the leading cancer diagnosis in women aside from non-melanoma skin cancer, making up an estimated 12% of all new cancer cases in women (1). The mean age at diagnosis is 61 years, with the largest age group, 55-64 years, making up 25.6% of all women diagnosed (14). Although less common among younger women, approximately a quarter of women diagnosed with breast cancer are considered to be of reproductive age.

Survival for breast cancer has improved over time since 1975 (2). The five-year survival for all women diagnosed with breast cancer between the years 2005-2011 was

89.4% (14). Survival for reproductive age women is slightly lower, however, with approximately 85% survival (1, 15). Although there continues to be a slight increase in the number of incident cases, there is also a slow decline in mortality leading to more affected individuals living longer after diagnosis with cancer. This increase in survival can be attributed to better screening procedures and treatment techniques (16). Also, with more individuals surviving and living longer after being diagnosed with breast cancer, there is increased attention to the long-term effects of treatment (3). Among reproductive-aged women, the ability to become pregnant after cancer is of concern because treatment is suggested to affect ovarian function (6). Understanding factors that can influence treatment-induced amenorrhea are important to identify. These factors can play a key role in assisting with proper counseling for young women newly diagnosed with breast cancer.

3. Risk factors for breast cancer

The most common risk factors for breast cancer include sex, age, family history, and race. Breast cancer is more common in women than men. Additionally, breast cancer is more prevalent among women above the age 55 (1). There are key differences in risk factors for breast cancer among premenopausal versus postmenopausal women. While breast cancer is more common in white women versus black women above the age of 45, younger black women have a higher incidence of invasive breast cancer as well as a higher mortality compared to younger white women (1). Breast cancer in younger women is also more likely to be hereditary than in older women (17). These hereditary risks include mutations in either or both the BRCA1 and BRCA2 gene. The number of

first-degree relatives diagnosed with BRCA1 and/or BRCA2-related breast cancer may additionally increase a woman's risk of developing breast cancer in her lifetime (18). Other biologic factors related to breast cancer in premenopausal women include exposure to high doses of radiation at an early age, through medical treatment or radon in the home, dense breast tissue, and other breast irregularities including lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS), atypical ductal hyperplasia, and atypical lobular hyperplasia (19). Behavioral factors suggested to increase risk of breast cancer include hormonal contraceptive use and drinking alcohol (20, 21). Alcohol is believed to change the way a woman's body metabolizes estrogen and in turn, cause estrogen levels to rise. With higher estrogen levels, there may be an increased breast cancer risk (21). Hormonal contraceptives can overstimulate cells in the breast, which may be associated with an increased risk of breast cancer (22). Physical activity, on the other hand, may decrease a woman's risk for breast cancer (23). However, the amount of physical activity required to reduce the risk of breast cancer is not established.

4. Receptor status

At diagnosis, breast cancer can be distinguished by multiple subtypes. These subtypes are commonly classified by evaluated biomarkers of breast cancer: ER, PR, and HER2 (12). These receptors are indicated to be either positive or negative based on their presence or absence on breast cancer cells. ER, PR, and HER2 receptors on the surface of cancer cells attach to their respective hormones and promote breast cancer cell growth (11). Four subtypes into which breast cancer can be further categorized include luminal A (ER+ or PR+, and HER2-), luminal B (ER+ or PR+ and HER2+), HER2-enriched (ER-

, PR-, and HER+), or triple-negative (ER-, PR-, HER2-). Luminal A is the most prevalent subtype, accounting for up to 70% of all breast cancers. The prevalence of luminal B and triple-negative cancers range from 10-20%. The HER-2 enriched subtype is the least prevalent, with a range of 5-15% of all breast cancers (24).

The prevalence of the breast cancer subtypes varies across racial/ethnic groups. A few studies indicate that black women, compared to white women, are more commonly diagnosed with triple-negative breast cancers, which have the worst prognosis (25-29). A study of 476 women (116 black and 360 white women) reported that among the women ages 20-34 diagnosed with triple-negative breast cancer, 56% were black and 42% were white (30). Thus, black women were overrepresented among women diagnosed with triple-negative breast cancer compared with a distribution of black women in this age range in the general population. Another study of 1,424 women also reported similar results, with 54% of triple-negative cancers among black women (31). Some studies also suggest that triple-negative breast cancers are more common in Hispanic women versus white women (29, 32). A study examining breast cancer subtypes among 260,174 women reported that Hispanic women (versus white women) have a 17% higher incidence of triple-negative cancer (29). This study also found that the association between race and triple-negative cancer was stronger among premenopausal women.

5. Treatment

After breast cancer diagnosis, women may be treated with surgery (mastectomy or lumpectomy), radiation, chemotherapy, immunotherapy, or hormone therapy. The type of treatment recommended by a woman's physician depends on the stage of breast cancer

the patient is diagnosed with (33). Women diagnosed with early stage cancers, stages zero (DCIS) and one, typically undergo surgery with or without radiation. Women with breast cancer stages two and up, as well as some women with stage one cancer, receive chemotherapy. Chemotherapy can be categorized as either adjuvant, where it occurs after surgery, or neoadjuvant, where it occurs prior to surgery (1). Adjuvant therapy is intended to clear the cancer remaining after surgery and prevent possible reoccurrence. Neoadjuvant therapy is prescribed to shrink the cancer before undergoing surgery. Chemotherapy is administered in cycles that vary in length based on the responsiveness of the cancer and side effects of the treatment (33).

Chemotherapy drugs can be categorized into several groups based on various factors including the way in which they work and their chemical structure (34). Some common drug groups are alkylating agents, which include cyclophosphamide, the drug most commonly prescribed to treat breast cancer; anthracyclines, including doxorubicin and epirubicin; antimetabolites, including 5-fluorouracil and methotrexate; and mitotic inhibitors, including taxanes such as paclitaxel and docetaxel (16). These drugs are most often administered in combination, forming a chemotherapy regimen. Regimens prove more effective in combating cancer versus singular drugs. The most common chemotherapy regimen for breast cancer is doxorubicin and cyclophosphamide (AC), which can either be administered alone or followed by paclitaxel or docetaxel. Other common regimens are cyclophosphamide and docetaxel (TC); cyclophosphamide, methotrexate, and 5-fluororacil (CMF); and docetaxel, carboplatin, and trastuzumab (TCH) (35).

Receptor status affects the treatment that is recommended to the breast cancer patient. Research shows that hormone receptor positive (ER and PR positive) cancers respond better to chemotherapy than hormone receptor negative cancers. Further, trastuzumab (Herceptin) improves survival of women diagnosed with HER2 positive breast cancer (36). Herceptin is believed to attach to HER2 receptors and stop them from signaling tumor cells to grow. It can be used in conjunction with a chemotherapy regimen, such as the AC or TCH regimen, or given as an adjuvant treatment after chemotherapy.

Tamoxifen (Nolvadex) is a selective estrogen receptor modulator (SERM), a form of hormone replacement therapy, also known to yield better treatment and prevent recurrence of breast cancer among those with ER or PR positive breast cancers (37). Tamoxifen binds to the ER and PR receptors on cancer cells, effectively blocking estrogen from being able to bind to the receptors and signal it to grow. It is usually recommended to be taken for five years after treatment, but may be prescribed concurrently.

6. Side effects of treatment

While treatments have become more effective and have improved survival over time, they may lead to long-term side effects including infertility and amenorrhea (6). Chemotherapy, in particular, has been reported to have a strong effect on fertility and ovarian reserve and to cause amenorrhea (4, 38). Pelvic radiation also affects fertility, but is not common in breast cancer patients (39). Chemotherapy damages the follicles which lie in the ovaries. These follicles, which release luteinizing hormone and follicle

stimulating hormone, then affect the hormone balance in the body. The change in hormone levels may subsequently result in treatment-induced amenorrhea (6). Treatment-induced amenorrhea, which is the loss of a woman's menstrual period for at least 6 consecutive months, can be either temporary or permanent (5). Permanent amenorrhea results in early menopause. Even when temporary, treatment-induced amenorrhea may be a marker of loss of childbearing capacity, through subfertility or a shortened reproductive window (7, 40).

Treatment-induced amenorrhea may occur in reproductive age women with early or late stage breast cancer who undergo chemotherapy (40). Though treatment-induced amenorrhea is not a desired side effect because of its association with impaired fertility, it may indicate that the chemotherapy treatment is effective (41, 42). A meta-analysis of 13 studies on premenopausal treatment-induced amenorrhea reported that amenorrhea was associated with positive prognoses among women with ER-positive breast cancers (42).

Although there is a strong association between chemotherapy and amenorrhea, not all breast cancer patients who undergo chemotherapy will experience treatment-induced amenorrhea. Factors that have been suggested to predict susceptibility to treatment-induced amenorrhea include age, chemotherapy agents, and cumulative dose of chemotherapy (7-10, 43, 44). A retrospective study of 191 women reported that treatment-induced amenorrhea was higher in women 40 and older versus those younger than 40 years (82% to 55%) (45). While more common in older women, treatment-induced amenorrhea is still of concern among women of younger reproductive ages because they are less likely to have achieved their desired family size. In a cohort of 1,127 women, researchers reported that 61% of women under the age of 40 versus 95%

of women 40 and older underwent treatment-induced amenorrhea (40). Additionally, Jacobsen et al. found that among 356 women with breast cancer between the ages of 20-35, half of the women reported experiencing amenorrhea (5).

The drugs included in a woman's treatment regimen may predict her susceptibility to experiencing treatment-induced amenorrhea. Cyclophosphamide, which is an alkylating agent and the most common chemotherapy prescribed for breast cancer is known to be associated with treatment-induced amenorrhea, and believed to be gonadotoxic (6, 7, 47). In one study, among 77 women, with the cyclophosphamide, doxorubicin regimen, 44% underwent treatment-induced amenorrhea (7). Aside from the agents alone, the dose of chemotherapy may further increase susceptibility to treatment-induced amenorrhea. In a study of 552 patients, cyclophosphamide, methotrexate, and fluorouracil (CMF) regimen was reported to result in amenorrhea in 10% of women after one dose, 33% after 6 months, and 61% after 12 months (40).

The addition of a taxane, such as paclitaxel or docetaxel, to a chemotherapy regimen is suggested to increase a woman's sensitivity to treatment-induced amenorrhea. However, studies have reported inconclusive results (48-50). A study of 122 women suggested that regimens including taxanes resulted in higher treatment-induced amenorrhea rates within the first year versus non-taxane based regimens (51). However, another study reported that among 111 premenopausal women, those who received taxanes (44%) resumed their menstrual cycles more often than those who had been treated with AC alone (33%) (52).

Although the association between chemotherapy and amenorrhea is well established, no studies have assessed the relation between breast cancer receptor status

and amenorrhea. Amenorrhea may result from hormone imbalance due to damage to the ovaries. ER, PR, and HER2 receptor statuses have also been previously associated with hormonally related factors, such as parity and oral contraceptive use (13, 53, 54). Thus, receptor status may be a marker for an unidentified hormonal factor that affects both receptor status and amenorrhea. However, receptor status and amenorrhea are also both related to treatment. Thus, it is of interest to assess whether receptor status is associated with amenorrhea after accounting for treatment.

## 7. Summary

Generally, reproductive age breast cancer survivors are living longer, but the treatments used to prolong survival, including chemotherapy, can result in long-term side effects (3). These effects are of concern for those who are interested in maintaining their fertility after cancer treatment. Studies have shown that chemotherapy can cause temporary or permanent amenorrhea (6, 49). Many factors may cause a woman to be more susceptible to treatment-induced amenorrhea including age and type of chemotherapy (7-10, 43). It is, however, unknown whether treatment-induced amenorrhea differs by hormone receptor status. Because receptor status is associated with hormonal factors such as parity (10), there may be an association with treatment-induced amenorrhea, which could be the result of underlying differences in susceptibility as well as differences in treatment.

This study aims to evaluate the relation between ER, PR, and HER2 receptor status and treatment-induced amenorrhea among reproductive age women diagnosed with breast cancer overall and after adjusting for treatment. Assessing this relation may help

to identify women more likely to experience treatment-induced amenorrhea, which could assist physicians in counseling newly diagnosed reproductive age patients on treatment options and potential outcomes.

# Chapter II: Manuscript

## Introduction

Breast cancer affects 1 out of every 8 women, or 12% of all women, in the United States (1). Survival for those diagnosed with breast cancer has improved over time and has led to increased concerns about the long-term side effects that result from treatment (2). Among reproductive aged women, amenorrhea and infertility are potential side effects of particular interest (3). Studying factors associated with these outcomes is important in order to provide women diagnosed with breast cancer with more information about the potential impact of treatment on their fertility.

Chemotherapy has been strongly associated with amenorrhea following treatment (4). Chemotherapy may damage the ovaries by impairing follicles, which affects the hormonal balance in the body, potentially leading to treatment-induced amenorrhea (6). Treatment-induced amenorrhea may be permanent, resulting in early menopause, or temporary, where the woman will resume her menstrual cycles at some point following chemotherapy (5). However, even temporary amenorrhea is of concern because it may be a marker for subfertility or a shortened reproductive window (6). Nevertheless, not all breast cancer patients who undergo chemotherapy experience amenorrhea. Factors that are believed to predict treatment-induced amenorrhea include age at diagnosis and chemotherapy agents (7-10). In particular, the alkylating agent cyclophosphamide, which is the chemotherapy agent most commonly prescribed for breast cancer, is strongly associated with treatment-induced amenorrhea (6, 47).

Identifying other factors that predict those at higher risk of experiencing treatment-induced amenorrhea would provide additional information that physicians

could use when counseling patients about treatment decisions. No studies have assessed the relation between breast cancer receptor status and amenorrhea. Receptor status likely affects amenorrhea in part through treatment because recommended treatments differ by receptor status and different treatments may have varying effects on amenorrhea. After adjusting for treatment, receptor status may continue to be associated with amenorrhea because of underlying hormonal factors that affect both receptor status and amenorrhea. Prior studies have reported that ER, PR, and HER2 status are associated with hormonally related factors, such as parity (12, 53). Thus, receptor status may serve as a proxy marker for underlying hormonal conditions with different risks of amenorrhea.

This study aimed to evaluate the relations between ER, PR, and HER2 status and treatment-induced amenorrhea among reproductive age breast cancer patients treated with chemotherapy. Assessing these relations may help identify women who are more likely to experience treatment-induced amenorrhea, which could assist physicians in counseling newly diagnosed patients of reproductive age on treatment options and potential outcomes.

# Methods

## Study Population

Data for this study were drawn from the Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women's Study, a population-based study of fertility in female survivors of young adult cancers. Eligible cancer survivors, alive at least 2 years after diagnosis, were identified in collaboration with the Georgia Cancer Registry. Women diagnosed with a reportable malignant cancer (55) or DCIS (ductal carcinoma in situ) between 1990-2009, who were aged 20-35 at diagnosis and 22-45 at the time of recruitment were eligible. The study was approved by the Institutional Review Boards of Emory University and the Georgia Department of Health.

This study was restricted to women in the FUCHSIA Women's Study diagnosed with breast cancer and treated with chemotherapy. Women who had a hysterectomy before cancer treatment were excluded. Women with missing data for ER, PR, and HER2 status or amenorrhea were also excluded.

## Outcome

The outcome, treatment-induced amenorrhea, was defined based on an in-depth computer assisted telephone interview. Participants were asked if their menstrual periods stopped during the course of cancer treatment. Treatment-induced amenorrhea was defined as not having a menstrual period for six months or longer beginning during cancer treatment.

**Exposure**

Breast cancer receptor status, ER, PR, and HER2, was abstracted from medical records. Receptors were also classified into four breast cancer subtypes: luminal A (ER/PR+, HER2-), luminal B (ER/PR+, HER2+), HER2-enriched (ER-, PR-, HER2+), and triple-negative (ER-, PR-, HER2-).

**Covariates**

Confounders associated with receptor status and treatment-induced amenorrhea were identified based on the literature and hypothesized causal graphs. They included age at diagnosis, age at menarche, body mass index (BMI) at diagnosis, parity, oral contraceptive use, and cancer stage. Age, parity, and oral contraceptive use data were obtained through the interview. BMI and cancer stage (based on American Joint Committee on Cancer [AJCC] categorization) data were collected from medical records.

Cancer treatment was hypothesized to be an intermediate between receptor status and amenorrhea. We assessed whether receptor status was associated with amenorrhea after conditioning on treatment and adjusting for confounders of the receptor-outcome and treatment-outcome relations. Treatments included tamoxifen, Herceptin, and type of chemotherapy class. All treatment info was abstracted from medical records. Chemotherapy was collapsed into the following classes: alkylating agents, topoisomerase inhibitors, mitotic inhibitors, and antimetabolites.

**Statistical Analysis**

Preliminary descriptive statistics were calculated, stratified by receptor status (ER, PR, HER2) and treatment-induced amenorrhea status.

Logistic models were fit to estimate the odds ratios (OR) for the association between receptor status and occurrence of treatment-induced amenorrhea. The unadjusted model included only indicator variables for the three cancer receptors (referent=negative status). Next, we fit a model adjusted for confounding. Women with missing BMI at diagnosis, cancer stage, and treatment data were excluded from this analysis. The third model was adjusted for confounding and included cancer treatment variables. We repeated these analyses restricting the population to those with the most common chemotherapy regimen, cyclophosphamide and doxorubicin (AC) with or without a taxane. We also fit these models to estimate the OR for cancer subtypes (luminal A, luminal B, HER2-enriched vs. triple-negative) and treatment-induced amenorrhea. An additional model was fit to estimate the OR for receptor status and amenorrhea adjusted for confounding and treatment among women who did not receive Herceptin.

All statistical analyses were performed using SAS Version 9.4 (SAS Institute).

## Results

Of the 1,282 cancer survivors who completed the FUCHSIA Women's Study interview, 415 women had a primary breast cancer or DCIS diagnosis between ages 20-35 (Figure 1). Thirty-three of these women had a hysterectomy prior to treatment for cancer and were excluded. Among the remaining 322 eligible women, 11 were unable to

recall whether they stopped menstruating during the course of their treatment and 5 stopped menstruating, but were unable to estimate for how long. Additionally, 41 women were missing ER, PR, and HER2 status all together and 16 had an unknown status for at least 1 receptor. The final population used for analysis in the study included 249 women.

In the final study population, 22.7% reported never experiencing amenorrhea during treatment, and of those who reported experiencing amenorrhea, 17.3% had not resumed menstruating by the interview (median 7 years after diagnosis, interquartile range [IQR], 5-11). Twenty-two percent stopped menstruation during treatment but resumed menses within 6 months and therefore, were classified as not having amenorrhea. Overall, 60.2% of the women were classified as amenorrheic (Table 1).

The median age at diagnosis was 32 (IQR, 30-34 years). The probability of reporting amenorrhea was similar across age at diagnosis (age 20-29: 62.1%; age 30-35: 59.8%). White women (54.8%) were less likely than black women (65.0%) or women of other races (78.3%) to report treatment-induced amenorrhea. White women were also more likely to be ER (63%) and PR (54.1%) positive (vs. ER and PR negative) than black women (ER positive: 47.5%, PR positive: 38.8%) and women of other races (ER positive: 34.8%, PR positive: 30.4%; Supplemental Table 1). All races were less likely to be HER2 positive (white: 30.1%, black: 28.8%, other: 26.1%) than HER2 negative. The median age at menarche was 12 years (IQR, 11-13). Those with an age at menarche around the median were less likely to report treatment-induced amenorrhea (57.1%) than those who were 10 and younger (63.6%) or 15 and older (72.2%). As the number of children given birth to increased, there was a decline in the number of women who reported treatment-induced amenorrhea. Women who smoked were slightly more likely

to report amenorrhea (64.7%) compared to women who never smoked before diagnosis (59.1%). Amenorrhea did not differ by other population characteristics.

The proportion of women reporting amenorrhea did not differ by ER or PR status, but HER2 positive women were more likely to report treatment-induced amenorrhea (67.1%) than HER2 negative women (57.4%).

Among breast cancer subtypes, luminal B women were most likely to report treatment-induced amenorrhea (75.6%), while luminal A women were least likely to report experiencing amenorrhea (53.9%). A large majority of luminal A and luminal B women were ER and PR positive (luminal A: 96.1% ER positive, 84.3% PR positive; luminal B: 97.6% ER positive, 75.6% PR positive; Supplemental Table 2).

Generally, there was an increase in treatment-induced amenorrhea by stage, where 42.9% of stage one women experienced amenorrhea and 76.7% of stage three women experienced amenorrhea. Reported amenorrhea differed by chemotherapy regimen with AC plus taxane and Herceptin reporting amenorrhea most frequently (84.6%) and women receiving AC alone reporting amenorrhea less frequently (46.7%). Reported amenorrhea was similar across chemotherapy drug classes, except for women treated with antimetabolites, who were less likely to report amenorrhea (46.9%). Women taking Herceptin were more likely to report treatment-induced amenorrhea than those who did not take Herceptin (77.8% versus 56.4% of those who did not take Herceptin). The proportion of women reporting amenorrhea did not differ substantially by BRCA1/BRCA2 status, radiation, surgery, or tamoxifen use.

In the model adjusted for confounding only, ER positive women were slightly less likely to report treatment-induced amenorrhea than those who were ER negative

(adjusted odds ratio [aOR] = 0.75; 95% confidence interval [CI], 0.31, 1.82), PR positive women were slightly more likely to report treatment-induced amenorrhea than PR negative women (aOR = 1.33; 95% CI, 0.55, 3.22), but HER2 was not associated with treatment-induced amenorrhea (aOR = 1.17; 95% CI, 0.61, 2.23) (Table 3).

In the model adjusted for confounding and treatment, women who were ER positive were again less likely to report treatment-induced amenorrhea than those who were ER negative (aOR = 0.74; 95% CI, 0.23, 2.34). Being PR positive was no longer associated with amenorrhea compared with being PR negative (aOR = 1.11; 95% CI, 0.43, 2.87), and women who were HER2 positive were about half as likely as HER2 negative women to report treatment-induced amenorrhea (aOR = 0.55; 95% CI, 0.23, 1.31). Herceptin appeared to strongly affect the estimated association between HER2 status and treatment-induced amenorrhea. Women who took Herceptin were much more likely to report treatment-induced amenorrhea than those did not take Herceptin (aOR = 3.92; 95% CI, 1.27, 12.12).

When restricted to women who did not receive Herceptin and adjusted for confounding and treatment, no difference was found in the association between HER2 status and treatment-induced amenorrhea (aOR = 0.56; 95% CI, 0.23, 1.37) from the adjusted model including all women.

The relation between ER status and amenorrhea was found to be reversed in models restricted to women treated with the AC chemotherapy regimen, where ER positive women were more likely than ER negative women to experience treatment-induced amenorrhea (aOR = 1.17; 95% CI, 0.32, 4.33). However, this association was weak and less precise. PR positive women continued to be more likely to experience

treatment-induced amenorrhea than PR negative women, with the relation becoming stronger in the restricted model (aOR = 1.64; 95% CI, 0.55, 4.90). The relation between HER2 status and amenorrhea remained the same as the model adjusted for treatment with HER2 positive women being half as likely to experience treatment-induced amenorrhea (aOR = 0.55, 95% CI, 0.20, 1.48).

The second set of models examined the relation between cancer subtypes and treatment-induced amenorrhea (Table 4). In the model adjusted for confounding only, luminal A women were less likely to report treatment-induced amenorrhea than triple-negative women (aOR = 0.61; 95% CI, 0.31, 1.23), but women who were luminal B were more likely than triple-negative women to report amenorrhea (aOR = 1.60; 95% CI, 0.55, 4.05). HER2-enriched women were about half as likely to report treatment-induced amenorrhea compared to triple-negative women (aOR = 0.47; 95% CI, 0.18, 1.25).

In the model adjusted for confounding and treatment, those who had luminal A breast cancer (aOR = 0.43; 95% CI, 0.13, 1.40), luminal B breast cancer (aOR = 0.51; 95% CI, 0.11, 2.25), and HER2-enriched breast cancer (aOR = 0.24; 95% CI, 0.08, 0.74) were all less likely to report experiencing treatment-induced amenorrhea than those who had triple-negative negative cancer. When restricted to those with the AC chemotherapy regimen, the relation between luminal A and treatment-induced amenorrhea slightly weakened and was imprecise (aOR = 0.72, 95% CI, 0.17, 3.01), and the luminal B subtype was not associated with treatment-induced amenorrhea (aOR = 1.19, 95% CI, 0.18, 7.80). The relation between HER2-enriched breast cancer and treatment-induced amenorrhea remained strong (aOR = 0.21, 95% CI, 0.05, 0.78).

## Discussion

Treatment with chemotherapy is associated with treatment-induced amenorrhea, but not all women get amenorrhea during chemotherapy. We evaluated whether receptor status could help identify women treated with chemotherapy at higher risk of treatment-induced amenorrhea. In our population, 92.8% of women, regardless of receptor status, were treated with an alkylating agent, which is associated with decreased fertility, and 67.5% of women were treated with the AC regimen specifically with or without other agents. HER2 positive women appeared to be less likely to experience amenorrhea after accounting for treatment, but Herceptin, which is commonly prescribed for women with HER2 positive tumors, seemed to increase the risk of amenorrhea. The association between receptor status and amenorrhea appeared to be less informative for ER and PR status.

Studies have examined many factors related to treatment-induced amenorrhea, but none to our knowledge have evaluated a relation between breast cancer receptor status or cancer subtypes and amenorrhea. However, researchers have previously examined the frequency of treatment-induced amenorrhea in populations restricted to or stratified by specific receptor statuses (56, 57). Vanhuyse *et al*. reported that among premenopausal women with receptor positive breast cancer, 57% experienced treatment-induced amenorrhea (56), which is similar to the frequency of amenorrhea among ER positive women in our study. Parulekar *et al*. stratified results by receptor status and reported that among women treated with cyclophosphamide based chemotherapy, 64% of receptor positive women and 58% of receptor negative women experienced amenorrhea (57). We

did not observe a different in the frequency of amenorrhea by ER receptor status, but our frequencies were similar to those reported by Parulekar *et al*.

This study has several limitations. A larger sample size of eligible cancer survivors would have improved precision in this study. Also, treatment-induced amenorrhea may have been misclassified because women were asked to recall the duration of amenorrhea many years after treatment. However, we would not expect recall to systematically differ by receptor status. We defined treatment-induced amenorrhea as amenorrhea for six months or longer to maximize specificity, but we may have missed some women who underreported the duration of their treatment-induced amenorrhea. We prioritized specificity over sensitivity because we expect women reporting amenorrhea for a longer duration to be at greatest risk for subfertility. Further, there is potential for survival bias because women who did not survive to the interview may have been less likely to experience treatment-induced amenorrhea, which may be a sign that their treatment was inadequate. While predicting amenorrhea is relevant for all women, long-term survivors may have the greatest concern about amenorrhea and fertility.

There are several strengths to this study. First, breast cancer treatment and receptor status were collected directly from medical records. We also examined the relation between receptor status and amenorrhea overall and accounting for treatment by adjusting for treatment and by restricting to a single chemotherapy regimen. The self-reported amenorrhea data was collected a median 7 years after diagnosis (IQR 5-11 years), which helped identify the length of amenorrhea after treatment.

Treatment-induced amenorrhea may have long-term effects on a woman's fertility or be a marker of impaired fertility. Understanding factors associated with experiencing treatment-induced amenorrhea could help clinicians identify women treated with chemotherapy who are at highest risk. Being HER2 positive was associated with a decreased probability of reporting amenorrhea after accounting for treatment. However, because Herceptin is associated with an increased risk of amenorrhea, the potential benefit of being HER2 positive may be counter balanced by treatment with Herceptin. Herceptin, which is believed to reduce the diameter and volume of the blood vessels that provide blood to cancer cells (58), may be associated with amenorrhea by affecting the supply of blood to the uterus rather than being toxic to the ovaries. However, this has not been established, and in contrast to our results, Abusief *et al*. did not observe an association between Herceptin and amenorrhea (49). In our data, HER2 status was only associated with amenorrhea after accounting for Herceptin use, but our results were consistent regardless of how we addressed Herceptin use (adjustment or restriction). For the other receptors (ER and PR), the value of knowing receptor type beyond treatment was less clear because the results were less consistent. Knowing HER2 status and whether Herceptin will be prescribed may help clinicians counsel premenopausal breast cancer patients on the potential long-term effects of treatment on fertility.

## References


1. Siegal RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66(1):7-30.
2. DeSantis CE, Lin CC, Mariotto AB, Siegal, RL, Stein, KD, Kramer JL, et al. Cancer treatment and survivorship statistics. CA Cancer J Clin 2014;64:252-71.
3. Partridge A, Gelber S, Peppercorn J, Sampson E, Knudsen K, Laufer M, et al. Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol 2004;22(20), 4174-83.
4. Sukumvanich P, Case LD, Van Zee K, Singletary SE, Paskett ED, Petrek JA, et al. Incidence and time course of bleeding after long-term amenorrhea after breast cancer treatment: a prospective study. Cancer 2010;116:3102-11.
5. Jacobson MH, Mertens AC, Spencer JB, Manatunga AK, Howards P. Menses resumption after cancer treatment–induced amenorrhea occurs early or not at all. Fertility and Sterility 2016;105(3).
6. De Vos D, Devroey P, Fauser BCJM. Primary ovarian insufficiency. Lancet 2010;376:911-21.
7. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. J Clin Oncol 2006;25(24), 5769-79.
8. Letourneau JM, Ebbel EE, Katz PP, Oktay KH, McCulloch CE, Ai WZ, et al. Acute ovarian failure underestimates age-specific reproductive impairment for young women undergoing chemotherapy for cancer. Cancer 2012;118:1933-39.

9. Torino F, Barnabei L, De Vecchis L, Sini V, Schittulli F, Marchetti P, et al. Chemotherapy-induced ovarian toxicity in patients affects by endocrine-responsive early breast cancer. Crit Rev Oncol Hematol 2014;89:27-42.
10. Petrek JA, Naughton MJ, Case LD, Paskett ED, Naftalis EZ, Singletary SE, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. J Clin Oncol 2006;24:1045-51.
11. Kos Z, Dabbs DJ. Biomarker assessment and molecular testing for prognostication in breast cancer. Histopathology 2015;68(1), 70-85.
12. Ruddy K, Guo H, Barry W, Dang C, Yardley D, Moy B, et al. Chemotherapy-related amenorrhea after adjuvant paclitaxel-trastuzumab (APT trial). Breast Cancer Res Treat 2015;151:589-96.
13. Howlander N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LAG, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014;106(5).
14. Anderson WF, Rosenberg PS, Prat A, Perou CM, Sherman ME. How many etiological subtypes of breast cancer: two, three, four, or more? J Natl Cancer Inst 2014;106(8).
15. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA. Elevateed breast cancer mortality in young women (<40 years) compared to older women is attributed to poorer survival in early stage disease. J Am Coll Surg 2009;208(3):341-7.

16. Anderson WF, Rosenberg PS, Katki H. Tracking and evaluating molecular tumor markers with cancer registry data: HER2 and breast cancer. J Natl Cancer Inst 2014;106(5).

17. Anders C, Johnson R, Litton J, Phillips M, Bleyer A. Breast cancer before age 40 years. Seminars in Oncology 2009;36(3), 237-49.

18. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer 1997;71(5):800-9.

19. Nkondjock A, Ghadirian P. Risk factors and risk reduction of breast cancer. Med Sci (Paris) 2005;21(2):175-80.

20. Mctiernan A. Behavioral risk factors in breast cancer: can risk be modified? Oncologist 2003;8(4):326-34.

21. Key TJ, Appleby PN, Reeves GK, Roddam AW, Helzlsouer KJ, Alberg AJ, et al. Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. Br J Cancer 2011;105(5):709-22.

22. Beaber EF, Malone KE, Tang MC, Barlow WE, Porter PL, Daling JR, et al. Oral contraceptives and breast cancer risk overall and by molecular subtype among young women. Cancer Epi Biomarkers Prev 2014;23(5):755-64.

23. Ainsworth BE, Sternfeld B, Slattery ML, Daguise V, Zahmn SH. Physical activity and breast cancer. Cancer 2000;83(3):611-20.

24. Caldarella A, Crocetti E, Bianchi S, Vezzosi V, Urso MB, Biancalani M, et al. Female breast cancer status according to ER, PR, and HER2 expression: a population based analysis. Pathol Oncol Res 2011;17:753-58.

25. Huo D, Ikpatt F, Khramtsov A, Dangou J, Nanda R, Dignam J, et al. Population differences in breast cancer: survey in indigenous african women reveals over-representation of triple-negative breast cancer. Jour Clin Oncol 2009;27(27):4515-21.
26. Carey LA, Cheang MCU, Perou CM. Chapter 29: Genomics, Prognosis, and Therapeutic Interventions, in Harris JR, Lippman ME, Morrow M, Osborne CK. Diseases of the Breast 2014;5th edition, Lippincott Williams & Wilkins.
27. Lund MJ, Butler EN, Hair BY, Andrews JH, Oprea-llies G, Bayakly AR, et al. Age/race differences in HER2 testing and in incidence rates for breast cancer triple subtypes: a population-based study and first report. Cancer 2010;116(11):2549-59.
28. Kohler BA, Sherman RL, Howlader N, Jemal A, Ryerson AB, Henry KA, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. J Natl Cancer Inst 2015;107(6).
29. Sineshaw HM, Gaudet M, Ward EM, Flanders WD, Desantis C, Lin CC, et al. Association of race/ethnicity, socioeconomic status, and breast cancer subtypes in the National Cancer Data Base (2010-2011). Breast Cancer Res Treat 2014;145(3):753-63.
30. Lund MJ, Trivers KF, Porter PL, Coates RJ, Leyland-Jones B, Brawley OW, et al. Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA. Breast Cancer Res Treat 2009;113:357–70.
31. Millikan RC, Newman B, Tse C, Moorman PG, Conway K, Smith LV, et al. Epidemiology of triple-negative breast cancer. Breast Cancer Res Treat 2008;109(1):123-39.

32. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LAG, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014;106(5).

33. PQD Adult Treatment Editorial Board. PDQ cancer information summaries. National Cancer Institute 2002-2016.

34. Mcarthur HL, Hudis CA. Breast cancer chemotherapy. The Cancer Journal 2007;13(3):141-7.

35. Cleator S, Parton M, Dowsett M. The biology of neoadjuvant chemotherapy for breast cancer. Endrocr Relat Cancer 2002;9:183-95.

36. Moja L, Brambilla C, Compagnoni A, Pistotti Vl. Trastuzumab containing regimens for early breast cancer. Protocols Cochrane Database of Systematic Reviews 2006.

37. Davies C, Godwin J, Gray R, Clarke M, Darby S, McGale P, et al. For the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378(9793):771-84.

38. Fornier MN, Modi Shanu, Panageas KS, Norton L, Hudis C. Incidence of chemotherapy-induced, long-term amenorrhea in patients with breast carcinoma age 40 years and younger after adjuvant anthracycline and taxane. Cancer 2005;104(8):1575-9.

39. Bese NS, Iribas A, Dirican A, Oksuz D, Atkovar G, Ober A. Ovarian ablation by radiation therapy: is it still an option for the ablation of ovarian function in endocrine responsive premenopausal breast cancer patients? Breast 2009;18(5):304-8.

40. Minton SE, Munster PN. Chemotherapy-induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer. Cancer Control 2002;9(6):466-72.

41. Tarannum M, Heiman D. Amenorrhea: evaluation and treatment. Am Fam Physician 2006;73(8):1374-82.

42. Zhou Q, Yin W, Du Y, Shen Z, Lu J. Prognostic impact of chemotherapy-induced amenorrhea on premenopausal breast cancer. Menopause 2015;22(10):1091-7.

43. Valentini A, Finch A, Lubinski J, Byrski T, Ghadirian P, Kim-Sing C, et al. Chemotherapy-Induced Amenorrhea in Patients With Breast Cancer With a BRCA1 or BRCA2 Mutation. Journal of Clinical Oncology 2013;31(31):3914-9.

44. Jung M, Shin HJ, Rha SY, Jeung HC, Hong S, Moon YW, et al. The clinical outcome of chemotherapy-induced amenorrhea in premenopausal young patients with breast cancer with long-term follow-up. Annals of Surgical Oncology Ann Surg Oncol 2010;17(12):3259-68.

45. Tham Y, Sexton K, Weiss H, Elledge R, Friedman LC, Kramer R. The rates of chemotherapy-induced amenorrhea in patients treated with adjuvant doxorubicin and cyclophosphamide followed by a taxane. Am Jour of Clin Oncol 2007;30(2):126-32.

46. Bakkum-Gamez JN, Laughlin SK, Jensen JR, Akogyeram CO, Pruthi S. Challenges in the Gynecologic care of premenopausal women with breast cancer. Mayo Clin Proc 2011;86(3):229-40.

47. Thomson AB, Critchley HO, Wallace WH. Fertility and progeny. Eur J Cancer 2002;38:1634-44.

48. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. J Clin Oncol 2006;25(24):5769-79.

49. Abusief ME, Missmer SA, Ginsburg ES, Weeks JC, Partridge AH. The effects of paclitaxel, dose density, and trastuzumab on treatment-related amenorrhea in premenopausal women with breast cancer. Cancer 2010;791-98.

50. Lee S, Kil WJ, Chun M, Jung YS, Kang SY, Oh YT. Chemotherapy-related amenorrhea in premenopausal women with breast cancer. Menopause 2009;98-103.

51. Fornier MN, Modi Shanu, Panageas KS, Norton L, Hudis C. Incidence of chemotherapy-induced, long-term amenorrhea in patients with breast carcinoma age 40 years and younger after adjuvant anthracycline and taxane. Cancer 2005;104(8):1575-79.

52. Han H, Ro J, Lee KS, Nam B, Seo JA, Lee DH, et al. Analysis of chemotherapy-induced amenorrhea rates by three different anthracycline and taxane containing regimens for early breast cancer. Breast Cancer Res Treat 2008;115(2):335-42.

53. Di Cosimo S, Alimonti A, Ferretti G, Sperduti I, Carlini P, Papaldo P, et al. Incidence of chemotherapy-induced amenorrhea depending on the timing of treatment by menstrual cycle phase in women with early breast cancer. Annals of Oncology 2004;15(7):1065-71.

54. Bethea TN, Rosenberg L, Hong C, Troester MA, Lunetta KL, Bandera EV, et al. A case–control analysis of oral contraceptive use and breast cancer subtypes in the African American Breast Cancer Epidemiology and Risk Consortium. Breast Cancer Res 2015;17(1):22.

55. Adamo M, Dickie L, Ruhl J. SEER program coding and staging manual 2015. Bethesda, MD: National Cancer Institute;2015.

56. Vanhuyse C, Fournier C, Bonneterre, J. Chemotherapy-induced amenorrhea: influence on disease-free survival and overall survival in receptor-positive premenopausal early breast cancer patients. Ann Oncol 2005;16(8):1283-88.

57. Parulekar WR, Day AG, Ottaway JA, Shepherd LE, Trudeau ME, Bramwell V et al. Incidence and prognostic impact of amenorrhea during adjuvant therapy in high risk premenopausal breast cancer: analysis of a National Cancer Institute of Canada clinical trials group study-NCIC CTG MA.5. J Clin Oncol 2005;23:6002-8.

58. Izume Y, Xu L, Di Tomaso E, Fukumura D, Jain RK. Tumour biology: Herceptin acts as an anti-angiogenic cocktail. Nature 2002;416:279-80.

## Tables

**Table 1.** Study population characteristics by amenorrhea status among premenopausal women diagnosed with breast cancer (n= 249)

| | **Amenorrhea (n=150)** | | **No amenorrhea[a] (n=99)** | |
|---|---|---|---|---|
| | n | % | n | % |
| Age at diagnosis (years) | | | | |
| 20-29 | 36 | 62.1 | 22 | 37.9 |
| 30-35 | 114 | 59.7 | 77 | 40.3 |
| Race | | | | |
| White | 80 | 54.8 | 66 | 45.2 |
| Black | 52 | 65.0 | 28 | 35.0 |
| Other | 18 | 78.3 | 5 | 21.7 |
| Education | | | | |
| Some college, technical school, or less | 45 | 58.4 | 32 | 41.6 |
| College graduate | 48 | 58.5 | 34 | 41.5 |
| Some graduate school or graduate school | 57 | 63.3 | 33 | 36.7 |
| Urban/Rural classification at diagnosis | | | | |
| Non-metropolitan | 16 | 55.2 | 13 | 44.8 |
| Small metropolitan | 30 | 57.7 | 22 | 42.3 |
| Large metropolitan | 103 | 61.7 | 64 | 38.3 |
| Missing | 1 | | 0 | |
| Marital status at diagnosis | | | | |
| Yes | 111 | 61.0 | 71 | 39.0 |
| No | 39 | 58.2 | 28 | 41.8 |
| Household income in the past 12 months | | | | |
| Less than $25,000 | 20 | 62.5 | 12 | 37.5 |
| $25,000 to $50,000 | 27 | 56.3 | 21 | 43.8 |
| $50,000 to $75,000 | 29 | 61.7 | 18 | 38.3 |
| $75,000 to $100,000 | 28 | 59.6 | 19 | 40.4 |
| Greater than $100,000 | 45 | 62.5 | 27 | 37.5 |
| Missing | 1 | | 2 | |
| Current insurance status | | | | |
| No Insurance | 10 | 55.6 | 8 | 44.4 |
| Private | 122 | 59.8 | 82 | 40.2 |
| Public (Government) | 17 | 65.4 | 9 | 34.6 |
| Missing | 1 | | 0 | |

| | | | | |
|---|---|---|---|---|
| BMI at diagnosis | | | | |
| Underweight | 2 | 66.7 | 1 | 33.3 |
| Normal | 70 | 61.4 | 44 | 38.6 |
| Overweight | 39 | 58.2 | 28 | 41.8 |
| Obese | 30 | 65.2 | 16 | 34.8 |
| Missing | 9 | | 10 | |
| Age at menarche (years) | | | | |
| ≤10 | 49 | 63.6 | 28 | 36.4 |
| 11-14 | 88 | 57.1 | 66 | 42.9 |
| ≥15 | 13 | 72.2 | 5 | 27.8 |
| Parity | | | | |
| 0 | 54 | 67.5 | 26 | 32.5 |
| 1 | 32 | 59.3 | 22 | 40.7 |
| 2 | 42 | 56.8 | 32 | 43.2 |
| 3 or more | 22 | 53.7 | 19 | 46.3 |
| Oral contraceptive use before diagnosis | | | | |
| Yes | 117 | 60.9 | 75 | 39.1 |
| No | 32 | 58.2 | 23 | 41.8 |
| Missing | 1 | | 1 | |
| Ever smoke before diagnosis | | | | |
| Yes | 33 | 64.7 | 18 | 35.3 |
| No | 117 | 59.1 | 81 | 40.9 |

*Note:* BMI = body mass index

[a] No amenorrhea classified as no loss of menstrual period during treatment or loss of menstrual period for less than 6 months

**Table 2**. Cancer characteristics by amenorrhea status among premenopausal women diagnosed with breast cancer (n=249)

| | **Amenorrhea (n=150)** | | **No amenorrhea[a] (n=99)** | |
|---|---|---|---|---|
| | n | % | n | % |
| **Cancer Characteristics** | | | | |
| ER status | | | | |
| Positive | 83 | 60.1 | 55 | 39.9 |
| Negative | 67 | 60.4 | 44 | 39.6 |
| PR status | | | | |
| Positive | 70 | 59.8 | 47 | 40.2 |
| Negative | 80 | 60.6 | 52 | 39.4 |
| HER2 status | | | | |
| Positive | 49 | 67.1 | 24 | 32.9 |
| Negative | 101 | 57.4 | 75 | 42.6 |
| Breast cancer subtype[b] | | | | |
| Luminal A | 55 | 53.9 | 47 | 46.1 |
| Luminal B | 31 | 75.6 | 10 | 24.4 |
| HER2 -enriched | 18 | 56.3 | 14 | 43.8 |
| Triple-negative | 46 | 62.2 | 28 | 37.8 |
| BRCA 1 status | | | | |
| Positive | 14 | 66.7 | 7 | 33.3 |
| Negative | 72 | 62.6 | 43 | 37.4 |
| Missing | 64 | | 49 | |
| BRCA 2 status | | | | |
| Positive | 5 | 62.5 | 3 | 37.5 |
| Negative | 82 | 64.1 | 46 | 35.9 |
| Missing | 63 | | 50 | |
| Stage | | | | |
| 0 | 3 | 42.9 | 4 | 57.1 |
| 1 | 26 | 45.6 | 31 | 54.4 |
| 2 | 80 | 63.0 | 47 | 37.0 |
| 3 | 33 | 76.7 | 10 | 23.3 |
| 4 | 4 | 57.1 | 3 | 42.9 |
| Missing | 4 | | 4 | |

| | | | | |
|---|---|---|---|---|
| **Treatment Characteristics** | | | | |
| Chemotherapy regimen | | | | |
| AC only | 14 | 46.7 | 16 | 53.3 |
| AC + taxane | 71 | 66.4 | 36 | 33.6 |
| AC + Herceptin | 2 | 40.0 | 3 | 60.0 |
| AC + taxane + Herceptin | 22 | 84.6 | 4 | 15.4 |
| Other | 41 | 50.6 | 40 | 49.4 |
| Chemotherapy drug class[c] | | | | |
| Alkylating Agents | 140 | 60.6 | 91 | 39.4 |
| Topoisomerase Inhibitors | 124 | 64.9 | 67 | 35.1 |
| Mitotic Inhibitors | 122 | 66.3 | 62 | 33.7 |
| Antimetabolites | 15 | 46.9 | 17 | 53.1 |
| Missing | 0 | | 1 | |
| Tamoxifen | | | | |
| Yes | 84 | 62.7 | 50 | 37.3 |
| No | 66 | 57.4 | 49 | 42.6 |
| Herceptin | | | | |
| Yes | 35 | 77.8 | 10 | 22.2 |
| No | 114 | 56.4 | 88 | 43.6 |
| Missing | 1 | | 1 | |
| Radiation | | | | |
| Yes | 106 | 59.2 | 73 | 40.8 |
| No | 44 | 62.9 | 26 | 37.1 |
| Surgery | | | | |
| Mastectomy | 38 | 51.4 | 36 | 48.6 |
| Less than mastectomy | 112 | 64.0 | 63 | 36.0 |

[a] No amenorrhea classified as no loss of menstrual period during treatment or loss of menstrual period for less than 6 months

[b] Luminal A (ER/PR +, HER2 -), Luminal B (ER/PR +, HER2 +), HER2-enriched (ER -, PR -, HER2 +), Triple-negative (ER-, PR-, HER2-)

[c] Not mutually exclusive

**Table 3.** Adjusted odds ratios (OR) and 95% confidence intervals (CI) for receptor status and amenorrhea in population of premenopausal women diagnosed with breast cancer (n=223)

| | Amenorrhea[a] | Total N | OR | 95%CI |
|---|---|---|---|---|
| Adjusted for confounding[b] (N=223) | | | | |
| ER | | | | |
| Yes | 77 | 126 | 0.75 | 0.31, 1.82 |
| No | 60 | 97 | 1.00 | Referent |
| PR | | | | |
| Yes | 66 | 108 | 1.33 | 0.55, 3.22 |
| No | 71 | 115 | 1.00 | Referent |
| HER2 | | | | |
| Yes | 44 | 66 | 1.17 | 0.61, 2.23 |
| No | 93 | 157 | 1.00 | Referent |
| Adjusted for confounding and treatment[c] (N=223) | | | | |
| ER | | | | |
| Yes | 77 | 126 | 0.74 | 0.23, 2.34 |
| No | 60 | 97 | 1.00 | Referent |
| PR | | | | |
| Yes | 66 | 108 | 1.11 | 0.43, 2.87 |
| No | 71 | 115 | 1.00 | Referent |
| HER2 | | | | |
| Yes | 44 | 66 | 0.55 | 0.23, 1.31 |
| No | 93 | 157 | 1.00 | Referent |
| Adjusted for confounding and treatment, restricted to AC[d] (N=149) | | | | |
| ER | | | | |
| Yes | 54 | 75 | 1.17 | 0.32, 4.33 |
| No | 46 | 74 | 1.00 | Referent |
| PR | | | | |
| Yes | 46 | 62 | 1.64 | 0.55, 4.90 |
| No | 54 | 87 | 1.00 | Referent |
| HER2 | | | | |
| Yes | 31 | 47 | 0.55 | 0.20, 1.48 |
| No | 69 | 102 | 1.00 | Referent |

Adjusted for confounding and treatment, restricted to Herceptin non-users[e](N=182)

| | | | | |
|---|---|---|---|---|
| ER | | | | |
| Yes | 56 | 101 | 0.71 | 0.21, 2.33 |
| No | 49 | 81 | 1.00 | Referent |
| PR | | | | |
| Yes | 47 | 85 | 1.11 | 0.41, 3.00 |
| No | 58 | 97 | 1.00 | Referent |
| HER2 | | | | |
| Yes | 14 | 28 | 0.56 | 0.23, 1.37 |
| No | 91 | 154 | 1.00 | Referent |

[a] Amenorrhea classified as loss of menstrual period during treatment for six months or longer

[b] Model was adjusted for age at diagnosis, age at menarche, BMI at diagnosis, oral contraceptive use, and cancer stage

[c] Model was adjusted for age at diagnosis, age at menarche, BMI at diagnosis, oral contraceptive use, cancer stage, tamoxifen, Herceptin, alkylating agents, topoismerase inhibitors, antimitotic inhibitors, and antimetabolites

[d] Model including women with AC chemotherapy regimen with or without a taxane and/or Herceptin. Adjusted for age at diagnosis, age at menarche, BMI at diagnosis, oral contraceptive use, cancer stage, tamoxifen, Herceptin, antimitotic inhibitors, and antimetabolites

[e] Model including women who did not receive Herceptin. Adjusted for age at diagnosis, age at menarche, BMI at diagnosis, oral contraceptive use, cancer stage, tamoxifen, alkylating agents, topoismerase inhibitors, antimitotic inhibitors, and antimetabolites

**Table 4.** Adjusted odds ratios (OR) and 95% confidence intervals (CI) for cancer subtype and amenorrhea in population of premenopausal women diagnosed with breast cancer (n=223)

| | Amenorrhea[a] | Total N | OR | 95%CI |
|---|---|---|---|---|
| Adjusted for confounding[b] (N=223) | | | | |
| Luminal A | | | | |
| Luminal A | 52 | 95 | 0.61 | 0.31, 1.23 |
| Triple-negative | 41 | 62 | 1.00 | Referent |
| Luminal B | | | | |
| Luminal B | 28 | 36 | 1.60 | 0.55, 4.05 |
| Triple-negative | 41 | 62 | 1.00 | Referent |
| HER2-enriched | | | | |
| HER2-enriched | 16 | 30 | 0.47 | 0.18, 1.25 |
| Triple-negative | 41 | 62 | 1.00 | Referent |
| Adjusted for confounding and treatment[c] (N=223) | | | | |
| Luminal A | | | | |
| Luminal A | 52 | 95 | 0.43 | 0.13, 1.40 |
| Triple-negative | 41 | 62 | 1.00 | Referent |
| Luminal B | | | | |
| Luminal B | 28 | 36 | 0.51 | 0.11, 2.25 |
| Triple-negative | 41 | 62 | 1.00 | Referent |
| HER2-enriched | | | | |
| HER2-enriched | 16 | 30 | 0.24 | 0.08, 0.74 |
| Triple-negative | 41 | 62 | 1.00 | Referent |
| Adjusted for confounding and treatment, restricted to AC[d] (N=149) | | | | |
| Luminal A | | | | |
| Luminal A | 37 | 93 | 0.72 | 0.17, 3.01 |
| Triple-negative | 32 | 46 | 1.00 | Referent |
| Luminal B | | | | |
| Luminal B | 20 | 24 | 1.19 | 0.18, 7.80 |
| Triple-negative | 32 | 46 | 1.00 | Referent |
| HER2-enriched | | | | |
| HER2-enriched | 11 | 23 | 0.21 | 0.05, 0.78 |
| Triple-negative | 32 | 46 | 1.00 | Referent |

Note: Luminal A (ER/PR +, HER2 -), Luminal B (ER/PR +, HER2 +), HER2-enriched (ER -, PR -, HER2 +), Triple-negative (ER-, PR-, HER2-)

[a] Amenorrhea classified as loss of menstrual period during treatment for six months or longer

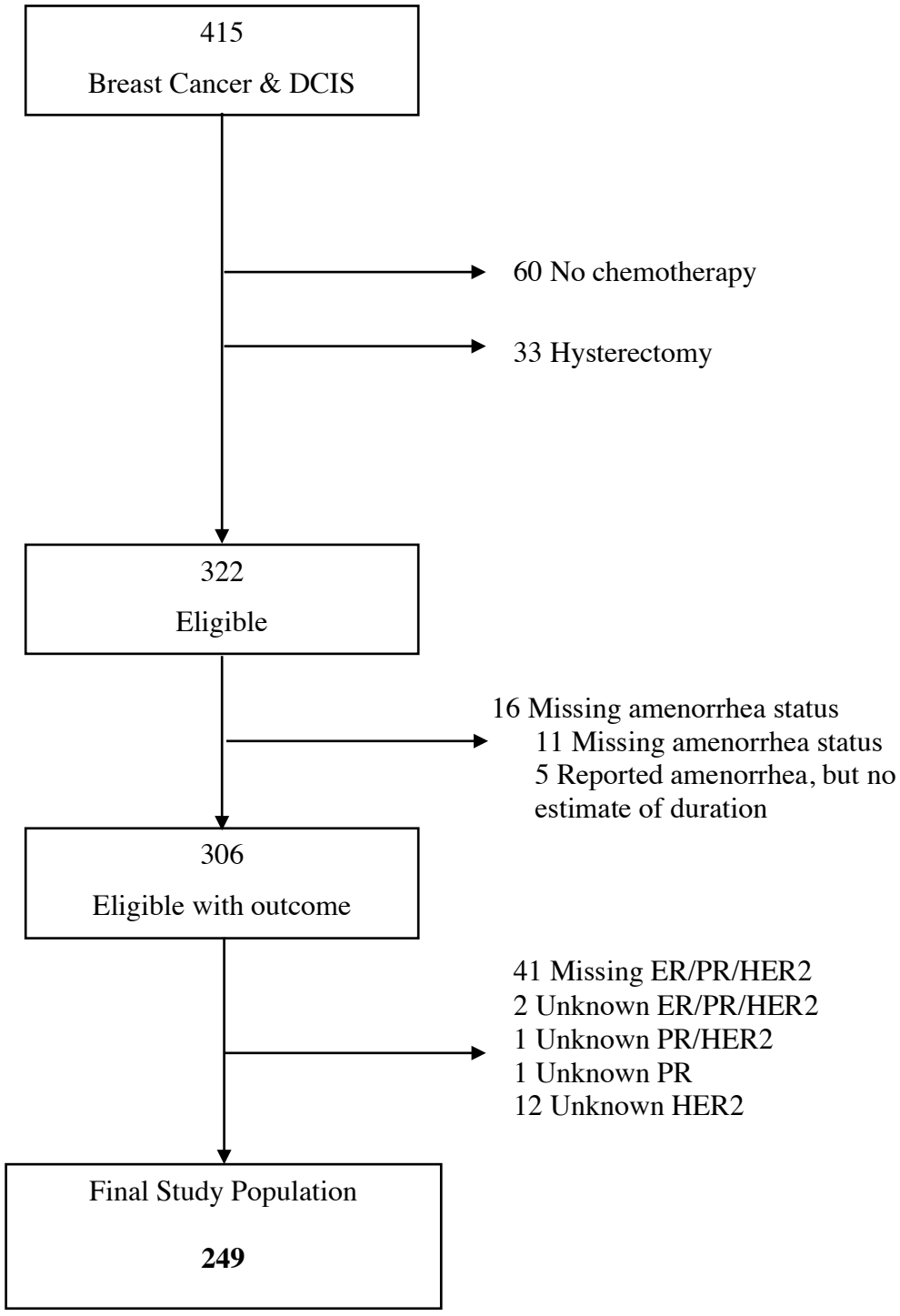
[b] Model was adjusted for age at diagnosis, age at menarche, BMI at diagnosis, oral contraceptive use, and cancer stage

[c] Model was adjusted for age at diagnosis, age at menarche, BMI at diagnosis, oral contraceptive use, cancer stage, tamoxifen, Herceptin, alkylating agents, topoismerase inhibitors, antimitotic inhibitors, and antimetabolites

[d] Model including women with AC chemotherapy regimen with or without a taxane and/or Herceptin. Adjusted for age at diagnosis, age at menarche, BMI at diagnosis, oral contraceptive use, cancer stage, tamoxifen, Herceptin, antimitotic inhibitors, and antimetabolites

## Figures

**Figure 1.** Population flowchart for study among premenopausal women diagnosed with breast cancer



## Appendix A: Supplementary Tables

**Supplemental Table 1.** Study population characteristics by receptor status among premenopausal women diagnosed with breast cancer (n= 249)

| | ER+ (n=138) | | ER- (n=111) | | PR+ (n=117) | | PR- (n=132) | | HER2+ (n=73) | | HER2- (n=176) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Age at diagnosis (years) | | | | | | | | | | | | |
| 20-29 | 35 | 25.4 | 23 | 20.7 | 32 | 27.4 | 26 | 19.7 | 23 | 31.5 | 35 | 19.9 |
| 30-35 | 103 | 74.6 | 88 | 79.3 | 85 | 72.6 | 106 | 80.3 | 50 | 68.5 | 141 | 80.1 |
| Race | | | | | | | | | | | | |
| White | 92 | 66.7 | 54 | 48.6 | 79 | 67.5 | 67 | 50.8 | 44 | 60.3 | 102 | 58.0 |
| Black | 38 | 27.5 | 42 | 37.8 | 31 | 26.5 | 49 | 37.1 | 23 | 31.5 | 57 | 32.4 |
| Other | 8 | 5.8 | 15 | 13.5 | 7 | 6.0 | 16 | 12.1 | 6 | 8.2 | 17 | 9.7 |
| Education | | | | | | | | | | | | |
| Some college, technical school, or less | 38 | 27.5 | 39 | 35.1 | 33 | 28.2 | 44 | 33.3 | 17 | 23.3 | 60 | 34.1 |
| College graduate | 49 | 35.5 | 33 | 29.7 | 40 | 34.2 | 42 | 31.8 | 21 | 28.8 | 61 | 34.7 |
| Some graduate school or graduate school | 51 | 37.0 | 39 | 35.1 | 44 | 37.6 | 46 | 34.8 | 35 | 47.9 | 55 | 31.3 |
| Urban/Rural classification at diagnosis | | | | | | | | | | | | |
| Non-metropolitan | 17 | 12.4 | 12 | 10.8 | 15 | 12.8 | 14 | 10.7 | 10 | 13.7 | 19 | 10.9 |
| Small metropolitan | 31 | 22.6 | 21 | 18.9 | 26 | 22.2 | 26 | 19.8 | 15 | 20.5 | 37 | 21.1 |
| Large metropolitan | 89 | 65.0 | 78 | 70.3 | 76 | 65.0 | 91 | 69.5 | 48 | 65.8 | 119 | 68.0 |
| Missing | 1 | | 0 | | 0 | | 1 | | 0 | | 1 | |
| Marital status at diagnosis | | | | | | | | | | | | |
| Yes | 102 | 73.9 | 80 | 72.1 | 88 | 75.2 | 94 | 71.2 | 56 | 76.7 | 126 | 71.6 |
| No | 36 | 26.1 | 31 | 27.9 | 29 | 24.8 | 38 | 28.8 | 17 | 23.3 | 50 | 28.4 |
| Household income in the past 12 months | | | | | | | | | | | | |
| Less than $25,000 | 19 | 14.0 | 13 | 11.8 | 18 | 15.7 | 14 | 10.7 | 8 | 11.1 | 24 | 13.8 |
| $25,000 to $50,000 | 20 | 14.7 | 28 | 25.5 | 13 | 11.3 | 35 | 26.7 | 12 | 16.7 | 36 | 20.7 |
| $50,000 to $75,000 | 29 | 21.3 | 18 | 16.4 | 25 | 21.7 | 22 | 16.8 | 14 | 19.4 | 33 | 19.0 |
| $75,000 to $100,000 | 25 | 18.4 | 22 | 20.0 | 23 | 20.0 | 24 | 18.3 | 14 | 19.4 | 33 | 19.0 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Greater than $100,000 | 43 | 31.6 | 29 | 26.4 | 36 | 31.3 | 36 | 27.5 | 24 | 33.3 | 48 | 27.6 |
| Missing | 2 | | 1 | | 2 | | 1 | | 1 | | 2 | |
| Current insurance status | | | | | | | | | | | | |
| No Insurance | 8 | 5.8 | 10 | 9.0 | 6 | 5.2 | 12 | 9.1 | 6 | 8.3 | 12 | 6.8 |
| Private | 112 | 81.8 | 92 | 82.9 | 98 | 84.5 | 106 | 80.3 | 59 | 81.9 | 145 | 82.4 |
| Public | 17 | 12.4 | 9 | 8.1 | 12 | 10.3 | 14 | 10.6 | 7 | 9.7 | 19 | 10.8 |
| Missing | 1 | | 0 | | 1 | | 0 | | 1 | | 0 | |
| BMI at diagnosis | | | | | | | | | | | | |
| Underweight | 1 | 0.8 | 2 | 2.0 | 1 | 0.9 | 2 | 1.7 | 1 | 2.6 | 2 | 1.2 |
| Normal | 70 | 53.8 | 44 | 44.0 | 57 | 50.9 | 57 | 48.3 | 3 | 7.9 | 81 | 50.0 |
| Overweight | 40 | 30.8 | 27 | 27.0 | 37 | 33.0 | 30 | 25.4 | 19 | 50.0 | 48 | 29.6 |
| Obese | 19 | 14.6 | 27 | 27.0 | 17 | 15.2 | 29 | 24.6 | 15 | 39.5 | 31 | 19.1 |
| Missing | 8 | | 11 | | 5 | | 14 | | 5 | | 14 | |
| Age at menarche (years) | | | | | | | | | | | | |
| ≤10 | 42 | 30.4 | 35 | 31.5 | 35 | 29.9 | 42 | 31.8 | 17 | 23.3 | 60 | 34.1 |
| 11-14 | 83 | 60.1 | 71 | 64.0 | 73 | 62.4 | 81 | 61.4 | 49 | 67.1 | 105 | 59.7 |
| ≥15 | 13 | 9.4 | 5 | 4.5 | 9 | 7.7 | 9 | 6.8 | 7 | 9.6 | 11 | 6.3 |
| Parity | | | | | | | | | | | | |
| 0 | 57 | 41.3 | 23 | 20.7 | 44 | 37.6 | 36 | 25.4 | 26 | 35.6 | 54 | 30.7 |
| 1 | 25 | 18.1 | 29 | 26.1 | 22 | 18.8 | 32 | 22.5 | 12 | 16.4 | 42 | 23.9 |
| 2 | 43 | 31.2 | 31 | 27.9 | 39 | 33.3 | 35 | 24.6 | 20 | 27.4 | 54 | 30.7 |
| 3 or more | 13 | 9.4 | 28 | 25.2 | 12 | 10.3 | 39 | 27.5 | 15 | 20.5 | 26 | 14.8 |
| Oral contraceptive use before diagnosis | | | | | | | | | | | | |
| Yes | 114 | 83.2 | 78 | 70.9 | 96 | 82.8 | 96 | 73.3 | 55 | 75.3 | 137 | 78.7 |
| No | 23 | 16.8 | 32 | 29.1 | 20 | 17.2 | 35 | 26.7 | 18 | 24.7 | 37 | 21.3 |
| Missing | 1 | | 1 | | 1 | | 1 | | 0 | | 2 | |
| Ever smoke before diagnosis | | | | | | | | | | | | |
| Yes | 30 | 21.7 | 21 | 18.9 | 22 | 18.8 | 29 | 22.0 | 16 | 21.9 | 35 | 19.9 |
| No | 108 | 78.3 | 90 | 81.1 | 95 | 81.2 | 103 | 78.0 | 57 | 78.1 | 141 | 80.1 |

*Note:* BMI = body mass index

**Supplemental Table 2**. Cancer characteristics by receptor status among premenopausal women diagnosed with breast cancer (n=249)

| | ER+ (n=138) | | ER- (n=111) | | PR+ (n=117) | | PR- (n=132) | | HER2+ (n=73) | | HER2- (n=176) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| **Cancer Characteristics** | | | | | | | | | | | | |
| Breast cancer subtype[a] | | | | | | | | | | | | |
| Luminal A | 98 | 71.0 | 4 | 3.6 | 86 | 73.5 | 16 | 12.1 | 0 | 0.0 | 102 | 58.0 |
| Luminal B | 40 | 29.0 | 1 | 0.9 | 31 | 26.5 | 10 | 7.6 | 41 | 56.2 | 0 | 0.0 |
| HER2-enriched | 0 | 0.0 | 32 | 28.8 | 0 | 0.0 | 32 | 24.2 | 32 | 43.8 | 0 | 0.0 |
| Triple-negative | 0 | 0.0 | 74 | 66.7 | 0 | 0.0 | 74 | 56.1 | 0 | 0.0 | 74 | 42.0 |
| BRCA 1 status | | | | | | | | | | | | |
| Positive | 3 | 3.8 | 18 | 31.0 | 5 | 7.6 | 16 | 22.9 | 3 | 6.7 | 18 | 19.8 |
| Negative | 75 | 96.2 | 40 | 69.0 | 61 | 92.4 | 54 | 77.1 | 42 | 93.3 | 73 | 80.2 |
| Missing | 60 | | 53 | | 51 | | 62 | | 28 | | 85 | |
| BRCA 2 status | | | | | | | | | | | | |
| Positive | 4 | 5.1 | 4 | 6.9 | 2 | 3.0 | 6 | 8.6 | 4 | 8.5 | 4 | 4.5 |
| Negative | 74 | 94.9 | 54 | 93.1 | 64 | 97.0 | 64 | 91.4 | 43 | 91.5 | 85 | 95.5 |
| Missing | 60 | | 53 | | 51 | | 62 | | 26 | | 87 | |
| Stage | | | | | | | | | | | | |
| 0 | 5 | 3.7 | 2 | 1.9 | 3 | 2.7 | 4 | 3.1 | 3 | 4.2 | 4 | 2.4 |
| 1 | 31 | 23.1 | 26 | 24.3 | 29 | 25.7 | 28 | 21.9 | 11 | 15.5 | 46 | 27.1 |
| 2 | 70 | 52.2 | 57 | 53.3 | 60 | 53.1 | 67 | 52.3 | 32 | 45.1 | 95 | 55.9 |
| 3 | 23 | 17.2 | 20 | 18.7 | 16 | 14.2 | 27 | 21.1 | 21 | 29.6 | 22 | 12.9 |
| 4 | 5 | 3.7 | 2 | 1.9 | 5 | 4.4 | 2 | 1.6 | 4 | 5.6 | 3 | 1.8 |
| Missing | 4 | | 4 | | 4 | | 4 | | 2 | | 6 | |
| **Treatment Characteristics** | | | | | | | | | | | | |
| Chemotherapy regimen | | | | | | | | | | | | |
| AC only | 15 | 10.9 | 15 | 13.5 | 13 | 11.1 | 17 | 12.9 | 6 | 8.2 | 24 | 13.6 |
| AC + taxane | 53 | 38.4 | 54 | 48.6 | 42 | 35.9 | 65 | 49.2 | 17 | 23.3 | 90 | 51.1 |
| AC + Herceptin | 3 | 2.2 | 2 | 1.8 | 2 | 1.7 | 3 | 2.3 | 4 | 5.5 | 1 | 0.6 |
| AC + taxane + Herceptin | 15 | 10.9 | 11 | 9.9 | 14 | 12.0 | 12 | 9.1 | 26 | 35.6 | 0 | 0.0 |
| Other | 52 | 37.7 | 29 | 26.1 | 46 | 39.3 | 35 | 26.5 | 20 | 27.4 | 61 | 34.7 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chemotherapy drug class [b] | | | | | | | | | | | | |
| Alkylating Agents | 128 | 36.6 | 103 | 35.8 | 109 | 36.6 | 122 | 35.9 | 69 | 35.4 | 162 | 36.6 |
| Topoisomerase Inhibitors | 99 | 28.3 | 92 | 31.9 | 84 | 28.2 | 107 | 31.5 | 59 | 30.3 | 132 | 29.8 |
| Mitotic Inhibitors | 105 | 30.0 | 79 | 27.4 | 88 | 29.5 | 96 | 28.2 | 60 | 30.8 | 124 | 28.0 |
| Antimetabolites | 18 | 5.1 | 14 | 4.9 | 17 | 5.7 | 15 | 4.4 | 7 | 3.6 | 25 | 5.6 |
| Missing | 0 | | 1 | | 0 | | 1 | | 0 | | 1 | |
| Tamoxifen | | | | | | | | | | | | |
| Yes | 122 | 88.4 | 12 | 10.8 | 104 | 88.9 | 30 | 22.7 | 38 | 52.1 | 96 | 54.5 |
| No | 16 | 11.6 | 99 | 89.2 | 13 | 11.1 | 102 | 77.3 | 35 | 47.9 | 80 | 45.5 |
| Herceptin | | | | | | | | | | | | |
| Yes | 27 | 19.7 | 18 | 16.4 | 25 | 21.4 | 20 | 15.4 | 42 | 57.5 | 3 | 1.7 |
| No | 110 | 80.3 | 92 | 83.6 | 92 | 78.6 | 110 | 84.6 | 31 | 42.5 | 171 | 98.3 |
| Missing | 1 | | 1 | | 0 | | 2 | | 0 | | 2 | |
| Radiation | | | | | | | | | | | | |
| Yes | 104 | 75.4 | 75 | 67.6 | 85 | 72.6 | 94 | 71.2 | 55 | 75.3 | 124 | 70.5 |
| No | 34 | 24.6 | 36 | 32.4 | 32 | 27.4 | 38 | 28.8 | 18 | 24.7 | 52 | 29.5 |
| Surgery | | | | | | | | | | | | |
| Mastectomy | 42 | 30.4 | 32 | 28.8 | 38 | 32.5 | 36 | 27.3 | 16 | 21.9 | 58 | 33.0 |
| Less than mastectomy | 96 | 69.6 | 79 | 71.2 | 79 | 67.5 | 96 | 72.7 | 57 | 78.1 | 118 | 67.0 |

[a] Luminal A (ER/PR +, HER2 -), Luminal B (ER/PR +, HER2 +), HER2-enriched (ER -, PR -, HER2 +), Triple-negative (ER-, PR-, HER2-)

[b] Not mutually exclusive