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Research Article

Lifestyle and Reproductive Factors Associated with Breast Cancer Risk in Young Women

Nicholas S Costantino[1], Teresa M Cox[2], Craig D Shriver[2] and Rachel E Ellsworth[3]*

[1]Clinical Breast Care Project, Chan Soon-Shiong Institute of Molecular Medicine at Windber, 620 Seventh Street, Windber, PA, USA

[2]Clinical Breast Care Project, Murtha Cancer Center, 8901 Wisconsin Ave, Bethesda, MD, USA

[3]Clinical Breast Care Project, Murtha Cancer Center, 620 Seventh Street, Windber, PA, USA

***Corresponding Author**: Rachel E Ellsworth, Clinical Breast Care Project, Murtha Cancer Center, 620 Seventh Street, Windber PA, USA.

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Abstract

Purpose: Breast cancer in young women (<40 years, YW) represents 5 - 7% of the breast cancer diagnoses each year. Because YW diagnosed with breast cancer have inferior outcomes to all other age groups, identification of risk factors for this population is critical.

Methods: Risk factors were evaluated in YW and with invasive breast cancer or benign breast conditions. Logistic regression modeling was used to determine odds ratios (OR) and analysis of covariance (ANCOVA) was used to determine the overall significance of including the variable of interest in a predictive regression model. Women 40 - 49 years were used as a comparison population.

Results: Risk factors for breast cancer in YW included age at first full term pregnancy (FFTP; OR 1.06; 95% CI 1.01, 1.12), duration (OR 1.09; 95% CI 1.04, 1.14) and age of initiation of oral contraceptive use (OR 0.93; 95% CI 0.87, 0.99), Hispanic ethnicity (OR 0.08; 95% CI 0.00, 0.40) and at least 90 minutes of physical activity per week (OR 0.44; 95% CI 0.24, 0.83). Age at initiation and duration of oral contraceptive use and physical activity were risk factors unique to YW, however, family history was not associated with increased risk in YW.

Conclusions: In YW, Hispanic ancestry is associated with decreased risk of breast cancer while later age at FFTP, earlier and longer use of oral contraceptives and decreased physical activity are associated with increased risk. FFTP, oral contraceptive use and physical activity have been associated with increased levels of estrogen within the breast, which may provide a microenvironment favoring tumor growth in a subset of YW. Strategies to minimize the impact of these factors may decrease breast cancer incidence in YW.

Keywords: *Young Women; Breast Cancer; Risk; Oral Contraceptives; Physical Activity*

Abbreviations

ANCOVA: Analysis of Covariance; CBCP: Clinical Breast Care Project; FFTP: First Full-Term Pregnancy; YW: Young Women

Introduction

Risk of breast cancer risk increases with age, with the highest incidence in women over age 65 and the lowest in women <40 years. Although young women (YW) have the lowest incidence of breast cancer (5 - 7%), this translates into >10,000 women diagnosed per year [1,2]. In addition, breast cancer in YW is associated with poor prognosis: tumors from YW are more likely to be larger, hormone receptor negative, poorly differentiated, and lymph node positive [3]. YW have shorter times to recurrence and distant metastasis with higher overall mortality than older patients and these disparities were greater in patients diagnosed with early, rather than late, stage breast cancer [3,4]. A recent study found that although ER+/HER2- tumors accounted for 49% of all tumors in YW ages 15 - 39, there was a significantly higher frequency of the more aggressive ER+/HER2+, ER-/HER2+ and ER-/HER2- tumors, when compared to women 40 - 49, or > 50 years [5].

Because breast cancer is a disease of aging, it is important to identify factors associated with increased risk in a subset of young women. Young age at diagnosis suggests a genetic component: positive family history of early onset breast cancer was strongly associated with increased risk in young women [6]. Pathogenic mutations in BRCA1, BRCA2 and TP53 were detected in 21% of women diagnosed < 30 years in North Western England [7] and 20% of African American women < 40 years living in Florida [8]. Non-genetic factors may also contribute to increased risk of breast cancer; for example, shorter duration of breastfeeding and higher waist-hip ratios have been associated with increased risk of the triple negative subtype of breast cancer that occurs at a significantly higher frequency in young compared to older women [5,9]. Reproductive factors such as earlier age at menarche, nulliparity and age at first full-term pregnancy (FFTP), have been associated with ER+HER2- tumors [10], which represent ~50% of tumors diagnosed in women < 40 years.

Although a number of breast cancer risk factors have been identified, age interactions have been detected. For example, nulliparity and obesity are associated with increased risk in postmenopausal women but decreased risk in premenopausal women [11]. To identify factors associated with increased breast cancer risk in young women, we evaluated reproductive and lifestyle factors in contemporary populations of women diagnosed with either invasive breast cancer or non-proliferative benign conditions < 40 years. To determine whether these factors were specific to young age rather than premenopausal status, results were compared to those for women age 40 - 49 years.

Materials and Methods

Patients were enrolled into the Clinical Breast Care Project at the breast clinics of Walter Reed National Military Medical Center, Washington DC, Anne Arundel Medical Center, Annapolis, MD or Joyce Murtha Breast Care Center, Windber, PA. All patients enrolled in the Clinical Breast Care Project (CBCP) met the following eligibility criteria: 1) adult over the age of 18 years, 2) mentally competent and willing to provide informed consent, and 3) presenting to the breast centers with evidence of breast disease. All subjects voluntarily agreed to participate and gave written informed consent. Once informed consent was granted, nurse researchers interviewed enrollees in person to collect over 500 fields of information regarding demographics, breast cancer history, reproduction, health history, and lifestyle choices [12]. Completed questionnaires were reviewed for quality assurance purposes and the data was entered in a manual dual-data entry fashion into the CBCP database.

The database was queried to identify all females enrolled in the CBCP between 2001 and 2014 who were diagnosed with invasive (n = 132) or benign (n = 370) breast conditions before age 40. Patients with invasive breast cancer included those diagnosed with stage I-IV tumors; patients with in situ disease were not included in this study. For the benign patients, patients diagnosed with conditions such as no abnormalities, fat necrosis, post-surgical changes, mastitis, subareolarabcess, microcalcifications, fibrocystic changes, stromal fibrosis, cysts, apocrine metaplasia, adenosis and fibroadenoma were included. Similar criteria were used to collect data for women 40 - 49 years (n = 264 benign, n = 451 invasive).

Fields evaluated included modifiable and non-modifiable risk factors. Presence of a family history was determined using the NCCN Familial Risk Assessment criteria [13]. Other factors included age at diagnosis, self-described ethnicity, age at menarche and menopausal status, with postmenopausal status defined as not having a period in > 1 year or being surgically menopausal, oral contraceptive use (age initiated and duration), parity (age at FFTP, number of children), breastfeeding, smoking, exercise and BMI.

Statistical analyses were carried out using R v 3.1.1 [14]. Logistic regression modeling was used to analyze the independent effects of explanatory variables on the odds of a patient having invasive breast cancer versus a non-proliferative benign condition. All models were adjusted for the confounding factor patient age at diagnosis, which was found to be predictive of invasive disease [OR 1.21, 95% CI (1.16, 1.28), $p < 0.001$] in univariate analysis. Odds ratios with 95% confidence intervals were calculated for each variable of interest. For continuous variables (age of menarche, age beginning and duration of oral contraceptive use, age of first pregnancy, number of children, and length of breast feeding), the odds ratio corresponds to the age-adjusted odds of having invasive disease versus a benign condition given a unit increase in the explanatory variable. For categorical variables (ethnicity, oral contraceptive use, parity, breastfeeding, smoking, exercise level, BMI group, and family history), the odds ratio represents the age-adjusted odds of having invasive disease as opposed to a

benign condition with respect to a reference category. Analysis of covariance (ANCOVA) was used to determine the overall significance of including the variable of interest in a predictive regression model. A p-value of 0.05 was used to define significance.

Results and Discussion

Over a thirteen year period, 132 women diagnosed with invasive breast cancer < 40 years enrolled in the CBCP. Thirteen of the invasive patients were diagnosed 1963-1999 and enrolled in the CBCP as long-term survivors; data from these patients for smoking, BMI and exercise were not included in the analyses as they may not accurately reflect time of diagnosis. All of the 370 YW with benign conditions enrolled in the CBCP at the time of diagnosis. Only one YW progressed from benign to invasive disease: a 34 year old African American with a moderate family history of breast cancer who had a biopsy of her left breast with no abnormalities detected in 2002 and an invasive ductal breast carcinoma in her right breast in 2006. Although all patients were diagnosed before age 40, benign women were significantly younger (29.7 years) at diagnosis compared to invasive patients (35.8 years; P < 0.001). Invasive patients were significantly more likely to be parous, menopausal, and obese and less likely to be of Hispanic ancestry, exercise at least 90 minutes/week, or to be current smokers. YW with invasive breast cancer were older at FFTP, used oral contraceptives an average of 45 months longer and breastfed an average of 5.5 months longer than their benign counterparts (Table 1).

	Benign (n = 370) n (%)	**Invasive (n = 132) n (%)**	**P-value[e]**
Age	29.65 ± 6.84	35.75 ± 3.60	<0.001
Family History			0.183
Yes	264 (76)	90 (70)	
No	82 (24)	38 (30)	
Ethnicity			0.001
African American	111 (31)	37 (28)	
Asian	16 (4)	4 (3)	
Hispanic	32 (9)	1 (1)	
Other	11 (3)	1 (1)	
European American	195 (53)	89 (67)	
Age menarche	12.62 ± 1.68	12.59± 1.54	0.422
Menopausal status			0.005
Premenopausal	363 (98)	122 (92)	
Postmenopausal	7 (2)	10 (8)	
Oral contraceptive use			0.065
Yes	270 (73)	107 (81)	
No	100 (27)	25 (19)	
Age began oral contraceptives	19.2 ± 3.64	19.3 ± 3.92	0.400
Length oral contraceptive use[a, b]	52.32± 53.34	97.48± 67.98	<0.001
Parous			<0.001
Yes	195 (53)	107 (81)	
No	175 (47)	25 (19)	
Age FFTP[c, d]	22.51 ± 4.54	24.69 ± 5.31	<0.001
Number live children	2.07± 1.07	2.03 ± 0.88	0.375
Breastfeed			0.543

Yes	126 (68)	73 (72)	
No	59 (32)	29 (28)	
Length breastfeed	9.52 ± 10.03	15.01 ± 17.62	0.048
BMI			0.011
< 18.5	5 (2)	2 (2)	
18.5 - 24.9	206 (58)	54 (46)	
25 - 29.9	96 (27)	32 (27)	
≥ 30	46 (13)	30 (25)	
Exercise			0.005
Never	129 (45)	36 (34)	
1 - 89 minutes/week	103 (36)	34 (32)	
≥ 90 minutes/week	53 (19)	36 (34)	
Smoking			0.032
Never	189 (64)	78 (68)	
Former	30 (10)	19 (16)	
Current	77 (26)	18 (16)	

Table 1: *Breast cancer risk factors in YW with benign and invasive breast diagnoses.*

[a]*Length of oral contraceptive use and breastfeeding measured in months; all other times in years*

[b]*For age began oral contraceptives, length oral contraceptive use, only those women who ever used oral contraceptives were included*

[c]*FFTP= first full-term pregnancy*

[d]*Age FFTP, breastfeeding and length or breastfeeding considered only in parous women*

[e]*p-values from Chi-square or Fisher's exact tests (categorical variables) and from Wilcoxon rank-sum or independent samples t-tests (continuous variables).*

Because patients diagnosed with benign conditions were significantly younger than those with invasive cancer, differences in risk factors between groups may be skewed (e.g. length of use or oral contraceptives may be lower in women with benign breast conditions because the women are, on average, younger than their invasive counterparts). To account for these differences, odds ratios were calculated after adjusting for age. Hispanic ethnicity was associated with a significantly lower risk of breast cancer in YW compared to those of European ancestry. When considering reproductive history, age of first oral contraceptive use had an inverse association with breast cancer risk, while duration of use and age at FFTP was associated with increased risk. Regular exercise (> 90 minutes/week) was associated with decreased risk (Table 2).

	OR (95% CI)[b]	**P-value[c]**
Age	1.21 (1.16, 1.28)	< 0.001
Family History		0.622
No	1 (Reference)	
Yes	1.13 (0.69, 1.85)	
Ethnicity		0.012
European American	1 (Reference)	

African American	0.93 (0.56, 1.52)	
Asian	0.60 (0.15, 1.97)	
Hispanic	0.08 (0.00, 0.40)	
Other	0.40 (0.02, 2.35)	
Age menarche	0.96 (0.84, 1.10)	0.605
Menopausal status		0.137
Premenopausal	1 (Reference)	
Postmenopausal	2.16 (0.79, 6.24)	
Oral contraceptive use		0.665
No	1 (Reference)	
Yes	1.13 (0.66, 1.96)	
Age began oral contraceptives	0.93 (0.87, 0.99)	0.031
Length oral contraceptive use	1.09 (1.04, 1.14)	<0.001
Parous		0.221
No	1 (Reference)	
Yes	1.41 (0.82, 2.47)	
Age FFTP	1.06 (1.01, 1.12)	0.024
Number live children	0.81 (0.61, 1.05)	0.112
Breastfeed		0.462
No	1 (Reference)	
Yes	1.23 (0.71, 2.17)	
Length breastfeed	1.02 (1.00, 1.05)	0.058
BMI[a]		0.294
18.5 - 24.9	1 (Reference)	
25 - 29.9	0.82 (0.47, 1.41)	
≥30	1.39 (0.75, 2.57)	
Exercise		0.036
Never	1 (Reference)	
1 - 89 minutes/week	0.56 (0.29, 1.06)	
≥90 minutes/week	0.44 (0.24, 0.83)	
Smoking		0.178
Never	1 (Reference)	
Former	1.30 (0.64, 2.59)	
Current	0.62 (0.32, 1.15)	

Table 2: *Age-adjusted risk of developing breast cancer < 40 years (n = 370 benign, n = 132 invasive).*

[a]*Given the small sample size (n = 7), underweight (BMI < 18.5) patients were not included in this analysis.*

[b]*Based on logistic regression modeling predictive of benign vs. invasive disease.*

[c]*Based on analysis of covariance (ANCOVA) comparing logistic regression models with and without the variable of interest.*

To determine whether these risk factors were specific to women < 40 years, similar comparisons were performed for women diagnosed 40 - 49 years (n = 264 benign, n = 451 invasive). Thirty-five women with invasive breast cancer were diagnosed prior to enrollment in the CBCP, and none have had a subsequent diagnosis of invasive breast cancer. As with the YW, Hispanic ancestry was protective and increasing age at FFTP was associated with increased risk. Age at initiation of oral contraceptive use and exercise were not associated with risk while family history, which was not associated with increased risk in YW, was associated with increased risk (Table 3).

	OR (95% CI)	P-value
	40 - 49 years	
Age	1.14 (1.08, 1.20)	< 0.001
Family History		< 0.005
Yes	1 (Reference)	
No	1.74 (1.19, 2.56)	
Ethnicity		0.033
European American	1 (Reference)	
African American	0.80 (0.55, 1.18)	
Asian	0.92 (0.35, 2.58)	
Hispanic	0.29 (0.13, 0.64)	
Other	0.64 (0.12, 3.51)	
Age menarche	0.91 (0.83, 1.00)	0.056
Menopausal status		0.205
Premenopausal	1 (Reference)	
Postmenopausal	1.34 (0.86, 2.11)	
Oral contraceptive use		0.675
No	1 (Reference)	
Yes	1.08 (0.73, 1.58)	
Age began oral contraceptives	1.03 (1.00, 1.07)	0.083
Length oral contraceptive use	1.02 (1.00, 1.05)	0.095
Parous		0.067
No	1 (Reference)	
Yes	0.70 (0.47, 1.02)	
Age FFTP	1.06 (1.03, 1.10)	< 0.001
Number live children	0.90 (0.75, 1.09)	0.282
Breastfeed		0.482
No	1 (Reference)	
Yes	1.14 (0.79, 1.65)	
Length breastfeed	1.00 (0.98, 1.01)	0.532
Lifestyle Choices		
BMI[a]		0.159
18.5 - 24.9	1 (Reference)	
25 - 29.9	0.81 (0.56, 1.18)	
≥ 30	1.22 (0.82, 1.83)	

Exercise		0.843
Never	1 (Reference)	
1 - 89 minutes/week	0.95 (0.62, 1.45)	
≥ 90 minutes/week	0.88 (0.56, 1.36)	
Smoking		0.073
Never	1 (Reference)	
Former	1.49 (0.96, 2.35)	
Current	0.81 (0.52, 1.26)	

Table 3: *Age-adjusted risk of developing breast cancer 40 - 49 years (n = 264 benign, n = 451 invasive).*

[a]Given the small sample size (n = 6), underweight (BMI < 18.5) patients were not included in this analysis.

Breast cancer in young women is associated with increased mortality, higher treatment costs and unique physical and psychosocial consequences. To develop effective risk reduction strategies, tumor promoting factors relevant to women < 40 must be identified. Age at FFTP and Hispanic ancestry showed similar effects in both age groups studied here, while age at initiation and duration of oral contraceptive use and physical activity were risk factors specific to YW. In contrast, family history was associated with increased risk in women 40 - 49 years but not YW.

Age at FFTP has long been recognized as a general risk factor for breast cancer, with a linear or 3.5% increase in relative risk for each yearly increase in age at FFTP [15,16]. Although one study failed to find an association between risk and age at FFTP in women < 40 years [17], a second study did detect increased risk (incidence rate ratio 1.36; 95% CI 1.27, 1.46) for women with age at FFTP > 25 years compared to those with FFTP < 25 years. In addition, this risk was quantitative, increasing with age [11]. In our study, we found that age at FFTP was a risk factor across both age groups.

Overall breast cancer incidence is lower in Hispanic (91.9/100,000) compared to non-Hispanic Black (124.3/100,000) and non-Hispanic White (128.1/100,000) women [1], and this decrease has been attributed to Hispanic women engaging in protective behaviors such as having more children and at an earlier age [18]. The 4-Corners Breast Cancer Study reports a 1.3-fold decrease in incidence in breast cancer in Hispanic compared to non-Hispanic white women age 30 - 50 years [19]. Within premenopausal controls, Hispanic women were more likely to have an earlier age at FFTP, have more children, have an earlier age at menarche, have no history of oral contraceptive use or breastfeeding and do not engage in regular physical activity. The population attributable risk for established breast cancer risk factors was lower in Hispanic women (36.4%) compared to non-Hispanic white women (75.4%) [19]. Within the CBCP, the only risk factor that differed significantly in Hispanic women was number of children, which was lower than in other populations; thus other, as yet undetected factors may confer protection within Hispanic women.

In the United States, use of oral contraceptives is widespread, with 82% of sexually active women aged 15 - 44 having used oral contraceptives [20]. In a meta-analysis evaluating the effect of oral contraceptives on breast cancer risk, any use of oral contraceptives was associated with slightly increased breast cancer risk (OR 1.08; 95% CI 1.00 - 1.17), without dependence on duration. A linear relationship was detected between age of initiation of oral contraceptives and age at diagnosis [21], with an odds ratio of 1.3 (95% CI 1.0 - 1.8) for those who began using oral contraceptives within five years of menarche [22]. Time since last use was inversely associated with risk and at 10 years after discontinuation, risk returns to the same levels as women who never used oral contraceptives [23]. When data from only premenopausal women were considered, the risk associated with oral contraceptive use was higher (OR 1.19; 95% CI 1.28 - 1.62) than when pre- and postmenopausal women were considered together [24]. In a population of young women (age 20 - 44), lifetime use of oral contraceptives > 15 years was associated with increased risk and this risk was stronger in women < 40 years [25]. In our study, mean age at initiation of oral contraceptives was significantly lower (19.3 years) for YW compared to women 40 - 49 years (21.3 years), thus contributing to increased risk in YW. Attenuation in risk in women 40 - 49 may reflect time since last use, as the median times since

cessation were 17 years, suggesting that the risk associated with oral contraceptive use for > 50% of women 40 - 49 years had diminished, while in YW with a median time of 7 years since cessation, effects from the oral contraceptives remain.

Physical activity is a protective factor against breast cancer: in a meta-analysis that included > 116,000 breast cancer cases, individuals with the highest physical activity levels had a summary relative risk of 0.88 (95% CI 0.85, 0.92) for all cancers, and risk reduction increased with increasing levels of activity. Women engaging in vigorous activity > 5 h/week may enjoy an 18% risk reduction compared to those with low levels of physical activity [26]. In our study, we detected a significant protective effect in YW who exercised > 90minutes/week; however this relationship was not detected in women 40 - 49. This inability to detect a relationship between risk and physical activity may reflect the way in which exercise data was collected in the CBCP: frequency (never, < 1 time/week, 1 - 3 times/week or > 3 times/week) and length (< 15 minutes, 15 - 20 minutes, 20 - 30 minutes or > 30 minutes) of exercise/week were recorded but not exercise intensity and type of activity. Given these parameters, exercise was classified into never, 1 - 89 minutes or ≥ 90 minutes/week. Most studies investigating the effect of physical activity on breast cancer found that the amount of exercise between women with the highest and lowest activity levels ranged from 3 to 7 hours/week. As we could not stratify women exercising ≥ 90 minute/week into more precise intervals, significant differences in risk may be underestimated in YW and masked in women 40 - 49 years.

Having a moderate or strong family history of breast or ovarian cancer was not associated with increased risk in YW, in contrast to a number of other studies which demonstrate that breast cancer risk increases by number and relationship to affected family members with an approximately two-fold increase in risk associated with a family history [11,27-29]. Most studies have found that this risk decreases with age, although one study found no significant age interaction [11]. In our study, the OR for family history was not significant for YW, but was for women 40 - 49 years. Although this difference may be attributable to small samples size of YW with invasive disease, family history in YW with benign diagnoses (24%) was significantly higher (P = 0.002) than in women 40 - 49 years with benign conditions (18%). The YW with benign conditions in this study, seen within a breast clinic, may represent a bias sample set and thus obfuscate the effect of family history in YW.

As noted above, the small number (n = 132) of YW with invasive breast cancer may limit the ability to detect significant associations with risk factors, including family history. Small sample sizes may also have affected associations with self-described ethnicity: one strength of this study is that African American women, frequently underrepresented in research protocols, accounted for ~30% of the patients; the numbers of women of Hispanic (7%) and Asian ancestry (4%), however, were small. In conjunction, the terms Hispanic and Asian are used to represent heterogeneous populations, who may have differences in tumor etiology. Future efforts to enrich for these populations and to more precisely determine ancestry may improve our understanding of how ethnicity affects early-onset breast cancer. Finally, women with benign breast conditions were used as controls in this study; however, these women may not have the same characteristics as disease-free controls, which may underestimate overall risk. It is important to note that less than 1% of benign patients (n = 1 YW, n = 1 40 - 49 years) were later diagnosed with invasive breast cancer, and because the majority of women < 40 years do not participate in routine mammographic screening, the use of benign patients allowed us to have a robust comparison for YW.

Conclusion

Factors associated with risk of breast cancer in YW include Hispanic ethnicity, age at FFTP, oral contraceptive use and physical activity. Of these, being Hispanic and age at FFTP are also associated with risk in women 40 - 49 years, while age at initiation and length of oral contraceptive use and physical activity were risk factors specific to YW. Most of these factors influence estrogen levels within the breast, which may facilitate tumorigenesis by stimulating cellular proliferation, generation of genotoxic metabolites through estrogen metabolism and inactivation of tumor suppressor genes [30]. Although these factors are associated with increased risk, the number of YW diagnosed with breast cancer each year is small, thus identification of which women are most affected by these risk factors is critical. These efforts will allow for the development of risk reduction strategies, such as alternate methods of contraception and regular physical activity, to decrease the incidence of early-onset breast cancer.

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Conflict of Interest

The authors have no conflicts of interest.

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