Title:

Reproductive factors, age at maximum height, and risk of three histologic types of breast cancer

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ABSTRACT

Numerous studies have evaluated the association between factors related to maturation and reproduction and breast cancer risk, but few have assessed how these factors are related to different histologic types of breast cancer among postmenopausal women. We used polytomous logistic regression to assess the effect of age at maximum height and reproductive factors on risk of invasive breast cancer by histologic type in three case groups (524 ductal, 324 lobular, 196 ductal-lobular) and 469 controls enrolled in a population-based case-control study of women aged 55-74 years residing in the Seattle-Puget Sound region of Washington State (2000–2004). Histologic type was determined by a centralized tissue review for 83% of cases. Age at menarche and age at maximum height were inversely associated with risk of ductal-lobular carcinoma (p-value for trend=0.04 for both exposures), but not ductal or lobular carcinoma. Relative to nulliparous women, parous women had a 50% reduced risk of all histologic types of breast cancer. We observed similar increases in risk across histologic types associated with having a first live birth at ≥30 years of age compared to ≤19 years of age. Compared to parous women who never breastfed, those who breastfed had a reduced risk of ductal carcinoma (odds ratio=0.7, 95% confidence interval: 0.5-0.9), but not lobular or ductal-lobular carcinoma. Further exploration of breast cancer risk by histology is merited in order to understand differences in the etiology of ductal, lobular, and ductal-lobular carcinoma.

INTRODUCTION

It is well established that some reproductive factors, including age at menarche, age at first full-term pregnancy, number of live births, and breastfeeding are related to a woman's risk of breast cancer (1-4). There is also evidence that age at maximum height, as an indicator of the timing of the pubertal growth peak, is associated with a woman's risk of breast cancer (5-9). One mechanism through which all of these maturation and reproductive exposures influence breast cancer risk is their impact on lifetime number of ovulatory cycles a woman experiences. The number of cycles a woman experiences influences her lifetime exposure to endogenous ovarian hormones, which is strongly related to breast cancer risk (2, 10). Additionally, both pregnancy and breastfeeding induce the differentiation of breast epithelial cells making them less susceptible to carcinogenic insults (11-13).

While numerous studies have evaluated the relationship between maturation and reproductive factors and breast cancer risk, few have assessed how they are related to different histologic types of breast cancer among postmenopausal women, the age group that comprises the majority of new breast cancer diagnoses. Although there is evidence that ductal and lobular tumors have molecular and pathologic differences, as well as differences in clinical characteristics (14-21), few studies have examined how factors relating to maturation and reproduction may impact risk of these histologic types differently (6, 22-28). Comparing results across these studies is challenging since different studies focused on different reproductive factors and many were heterogeneous regarding menopausal status of the study groups and classification of histologic case groups. Consequently, in an effort to further elucidate the differences in risk factors for ductal, lobular, and ductal-lobular breast carcinomas, we evaluated the associations of several maturation and reproductive factors with different histologic types of breast cancer using data from a recently completed population-based case-control study of postmenopausal breast cancer that involved a centralized pathology review. We included a histopathologic review of all available tissue samples in this study in order to accurately and consistently categorize cases by histologic type of invasive breast carcinoma.

METHODS

We utilized data from the Seattle Area Hormone and Reproductive Epidemiology Breast Cancer Study (SHARE), which is a population-based case-control study of invasive ductal, invasive lobular, and invasive ductal-lobular breast carcinoma among women 55-74 years of age living in the Seattle-Puget Sound region (King, Pierce, and Snohomish Counties). This study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board and its methods have been described in detail elsewhere (29).

Cases

Cases were identified through the Cancer Surveillance System (CSS), a population-based cancer registry that is part of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. All women 55-74 years of age who were diagnosed with a primary invasive breast cancer from January 1, 2000 to April 31, 2004, who did not have a previous history of *in situ* or invasive breast cancer, and who had a landline home telephone were eligible for consideration as cases for this study. All lobular and ductal-lobular cases that met the eligibility criteria were approached to be part of the study. Since ductal cancer is the most common type of breast cancer (accounting for 70-75% of all cases), only a random 25% of ductal cases who met the eligibility criteria were contacted to be part of the study. Ductal cases were frequency-matched to the combined lobular and ductal-lobular group 1:1 by five-year age groups. A total of 1,251 cases were identified, and 83% of them were interviewed (524 ductal, 324 lobular, and 196 ductal-lobular cases). The reasons for eligible cases not being interviewed included refusal by the case or unknown location of the case (14%), death prior to interview (2%), and the case's physician not allowing his/her patient to be contacted for study participation (1%).

This study involved a centralized review of pathology reports for all cases and a centralized review of tumor tissue blocks for those cases with available tissue. A two-tiered process for assigning histologic type was used. Tumor tissue specimens from 869 cases (83%) were ascertained from local hospitals and centrally reviewed by pathologists in the Porter Laboratory at the Fred Hutchinson Cancer Research Center (FHCRC). Ductal and lobular tumors were classified based on the recommendations of the World Health Organization (WHO) (30). Ductal-lobular cases included cases with two separate areas of invasive ductal and invasive lobular tumors in the same breast and cases with one tumor with both

ductal and lobular features. One of two pathologists assessed the histology of a case based on the review of all slides and the diagnostic criteria. All slides then underwent a second histology review by another study pathologist and any discrepancies were decided by consensus review or sent for review by a consultant pathologist. There were 61 cases with discrepancies between study pathologists or between the review of pathology reports and the categorization based on tumor tissue review. These cases were reviewed by a consultant pathologist to determine a final histology category. For the 869 cases with available tumor tissue, the final histology classifications were made based on the tumor tissue review. When comparing the histology classifications based on tumor tissue review to those based on the review of pathology reports, there was 94% agreement (kappa statistic = 0.91).

For the 175 cases for whom we could not obtain tissue, the final histologic classification was based upon a review of pathology reports conducted by trained abstractors. If there were multiple pathology reports for a case (e.g. a biopsy report and a lumpectomy report), then the histology from the tumor specimen with the largest invasive component was given priority for the final histology classification. Again, cases were classified as ductal-lobular only if there was documentation that the tumor contained both invasive ductal and invasive lobular components. Cases with only invasive ductal tumors or only invasive lobular tumors were classified as ductal and lobular, respectively, regardless of the presence of any histologic type of *in situ* carcinoma. Overall, there were 61 cases with both invasive ductal carcinoma and lobular carcinoma *in situ* who were classified as ductal cases and 63 cases with both invasive lobular carcinoma and ductal carcinoma *in situ* who were classified as lobular cases.

Controls

Population-based controls who were female residents of King, Pierce, and Snohomish counties were identified through random digit dialing (RDD) using the Mitosky-Waksberg method with a clustering factor of 5 (31). Using one-step recruitment, controls were frequency-matched 1:1 to the combined lobular and ductal-lobular case group by age (5-year age groups) and reference year (31, 32). Among the total of 29,735 random telephone numbers that were called, there were 9,876 that were confirmed residential numbers or assumed to be residential numbers, and 87% of these numbers completed the screening questions for study eligibility. A total of 660 women 55-74 years of age who had never been diagnosed with invasive or *in situ* breast cancer were identified as eligible controls and 469 (71%) were interviewed.

Data Collection

All cases and controls provided written informed consent and completed an approximately 90 minute in-person interview with the assistance of a trained interviewer. The interview collected demographic, anthropometric, reproductive, contraceptive, medical history, and lifestyle information for the time period prior to the reference date. For cases, the reference date was the date of breast cancer diagnosis and for controls, the reference date was assigned to reflect the distribution of reference dates among the cases.

With respect to our primary exposures of interest, age at menarche was grouped as ages 8-11, 12-13, and ≥14 years. Age at maximum height was grouped as ages ≤14, 15-16, and ≥17 years. The interval between age at menarche and first live birth was grouped as 1-8, 9-12, and ≥13 years based on the tertile distribution of this variable. Number of live births was classified as 1, 2, 3, and ≥4. Age first breastfed was categorized as never, ≤19, 20-24, 25-29, and ≥30 years of age. Age last breastfed was categorized as never, ≤24, 25-29, 30-34, and ≥35 years of age. Age at first live birth and age at last live birth used the same age groupings as age first breastfed and age last breastfed, respectively. Ever breastfeeding was defined as breastfeeding for at least one month. Total breastfeeding was defined as total lifetime duration of breastfeeding measured in months and was grouped into the following categories: never, <1, 1.0-5.9, 6.0-11.9, 12.0-23.9, and ≥24.0 months.

Data Analysis

Polytomous logistic regression was used to compare ductal, lobular, and ductal-lobular cases to controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed as estimates of the relative risk, and all variables were modeled categorically. Tests for non-linearity were conducted for variables with greater than two categories using a grouped linear term. For those variables that did not significantly depart from linearity, a test for linear trend was conducted. The never or zero variable category was excluded from the trend tests. All tests were two-sided and p-values of <0.05 were considered to be statistically significant. All analyses were adjusted for age (5-year age groups) and reference year. In addition, analyses of the relationships between ever breastfeeding and duration of breastfeeding and breast cancer risk were adjusted for number of live births because it was *a priori* considered to be a confounder of these relationships.

The variables listed in Table 1, with the exception of estrogen and progesterone receptor status, were systematically assessed as potential confounders of the relationships between age at maximum height and reproductive characteristics and risk of ductal, lobular, and ductal-lobular breast carcinoma. In addition, the following variables were assessed as potential confounders: age at menopause (<47, 47-50, 51-53, ≥54 years); income (<$20,000, $20-34,000, $35-69,000, ≥$70,000); marital status (married/living with male or female partner, divorced/separated, widowed, single never married); average grams of alcohol consumed per week (0, <24.75, ≥24.75); and smoking (ever, never). The maturation and reproductive factors of interest were also assessed as potential confounders of each other. A covariate was considered to be a confounder if it consistently altered the ORs across the covariate's categories for each histologic type by at least 10%, if the direction of the effect of the covariate on the exposure of interest was plausible, and if the covariate was not another characteristic of the exposure of interest (e.g. age at first breastfed with a category for those who never breastfed and duration of breastfeeding with a never category). None of the variables listed above or the reproductive factors of interest were found to be confounders of the relationship between age at menarche, age at maximum height, parity, number of live births, ever breastfed, or duration of breastfeeding and development of ductal, lobular, or ductal-lobular breast carcinoma. Age at first live birth and age first breastfed were not adjusted for each other because the two variables are highly correlated. Similarly, age at last live birth and age last breastfed were not adjusted for each other. Thus, all of our final analyses were adjusted for age and reference date, and analyses of ever breastfed and duration of breastfeeding were additionally adjusted for number of live births.

For covariates hypothesized *a priori* as possible modifiers of effects of interest an interaction term was formed and tested. If the interaction term was significant ($p<0.05$) for all histologic types when added to a model with the variable of interest, the covariate, and the matching variables, then the covariate was considered an effect modifier. For age at menarche the following variables were considered as potential effect modifiers: number of live births, age at first live birth, ever breastfed, duration of breastfeeding, and age first breastfed. For number of live births, the variables considered were age at first live birth, ever breastfed, duration of breastfeeding, and age first breastfed. The potential effect modifiers considered for age at first live birth, age at last live birth, age first breastfed, and age last breastfed were number of live

births and each other. For ever breastfed and duration of breastfeeding we considered: number of live births, age at first and last live birth, and age first and last breastfed. We did not observe statistically significant effect modification based on likelihood ratio testing. All analyses were performed using Stata 9.2 (StataCorp LP, College Station, Texas).

Analyses of age at menarche, age at maximum height, and parity were conducted among all study women. Analyses of the interval between age at menarche and age at first live birth, number of live births, age at first live birth, age at last live birth, ever breastfed, duration of breastfeeding, age first breastfed, and age last breastfed were conducted among women who reported having one or more live births (n=456 ductal, 277 lobular, 165 ductal-lobular, and 431 controls). Differences in risk estimates across histologic type were assessed using p-values from unconditional logistic regression models that treated either ductal cases or lobular cases as the reference category and excluded controls. Specifically, a variable was created with ductal cases as the reference group and lobular and ductal-lobular cases as separate comparison groups as well as a variable with lobular cases as the reference group and ductal and ductal-lobular cases as comparison groups. These variables were then used in the unconditional logistic regression models from the main analyses to obtain p-values for the difference in risk estimates between the case groups.

RESULTS

Ductal-lobular cases were somewhat younger and more likely to have a BMI <25.0 kg/m^2 compared to ductal cases, lobular cases, or controls (Table 1). Lobular and ductal-lobular cases were somewhat more likely to have graduated from college than ductal cases or controls. Regardless of histologic type, cases were more likely than controls to have a first degree family history of breast cancer, to have experienced natural menopause, and to be current users of combined estrogen and progestin postmenopausal hormones. The majority of ductal, lobular, and ductal-lobular cases had tumors that were estrogen receptor (ER) positive and progesterone receptor (PR) positive. The ductal-lobular case group contained the greatest percentage of ER and PR positive tumors (82.6%); whereas, the ductal case group contained a greater percentage of ER and PR negative tumors (14.0%) than either the lobular

(3.2%) or ductal-lobular (4.1%) case groups (Table 1). Because of small numbers, the results stratified by ER and PR status are not presented here.

Age at menarche was not related to risk of ductal or lobular carcinoma, but was inversely associated with risk of ductal-lobular carcinoma (p-value for trend=0.04, Table 2). We compared the risk estimates for each histologic group to determine if they were statistically different than the risk estimates for other histologic groups. We found that the risk estimate for menarche at 8-11 years of age compared to ≥14 years of age for ductal-lobular carcinoma was statistically different than the risk estimate for lobular carcinoma (p=0.02) and that the difference between the risk estimates for ductal-lobular and ductal carcinoma approached a statistically significant difference (p=0.05). Women who reached their maximum height at an earlier age had an increased risk of ductal-lobular carcinoma (p-value for trend=0.04) compared to controls, however the individual risk estimates for ductal-lobular carcinoma were not statistically different than the risk estimates for ductal or lobular carcinoma. We also observed a suggestion of an association between age when maximum height was attained and risk of ductal carcinoma compared to controls, but this association was within the limits of chance (p-value for trend=0.10). The interval between age at menarche and first live birth was not related to risk of ductal, lobular, or ductal-lobular carcinoma (Table 3).

Compared to nulliparous women, parous women had a fifty percent reduction in risk of ductal, lobular, and ductal-lobular carcinoma (Table 2). Sixty to eighty percent reductions in risk of ductal, lobular, and ductal-lobular carcinoma were observed among women who had 2, 3, or ≥4 live births compared to women who had 1 live birth; however, most of these risk estimates were within the limits of chance (Table 3). Women who had their first live birth when they were ≥30 years of age had increased risks of ductal, lobular, and ductal-lobular carcinoma compared to women who had their first live birth at ≤19 years of age; however, this association was within the limits of chance for ductal and lobular carcinoma. An older age at last live birth was associated with an increased risk of ductal-lobular (p-value for trend=0.01), but not with ductal or lobular carcinoma. When comparing the risk estimates for the histologic case groups, we found no statistically significant differences between the risk estimates for each histologic type for parity, number of live births, age at first live birth, and age at last live birth.

Compared to parous women who never breastfed, those who ever breastfed had a reduced risk of ductal carcinoma (OR=0.7, 95% CI: 0.5-0.9, Table 4), but not of lobular or ductal-lobular carcinoma, after adjusting for number of live births. However, no statistically significant differences between the risk estimates for each histologic type were observed. The decrease in risk of ductal carcinoma associated with breastfeeding was limited to women who breastfed for one month or longer, though no trend was observed (p-value for trend=0.43). The risk estimate for ductal carcinoma associated with breastfeeding for at least 24 months (OR=0.6, 95% CI: 0.3-1.0) was significantly different ($p<0.001$) than the risk estimate for ductal-lobular carcinoma (OR=1.9, 95% CI: 1.0-3.6). Both the ages when women first breastfed and last breastfed were unrelated to risk of ductal carcinoma and lobular carcinoma. However, risk of ductal-lobular carcinoma increased with age last breastfed (Table 4, p-value for trend=0.004). Specifically, women who were ≥35 years of age when they last breastfed had a 2.3-fold (95% CI: 1.2-4.4) increased risk of ductal-lobular carcinoma compared to those who never breastfed and this risk estimate was significantly different (p=0.01) than the risk estimate for ductal carcinoma (OR=1.1, 95% CI: 0.6-1.9).

DISCUSSION

The results from this analysis should be considered within the context of the limitations of this study. Among the eligible cases, 83% were interviewed and among eligible controls, 71% were interviewed. If women who declined to be interviewed were different than those who participated with respect to the maturation and reproductive exposures of interest, then the results could be biased. However, an analysis of potential non-response bias from a previous case-control study of breast cancer found that, with the exception of height, there was little impact on the risk estimates when adding available data from non-respondents (33). Exposure information was gathered via self-report and required the participants to remember some maturation and reproductive events that occurred many years earlier. In an effort to improve the accuracy of responses, a life calendar was used to chart important events in a woman's life. If there was inaccurate recall, it is unlikely that it would differ by histologic case group and we expect that the resultant bias would be non-differential and thus bias our risk estimates toward the null. Additionally, tumor tissue was not obtained for 17% of cases and so histologic classification of these cases was based only on a centralized review of pathology reports.

However, this difference is unlikely to bias our results appreciably because there was 94% agreement between the histology classification made from the tissue review and from the pathology report review for the 869 cases for whom both sources of data were available.

This is the first study to include a histopathologic review of tissue specimens and a centralized review of pathology reports, which allowed us to classify ductal-lobular tumors as those containing both an invasive ductal and invasive lobular component. In contrast, when classification is based on *International Classification of Diseases for Oncology* (ICD-O) codes, a ductal-lobular tumor (ICD-O histologic code 8522) is only required to have one component, either ductal or lobular, that is invasive (34). For instance, in studies using ICD-O codes to classify tumors, a tumor with an invasive ductal and a lobular *in situ* component, as well as a tumor with an invasive lobular and a ductal *in situ* component are both classified as ductal-lobular. Additionally, some prior studies that examined histologic type of breast cancer by ICD-O codes included ductal-lobular tumors in the same group as invasive lobular tumors (ICD-O histologic code 8520) (6, 23, 24). Therefore, for both of the above reasons, our approach for evaluating ductal-lobular tumors was unique and provided an opportunity to assess associations that may have been obscured in other studies due to the heterogeneity of the tumors included in the ductal-lobular category.

Both age at menarche and age at maximum height are markers of puberty, a time during which the breast is undergoing rapid development, and our study suggests that these ages are more strongly associated with risk of ductal-lobular carcinoma than with risk of ductal or lobular carcinoma. Although few of the case-case comparisons yielded statistically significant differences, this could be due to the relatively small sample size in the ductal-lobular case group, which limited our power to detect a difference in ductal-lobular as compared to ductal or lobular risk estimates. While we found that age at menarche was inversely associated with risk of ductal-lobular carcinoma, but not ductal or lobular carcinoma, other studies of primarily or only postmenopausal women have had conflicting results. Two studies found a decreased risk of lobular carcinoma and not ductal carcinoma associated with a later age at menarche (6, 23), another found a slightly stronger decreased risk associated with ductal rather than lobular carcinoma (24), and a fourth study found a similar decreased risk for both ductal carcinoma and lobular carcinoma (25). One of these studies excluded ductal-lobular tumors (25), while the others

classified histology based on ICD-O codes, but combined the ICD-O categories for invasive lobular and ductal-lobular tumors because when assessed separately, there were no significant differences between the two categories (6, 23, 24). In the only other study to our knowledge that assessed age at maximum height as a risk factor for breast cancer by histologic type among older women, Li *et al.* found an inverse association with risk of ductal, but not lobular carcinoma; whereas, we found that age at maximum height was inversely associated with risk of ductal-lobular carcinoma, but not associated with risk of ductal or lobular carcinoma (6). It is difficult to compare our ductal-lobular results relating to reproductive factors and age at maximum height to prior studies because previous studies combined the ICD-O categories for invasive lobular and ductal-lobular tumors (6, 23, 24), rather than separately categorizing ductal, lobular, and ductal-lobular tumors via a centralized tumor tissue review.

There is also conflicting evidence regarding differences in risk of breast cancer by histologic type according to other reproductive factors including parity, number of live births, and age at first live birth. Our results suggest that parous women have a similar reduction in breast cancer risk across ductal, lobular, and ductal-lobular groups compared to nulliparous women, which is consistent with one previous report (25), but conflicts with another study that did not find an association between parity and risk of ductal or lobular carcinoma (24). We observed a suggestion of a similar risk reduction across histologic groups among women having two or more live births compared to those having one live birth. Li *et al.* found similar decreased risks of ductal and lobular carcinoma for women having four or more full-term births compared to those having one full-term birth (24). However, another study of older women found that having two or more births compared to one birth was associated with a decreased risk of ductal carcinoma, but not lobular carcinoma (25). The majority of studies examining age at first live birth among primarily postmenopausal women have found a slightly stronger positive association with lobular carcinoma than ductal carcinoma for increasing age at first live birth, however the differences by histology were not statistically significant (6, 23, 25). Our study, along with one other among postmenopausal women (24), found similar increases in risk across histologic types associated with having a first live birth at ≥30 years of age compared to ≤19 years of age.

To our knowledge, only one other published study has examined the effect of breastfeeding on risk of different histologic types of breast cancer among postmenopausal women and it found a reduced

risk of ductal carcinoma, but not lobular carcinoma among women who breastfed for at least 24 months compared to those who never breastfed, after accounting for number of live births (24). We found that ever breastfeeding was associated with a decreased risk of ductal, but not lobular or ductal-lobular carcinoma compared to never breastfeeding, and that this reduction in risk was limited to women who breastfed for at least one month. Though it is already established that breastfeeding reduces the risk of invasive breast cancer in the aggregate, our observation suggests that the cell differentiation induced by breastfeeding may primarily exert its protective effect on the development of invasive ductal tumors, rather than tumors of other histologic types. When examining other aspects of breastfeeding, we found that an increasing age when last breastfed is associated with an increased risk of ductal-lobular carcinoma. No other studies have assessed this association among postmenopausal women thus far, and this finding requires confirmation.

Our findings suggest that early hormonal exposures associated with breast development and the beginning of ovulation during puberty may be associated more strongly with ductal-lobular, rather than with ductal or lobular carcinoma, while the cell differentiation induced by breastfeeding may be more strongly associated with protection against ductal, rather than lobular or ductal-lobular carcinoma. Our results also suggest that ductal-lobular carcinoma has distinct risk factors differing from ductal and lobular carcinoma. However, these results require replication and should be interpreted with caution considering the relatively small number of ductal-lobular cases in some categories and that the mechanisms underlying these differences are unclear. In order to further explore the risk factors associated with ductal-lobular carcinoma and the potential differences in etiology compared to ductal and lobular carcinoma, future studies are needed that classify cases via a centralized histopathologic review of tissue specimens, and can thereby identify risk factors for tumors with both an invasive ductal and invasive lobular component.

REFERENCES

1. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet, *360:* 187-195, 2002.

2. Bernstein, L. Epidemiology of endocrine-related risk factors for breast cancer. J Mammary Gland Biol Neoplasia, *7:* 3-15, 2002.

3. Bernstein, L., and Ross, R. K. Endogenous hormones and breast cancer risk. Epidemiol Rev, *15:* 48-65, 1993.

4. Kelsey, J. L., Gammon, M. D., and John, E. M. Reproductive factors and breast cancer. Epidemiol Rev., *15:* 36-47, 1993.

5. Ahlgren, M., Melbye, M., Wohlfahrt, J., and Sorensen, T. I. Growth patterns and the risk of breast cancer in women. N Engl J Med, *351:* 1619-26, 2004.

6. Li, C. I., Littman, A. J., and White, E. Relationship between age maximum height is attained, age at menarche, and age at first full-term birth and breast cancer risk. Cancer Epidemiol Biomarkers Prev, *16:* 2144-9, 2007.

7. Li, C. I., Malone, K. E., White, E., and Daling, J. R. Age when maximum height is reached as a risk factor for breast cancer among young U.S. women. Epidemiology, *8:* 559-65, 1997.

8. Li, C. I., Stanford, J. L., and Daling, J. R. Anthropometric variables in relation to risk of breast cancer in middle-aged women. Int J Epidemiol, *29:* 208-13, 2000.

9. Palmer, J. R., Rao, R. S., Adams-Campbell, L. L., and Rosenberg, L. Height and breast cancer risk: results from the Black Women's Health Study (United States). Cancer Causes Control, *12:* 343-8, 2001.

10. Clavel-Chapelon, F. Cumulative number of menstrual cycles and breast cancer risk: results from the E3N cohort study of French women. Cancer Causes Control, *13:* 831-8, 2002.

11. Hormones and breast cancer. Hum Reprod.Update., *10:* 281-293, 2004.

12. Russo, J., Moral, R., Balogh, G. A., Mailo, D., and Russo, I. H. The protective role of pregnancy in breast cancer. Breast Cancer Res, *7:* 131-42, 2005.

13. Russo, J., Tay, L. K., and Russo, I. H. Differentiation of the mammary gland and susceptibility to carcinogenesis. Breast Cancer Res Treat., *2:* 5-73, 1982.

14. Acs, G., Lawton, T. J., Rebbeck, T. R., LiVolsi, V. A., and Zhang, P. J. Differential expression of E-cadherin in lobular and ductal neoplasms of the breast and its biologic and diagnostic implications. Am J Clin Pathol, *115:* 85-98, 2001.

15. Dixon, J. M., Anderson, T. J., Page, D. L., Lee, D., and Duffy, S. W. Infiltrating lobular carcinoma of the breast. Histopathology, *6:* 149-61, 1982.

16. Lee, A. H., Dublin, E. A., Bobrow, L. G., and Poulsom, R. Invasive lobular and invasive ductal carcinoma of the breast show distinct patterns of vascular endothelial growth factor expression and angiogenesis. J Pathol, *185:* 394-401, 1998.

17. Li, C. I., Uribe, D. J., and Daling, J. R. Clinical characteristics of different histologic types of breast cancer. Br J Cancer, *93:* 1046-52, 2005.

18. Oyama, T., Kashiwabara, K., Yoshimoto, K., Arnold, A., and Koerner, F. Frequent overexpression of the cyclin D1 oncogene in invasive lobular carcinoma of the breast. Cancer Res, *58:* 2876-80, 1998.

19. Sims, A. H., Howell, A., Howell, S. J., and Clarke, R. B. Origins of breast cancer subtypes and therapeutic implications. Nat Clin Pract Oncol, *4:* 516-25, 2007.

20. Stierer, M., Rosen, H., Weber, R., Hanak, H., Spona, J., and Tuchler, H. Immunohistochemical and biochemical measurement of estrogen and progesterone receptors in primary breast cancer. Correlation of histopathology and prognostic factors. Ann Surg, *218:* 13-21, 1993.

21. Yoder, B. J., Wilkinson, E. J., and Massoll, N. A. Molecular and morphologic distinctions between infiltrating ductal and lobular carcinoma of the breast. Breast J, *13:* 172-9, 2007.

22. Li, C. I., Daling, J. R., Malone, K. E., et al. Relationship between established breast cancer risk factors and risk of seven different histologic types of invasive breast cancer. Cancer Epidemiol Biomarkers Prev, *15:* 946-54, 2006.

23. Li, C. I., Malone, K. E., Daling, J. R., et al. Timing of menarche and first full-term birth in relation to breast cancer risk. Am J Epidemiol, *167:* 230-9, 2008.

24. Li, C. I., Malone, K. E., Porter, P. L., Weiss, N. S., Tang, M. T., and Daling, J. R. Reproductive and anthropometric factors in relation to the risk of lobular and ductal breast carcinoma among women 65-79 years of age. Int J Cancer, *107:* 647-651, 2003.

25. Rosenberg, L. U., Magnusson, C., Lindstrom, E., Wedren, S., Hall, P., and Dickman, P. W. Menopausal hormone therapy and other breast cancer risk factors in relation to the risk of different histological subtypes of breast cancer: a case-control study. Breast Cancer Res, *8:* R11, 2006.

26. Stalsberg, H., Thomas, D. B., and Noonan, E. A. Histologic types of breast carcinoma in relation to international variation and breast cancer risk factors. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Cancer, *44:* 399-409, 1989.

27. Ursin, G., Bernstein, L., Lord, S. J., et al. Reproductive factors and subtypes of breast cancer defined by hormone receptor and histology. Br J Cancer, *93:* 364-371, 2005.

28. Wohlfahrt, J., Mouridsen, H., Andersen, P. K., and Melbye, M. Reproductive risk factors for breast cancer by receptor status, histology, laterality and location. Int J Cancer, *81:* 49-55, 1999.

29. Li, C. I., Malone, K. E., Porter, P. L., et al. Relationship between menopausal hormone therapy and risk of ductal, lobular, and ductal-lobular breast carcinomas. Cancer Epidemiol Biomarkers Prev, *17:* 43-50, 2008.

30. Tavassoli, F. A. Tumors of the Breast. World Health Organization Classification of Tumors Pathology and Genetics of Tumors of the Breast and Female Genital Organs 2003, pp. 9-112. Lyon: IARC Press.

31. Waksberg, J. Sampling methods for random digit dialing. J Am Stat Assoc, *73:* 40, 1978.

32. Harlow, B. L., and Davis, S. Two one-step methods for household screening and interviewing using random digit dialing. Am J Epidemiol, *127:* 857-63, 1988.

33. Madigan, M. P., Troisi, R., Potischman, N., et al. Characteristics of respondents and non-respondents from a case-control study of breast cancer in younger women. Int J Epidemiol, *29:* 793-8, 2000.

34. International Classification of Diseases for Oncology, 2nd edn. Geneva: World Health Organization, 1990.

Table 1: Selected characteristics of all study women

Characteristic	Control (n = 469) n	%	Ductal (n = 524) n	%	Lobular (n = 324) n	%	Ductal-lobular (n = 196) n	%
Reference age								
55-59	137	29.2	145	27.7	92	28.4	67	34.2
60-64	121	25.8	130	24.8	83	25.6	51	26.0
65-69	114	24.3	132	25.2	83	25.6	43	21.9
70-74	97	20.7	117	22.3	66	20.4	35	17.9
Race/ethnicity*								
Non-Hispanic white	423	90.2	472	90.1	302	93.2	178	90.8
African American	8	1.7	12	2.3	8	2.5	4	2.0
Asian/Pacific Islander	9	1.9	18	3.4	3	0.9	6	3.1
Native American	10	2.1	12	2.3	4	1.2	1	0.5
Hispanic white	19	4.1	10	1.9	7	2.2	7	3.6
Education								
1st-11th	24	5.1	37	7.1	20	6.2	9	4.6
HS or GED	126	26.9	148	28.2	83	25.6	45	23.0
Post HS/some college	182	38.8	185	35.3	104	32.1	72	36.7
College grad/post college	137	29.2	154	29.4	117	36.1	70	35.7
First degree family history of breast cancer								
No	383	84.4	401	78.6	244	76.7	147	76.6
Yes	71	15.6	109	21.4	74	23.3	45	23.4
Missing	15		14		6		4	
Body mass index, kg/m^2								
< 25.0	180	38.5	212	40.8	130	40.5	89	46.1
25.0 - 29.9	145	31.1	157	30.2	108	33.6	63	32.6
≥ 30	142	30.4	151	29.0	83	25.9	41	21.2
Missing	2		4		3		3	
Oral contraceptive duration (months)								
0	156	33.3	196	37.6	122	37.9	61	31.3
1-59	171	36.5	178	34.2	126	39.1	78	40.0
≥ 60	141	30.1	147	28.2	74	23.0	56	28.7
Missing	1		3		2		1	
Menopausal status								
Natural menopause	266	58.0	349	67.8	211	67.0	133	70.4
Simple hysterectomy	116	25.3	102	19.8	62	19.7	25	13.2
Surgical menopause	77	16.8	64	12.4	42	13.3	31	16.4
Missing	10		9		9		7	
Postmenopausal hormone use								
Never	94	21.3	120	24.9	52	17.0	29	15.6
Former	103	23.4	76	15.8	41	13.4	25	13.4
Current estrogen	149	33.8	128	26.6	82	26.9	45	24.2
Current estrogen+progestin	95	21.5	157	32.6	130	42.6	87	46.8
Missing	28		43		19		10	

Estrogen and progesterone receptor status								
ER+ / PR+	–	–	375	72.0	230	73.3	161	82.6
ER+ / PR-	–	–	65	12.5	67	21.3	24	12.3
ER- / PR+	–	–	8	1.5	7	2.2	2	1.0
ER- / PR-	–	–	73	14.0	10	3.2	8	4.1
Missing			3		10		1	

* Non-white Hispanics (n = 6) were included in their respective racial categories.

Table 2: Relationship between reproductive factors and age at maximum height and risk of invasive ductal, lobular, and ductal-lobular breast carcinoma

	Control (n = 469)		Ductal (n = 524)				Lobular (n = 324)				Ductal-lobular (n = 196)			
	n	%	n	%	OR†	95% CI	n	%	OR†	95% CI	n	%	OR†	95% CI
Age at menarche‡														
≥ 14	106	22.6	108	20.6	1.0	Ref.	79	24.4	1.0	Ref.	31	15.9	1.0	Ref.
12-13	260	55.4	309	59.0	1.2	0.8–1.6	177	54.6	0.9	0.6–1.3	112	57.4	1.5	0.9–2.3
8-11	103	22.0	107	20.4	1.1	0.7–1.5	68	21.0	0.9	0.6–1.4	52	26.7	1.7	1.0–3.0*
p for trend					p = 0.80				p = 0.60				p = 0.04	
Age at maximum height§														
≥ 17	164	35.3	146	28.3	1.0	Ref.	102	31.8	1.0	Ref.	54	28.0	1.0	Ref.
15-16	164	35.3	206	40.0	1.4	1.0–1.9*	120	37.4	1.2	0.9–1.7	68	35.2	1.3	0.8–1.9
≤ 14	137	29.5	163	31.7	1.3	1.0–1.8	99	30.8	1.2	0.8–1.7	71	36.8	1.6	1.0–2.4*
p for trend					p = 0.10				p = 0.43				p = 0.04	
Parity‖														
Nulliparous	36	7.7	68	13.0	1.0	Ref.	47	14.5	1.0	Ref.	28	14.3	1.0	Ref.
Parous	433	92.3	456	87.0	0.5	0.3–0.8*	277	85.5	0.5	0.3–0.7*	168	85.7	0.5	0.3–0.8*

* Two-sided p-value < 0.05

† OR = odds ratio comparing cases to controls using polytomous logistic regression

‡ Adjusted for reference age and reference year. Excludes 1 woman with an unknown age at menarche.

§ Adjusted for reference age and reference year. Excludes 19 women with an unknown age at maximum height.

‖ Adjusted for reference age and reference year. Among parous women, 5 women had only stillbirths.

Table 3: Relationship between pregnancy characteristics and risk of invasive ductal, lobular, and ductal-lobular breast carcinoma, among women with ≥1 live births

	Control (n = 431)		Ductal (n = 456)				Lobular (n = 277)				Ductal-lobular (n = 165)			
	n	%	n	%	OR†	95% CI	n	%	OR†	95% CI	n	%	OR†	95% CI
Interval (years) between age at menarche and age at first live birth‡														
1-8	160	37.1	179	39.3	1.0	Ref.	93	33.6	1.0	Ref.	56	34.1	1.0	Ref.
9-12	161	37.4	148	32.5	0.8	0.6–1.1	107	38.6	1.2	0.8–1.6	58	35.4	1.1	0.7–1.6
≥ 13	110	25.5	129	28.3	1.1	0.8–1.5	77	27.8	1.2	0.8–1.8	50	30.5	1.3	0.8–2.1
p for trend					p = 0.75				p = 0.30				p = 0.27	
Number of live births§														
1	42	9.7	63	13.8	1.0	Ref.	36	13.0	1.0	Ref.	20	12.1	1.0	Ref.
2	160	37.1	145	31.8	0.6	0.4–0.9*	100	36.1	0.7	0.4–1.2	63	38.2	0.8	0.4–1.5
3	117	27.1	124	27.2	0.6	0.4–1.0	81	29.2	0.7	0.4–1.3	44	26.7	0.8	0.4–1.4
≥ 4	112	26.0	124	27.2	0.7	0.4–1.1	60	21.7	0.6	0.3–1.0*	38	23.0	0.7	0.4–1.3
p for trend					p = 0.36				p = 0.11				p = 0.27	
Age at first live birth§														
≤ 19	87	20.2	104	22.8	1.0	Ref.	54	19.5	1.0	Ref.	31	18.8	1.0	Ref.
20 - 24	216	50.1	212	46.5	0.8	0.6–1.1	130	46.9	0.9	0.6–1.4	81	49.1	1.0	0.6–1.7
25 - 29	100	23.2	95	20.8	0.8	0.5–1.2	64	23.1	1.0	0.6–1.6	32	19.4	0.9	0.5–1.5
≥ 30	28	6.5	45	9.9	1.4	0.8–2.5	29	10.5	1.7	0.9–3.2	21	12.7	2.1	1.0–4.3*
p for trend					p = 0.72				p = 0.20				p = 0.24	
Age at last live birth§														
≤ 24	92	21.3	99	21.7	1.0	Ref.	58	20.9	1.0	Ref.	31	18.8	1.0	Ref.
25 - 29	178	41.3	172	37.7	0.9	0.6–1.3	111	40.1	1.0	0.7–1.5	51	30.9	0.9	0.5–1.5
30 - 34	110	25.5	114	25.0	1.0	0.6–1.4	71	25.6	1.0	0.7–1.6	54	32.7	1.5	0.9–2.6
≥ 35	51	11.8	71	15.6	1.3	0.8–2.0	37	13.4	1.2	0.7–2.0	29	17.6	1.8	1.0–3.3
p for trend					p = 0.37				p = 0.58				p = 0.01	

* Two-sided p-value < 0.05

† OR = odds ratio comparing cases to controls using polytomous logistic regression

‡ Adjusted for reference age and reference year. Excludes 1 woman with an unknown number of live births and 1 woman with an unknown age at menarche.

§ Adjusted for reference age and reference year. Excludes 1 woman with an unknown number of live births.

Table 4: Relationship between breastfeeding and risk of invasive ductal, lobular, and ductal-lobular breast carcinoma, among women with ≥1 live births

	Control (n = 431)		Ductal (n = 456)				Lobular (n = 277)				Ductal-lobular (n = 165)			
	n	%	n	%	OR†	95% CI	n	%	OR†	95% CI	n	%	OR†	95% CI
Ever breastfed‡														
Never	140	34.7	177	42.4	1.0	Ref.	93	35.8	1.0	Ref.	54	35.8	1.0	Ref.
Ever	264	65.3	240	57.6	0.7	0.5–0.9*	167	64.2	0.9	0.7–1.3	97	64.2	0.9	0.6–1.4
Total breastfeeding§, months														
Never	140	32.5	177	39.0	1.0	Ref.	93	33.6	1.0	Ref.	54	32.7	1.0	Ref.
< 1.0	27	6.3	37	8.1	1.1	0.6–1.9	17	6.1	1.0	0.5–1.9	14	8.5	1.4	0.7–3.0
1.0 - 5.9	112	26.0	96	21.1	0.7	0.5–0.9*	65	23.5	0.9	0.6–1.3	32	19.4	0.7	0.4–1.2
6.0 - 11.9	62	14.4	61	13.4	0.8	0.5–1.2	43	15.5	1.0	0.6–1.6	19	11.5	0.8	0.4–1.5
12.0 - 23.9	56	13.0	58	12.8	0.8	0.5–1.3	42	15.2	1.1	0.7–1.8	24	14.5	1.1	0.6–2.0
≥ 24.0	34	7.9	25	5.5	0.6	0.3–1.0	17	6.1	0.8	0.4–1.6	22	13.3	1.9	1.0–3.6
p for trend††					p = 0.43				p = 0.85				p = 0.11	
Age when first breastfed‖														
Never	140	34.7	177	42.2	1.0	Ref.	93	35.8	1.0	Ref.	54	35.8	1.0	Ref.
≤ 19	43	10.6	42	10.0	0.8	0.5–1.2	23	8.8	0.8	0.4–1.4	17	11.3	1.0	0.5–1.9
20 - 24	117	29.0	113	27.0	0.7	0.5–1.0	78	30.0	1.0	0.7–1.4	36	23.8	0.8	0.5–1.3
25 - 29	75	18.6	55	13.1	0.6	0.4–0.9*	42	16.2	0.8	0.5–1.3	27	17.9	0.9	0.5–1.6
≥ 30	29	7.2	32	7.6	0.9	0.5–1.6	24	9.2	1.2	0.7–2.3	17	11.3	1.5	0.7–3.0
p for trend††					p = 0.83				p = 0.52				p = 0.35	
Age when last breastfed**														
Never	140	34.7	177	42.3	1.0	Ref.	93	35.8	1.0	Ref.	54	35.8	1.0	Ref.
≤ 24	64	15.8	66	15.8	0.8	0.5–1.2	44	16.9	1.0	0.6–1.6	21	13.9	0.8	0.5–1.5
25 - 29	103	25.5	73	17.5	0.5	0.4–0.8*	59	22.7	0.8	0.5–1.3	23	15.2	0.6	0.3–1.0*
30 - 34	68	16.8	63	15.1	0.7	0.5–1.1	39	15.0	0.8	0.5–1.4	28	18.5	1.1	0.6–1.8
≥ 35	29	7.2	39	9.3	1.1	0.6–1.9	25	9.6	1.3	0.7–2.5	25	16.6	2.3	1.2–4.4*
p for trend††					p = 0.36				p = 0.67				p = 0.004	

* Two-sided p-value < 0.05

† OR = odds ratio comparing cases to controls using polytomous logistic regression

‡ Adjusted for reference age, reference year, and number of live births. Excludes 97 women with an unknown duration of breastfeeding or who breastfed <1 month.

§ Adjusted for reference age, reference year, and number of live births. Excludes 2 women with an unknown duration of breastfeeding.

‖ Adjusted for reference age and reference year. Excludes 95 women who breastfed <1 month.

** Adjusted for reference age and reference year. Excludes 96 women with an unknown age when last breastfed or who breastfed <1 month.

†† Test for trend excludes the never category.