

Risk Factors for Breast Cancer in Women Undergoing Mammography

Karen L. Reuter¹
Stephen P. Baker²
F. John Krolikowski³

To determine risk factors for carcinoma of the breast, we compared women with cancer on screening and diagnostic mammography with those in whom cancer was not detected. For 39 months, medical histories were collected by mammography technologists on 3492 women having routine screenings or diagnostic mammograms at our institution. Potential risk factors of women with biopsy-proved breast cancer were compared with those in women who had normal findings on mammograms or negative biopsy results (control subjects). Of the 3492 women, 49 had biopsy-proved breast cancer. There were 3361 patients in the control group, including those women with normal findings on mammograms (3294) and those with negative biopsy results (67). Eighty-two women had incomplete questionnaires or were lost to follow up. Nearly all of the patients with breast cancer were postmenopausal compared with 68% of the control subjects. The mean length of lactation for breast cancer patients was significantly less than for control subjects: 5.6 vs 7.5 weeks ($p = .015$). This was true also for the postmenopausal patients: 8.1 vs 6.1 weeks ($p = .041$). Postmenopausal breast cancer patients had menstruated significantly more years ($p = .016$) than the postmenopausal control subjects: 34 vs 31 years, although the mean age at menarche was not different. When corrected for age, there was no significant difference in the total duration of menstruation in the postmenopausal cancer patients compared with the postmenopausal control subjects. Postmenopausal breast cancer patients had a significantly greater ($p = .021$) average body weight than postmenopausal control subjects: 71.7 vs 66.7 kg, although body weight was the same when all patients were considered. Similar results were found when Quetelet's index for obesity (weight in kg/height in cm^2) ($p = .004$) was calculated for postmenopausal patients: 28 for cancer patients and 26 for control subjects. There was no significant difference in height between the cancer patients and control subjects when all patients or just the postmenopausal patients were considered. History of oral contraceptive use was significantly less common among postmenopausal breast cancer patients than among postmenopausal control subjects: 9% vs 20%. Patients with breast cancer had lower parity than the control subjects.

In our series of patients, women in whom breast cancer was detected on mammography lactated less, showed no significant difference in years of menstruation when corrected for age, had a greater average body weight, used oral contraceptives less often, and had fewer children than women in whom no cancer was detected on mammography.

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We compared women with biopsy-proved breast cancer with those with normal mammographic findings regarding risk factors that have been conflicting in the literature. These factors include lactation, age at menarche, weight and height, and use of oral contraceptives. Numerous studies have examined the relationship of lactation and breast cancer; some showed no protective effect from nursing [1-10]; others showed a protective effect [11-21]; and some had mixed results [22, 23], showing protection for premenopausal women only or for postmenopausal women only. Some studies have found a longer total duration of menses in breast

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¹ Departments of Radiology and Obstetrics and Gynecology, University of Massachusetts Medical Center, 55 Lake Ave. N., Worcester, MA 01655. Address reprint requests to K. L. Reuter, Department of Radiology.

² Biomedical Computing Center, University of Massachusetts Medical Center, Worcester, MA 01655.

³ Department of Pathology, University of Massachusetts Medical Center, Worcester, MA 01655. Present address: Genica Corp., 363 Plantation St., Worcester, MA 01655.

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cancer patients [21, 24, 25]; some have shown an earlier age of menarche in breast cancer patients [5, 12, 25]. The relationship of body weight and height has been correlated with the prevalence of breast cancer. In some studies, such as one in Sweden [25], no difference was found in the two parameters of weight and height when comparing breast cancer patients with control subjects. Other investigations have shown statistically significant positive associations between increased weight and height and breast cancer [26, 27]; still others only showed a correlation between body mass and breast cancer [1, 28, 29]. A few investigations found this correlation for postmenopausal patients only [28–31]. Some studies have shown no relationship between the use of oral contraceptives and breast cancer [32–34], while other investigations have noted that patients who have taken oral contraceptives have an increased risk of breast cancer [35–38].

Subjects and Methods

Data on risk factors for breast cancer were collected for 39 months from questionnaires filled out by mammographic technologists on 3492 patients. These were consecutive patients having mammograms in our department and included patients undergoing routine screening mammography and those having mammograms for specific breast problems. The age range of the patients was 18–92 years (mean, 53 years). The patients were divided into those who were premenopausal (mean age, 40 years) and those who were postmenopausal (mean age, 59 years). Eighty-two women had incomplete questionnaires or were lost to follow up.

Women were asked specific questions regarding their reproductive history including age at menarche, age at first live birth, total number of live births, duration of lactation, and age at menopause if the patients were postmenopausal. Other areas questioned were the amount of fat in the diet; use of tobacco, oral contraceptives, and medications; history of breast surgery; and family history of cancer including special reference to breast cancer. Patients with children were asked how many months they had nursed each child to a maximum of five children. An answer of 1 month or less was listed as 1 month. A nursing period of 6 weeks was listed as 2 months because of questionnaire limitations and the fact that lactation ceases slowly. If not all five children were nursed, but a subsequent child was, that number of months nursed was listed under nursing of the fifth child. The numbers of miscarriages, abortions, and ectopic pregnancies were noted. The total number of years the patient menstruated was calculated. Data about hysterectomies and oophorectomies, including dates of both types of procedures, were collected. The patients were asked to list their weight and height. They were asked if they had ever taken oral contraceptives, if they were currently taking them, and how long they had taken them continuously or intermittently. The patients were not asked about the type or dose.

The control group comprised women without known breast cancer. These included 3294 patients with normal mammograms and 67 women in whom abnormalities on mammograms were proved to be benign by biopsy. The cancer group included women who had breast biopsies that were positive for malignancy (49 patients). All patients (both control subjects and cancer patients combined) were divided into those who were premenopausal (1110 women, of whom seven had proved breast cancer) and those who were postmenopausal (2382 women, of whom 42 had proved breast cancer). Patients were considered postmenopausal if they had not menstruated for at least 1 year or had had a hysterectomy at the age of 45 years or greater.

Risk factors for breast cancer were assessed by both univariate and multivariate methods.

Individual potential categorical risk factors were evaluated by the chi-square and Fisher's exact tests to evaluate independence in proportions with each factor between groups. Differences between group outcomes for individual continuous factors were evaluated by Student's *t* test. Confidence intervals for estimates of relative risk were constructed by using the formula of Greenland and Robins [39].

A multivariate analysis comparing women having biopsy-proved breast cancer with control subjects was performed incorporating the following variables as potential risk factors: total number of months nursed; women who nursed for 24 months or longer; age at menarche; total number of years of menstruation; weight and height and the calculated Quetelet's index; and the length of use of oral contraceptives. Also considered were the patient's age; the number of live births; her age at first live birth; menopausal status; restriction of dietary fat; the length of time of tobacco use; and family history of cancer, including specifically breast cancer.

Logistic regression analysis was performed to provide simultaneous multivariate evaluation of all risk factors (both categorical and continuous). Stepwise logistic regression was performed with known risk factors and variables that were significantly associated with breast cancer in the univariate analysis as the candidate-independent variables. Both forward and backward stepping were allowed. Confidence intervals for the magnitude of effects were constructed by using coefficients and standard errors from the logistic analyses and formulas from Hosmer and Lemeshow [40]. Analyses were performed by using SPSSX [41], BMDPLR [42], and EPIINFO [43] software. Statistical significance was defined as differences with a *p* value of .05 or less.

Results

A significant difference ($p = .015$) in the mean number of weeks of lactation was observed in comparing the cancer patients (5.6 weeks) with the control subjects (7.5 weeks) (Table 1). Forty-two of the 2382 postmenopausal women had proved breast cancer. The mean number of weeks of lactation was significantly different ($p = .041$) between the postmenopausal cancer patients (6 weeks) and the postmenopausal control subjects (8 weeks). Only seven premenopausal women had known breast cancer, and five of these women never lactated. There were too few premenopausal cancer patients for statistical analysis of this subgroup. In regard to the effect of long-term lactation (24 months or longer) in all women, 151 of the control subjects and only one cancer patient had lactated that long. Women who had *not* experienced long-term lactation were 2.5 times more likely to have breast cancer than those who had. In evaluating only postmenopausal women, 103 control subjects had experienced long-term lactation compared with only one cancer patient, the odds ratio being 2.15. Neither of these odds ratios was statistically significant.

Postmenopausal breast cancer patients had significantly ($p = .016$) longer duration of menstruation (34 years) than did the postmenopausal control subjects (31 years). However, when corrected for age, there was no significant difference in the duration of menstruation in postmenopausal cancer patients compared with postmenopausal control subjects. The average age at menarche was not significantly different between breast cancer patients and control subjects or between

TABLE 1: Risk Factors Studied: Comparison Between Cancer Patients and Control Subjects

Risk Factors	Cancer Patients (n = 49)	Control Subjects (n = 3361)	p Value
Mean duration of lactation (weeks)			
Premenopausal + postmenopausal	5.6 (n = 49)	7.5 (n = 3361)	.015*
Premenopausal ^b	(n = 7)	(n = 1089)	
Postmenopausal	6.1 (n = 42)	8.1 (n = 2272)	.041*
Mean duration of menstruation (years)			
Postmenopausal ^c	34.0	31.0	.016 ^d
Mean age at menarche (years)			
Premenopausal + postmenopausal	12.9	12.8	NS
Mean weight (kg)			
Premenopausal + postmenopausal	72.1	66.2	.021*
Postmenopausal	71.7	66.7	.045*

* Significant ($p < .05$).^b Statistical analysis was not performed in this group of women because five of the seven cancer patients never lactated.^c When adjusted for age, age was a confounding factor, and there was then no significant difference in the duration of menstruation in the two study groups.^d Significant ($p < .01$).

those groups when evaluating the premenopausal and postmenopausal women separately (Table 1).

In our series, breast cancer patients were significantly ($p = .021$) heavier (mean, 72.1 kg) than the control subjects (mean, 66.2 kg). Among postmenopausal women only, the mean weight of the cancer patient was 71.7 kg compared with 66.7 kg for the control subjects ($p = .045$) (Table 1). When only the premenopausal patients were evaluated, the difference in weight between cancer patients and control subjects was not significant. Quetelet's index for obesity was significantly larger ($p = .004$) among all the cancer patients (27.9) than among all the control subjects: 25.2 (see Fig. 1). The Quetelet's index for premenopausal cancer patients was 26.6, but for control subjects it was 24.3. Regarding just postmenopausal patients, Quetelet's index for the cancer patients was 28.1, but for the control subjects it was 25.6. No significant difference was seen in the mean height between breast cancer patients and control subjects.

Twenty-one percent of patients with cancer had taken birth control pills compared with 32% of the control subjects ($p = .088$). Only 9% of postmenopausal patients with breast cancer had taken birth control pills compared with 20% of postmenopausal control subjects ($p = .083$). Neither of these p values for the chi-square analysis was significant. The odds ratios were not significantly different. The number of premenopausal breast cancer patients was too small for statistical validity.

Univariate analysis did not indicate any significant difference between breast cancer patients and control subjects regarding the age at first live birth, amount of fat in the diet, use of tobacco or medications, and family history of cancer.

When all women were considered as a single group in the multivariate analysis, Quetelet's index and menstrual status were the only significant predictors of the development of

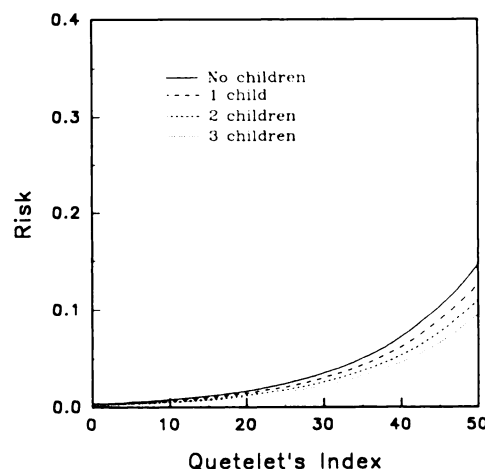


Fig. 1.—Graph shows additional risks for breast cancer in postmenopausal women due to obesity, with separate curves for differences in parity. Quetelet's index = (weight in kg/height in cm²).

cancer. Most breast cancer occurred in older, postmenopausal women. The mean age of the postmenopausal cancer patients was 60 years and of the postmenopausal control subjects, 53 years. Forty-two of the 49 women with breast cancer were postmenopausal. When only postmenopausal women were considered, Quetelet's index ($p = .008$) and parity ($p = .043$) were significant predictors of cancer prevalence. A lower Quetelet's index and increased parity were protective against breast cancer (Fig. 1). Parity was measured on a continuum. Point estimates with the accompanying confidence intervals for the odds ratios were as follows (in all cases being compared with those women who had borne no children). For those women with one child, the point estimate was 0.852 with a confidence interval of 0.722–1.00. For those who had borne two children, the point estimate was 0.725 with a confidence interval of 0.615–0.855. For those who had borne three children, the point estimate was 0.618 with a confidence interval of 0.524–0.728. Women who had borne no children had a 0.38 times increased risk for breast cancer compared with women who had two children. Women who had had no children had 0.62 times the risk for breast cancer compared with women who had borne three children. These effects of parity were statistically significant. Confidence intervals constructed from the coefficient for the effect of parity and the standard error for that coefficient did not include 1.00 for those women who had two or more children. Our study corroborated previous investigations indicating a significant protective effect of higher parity for postmenopausal women against breast cancer.

Discussion

Published reports of the relationship between breast-feeding and breast cancer have been contradictory [1–23]. Among the Canadian Eskimos, breast cancer was rare when breast-feeding lasted more than 3 years for each child but has increased as breast-feeding has become less common in

modern times [44]. Similar changes have been observed in Arab populations [45]. Among the Tanka Chinese, where breast-feeding was usually accomplished with only the right breast because of the traditional dress, the majority of breast cancers were in the unsuckled left breast [11]. However, many series have shown a slight predominance of left-sided breast cancer, especially for adenocarcinoma, not related to breast-feeding [30].

The prevalence of breast cancer in women has been related to their reproductive hormone status. Several studies have noted that breast cancer patients had a longer mean duration of regular menses compared with control subjects [5, 21, 24, 25, 30]. Wynder et al. [5], Wainwright [12], and Adami et al. [25] found an earlier average age at menarche in breast cancer patients compared with control subjects. Delayed menopause was noted in breast cancer patients by Wynder [5], Olch [24], and Adami et al. [25].

The relationship of body weight and height has been correlated with the prevalence of breast cancer. Adami et al. [25] found no correlation between these parameters and breast cancer in Sweden, but another investigation in that country [26] did reveal a positive correlation between weight and height and breast cancer in all women. Similar results were found in Poland. However, the weight relationship to breast cancer in Poland was only seen in women over 50 years old [27]. A study of Chinese women by Yuan et al. [30] showed only a slight decrease in breast cancer risk from lower weight and lower Quetelet's index in postmenopausal women. In evaluating women in the United States, London et al. [47] found no correlation between weight and breast cancer in postmenopausal women, but increased height was weakly related to breast cancer risk. Other investigations in the United States [1, 28] did show an increased risk of breast cancer in postmenopausal women who were heavier and taller. An Israeli study [29] had similar conclusions.

Conflicting reports have been published on the relationship between the risk of developing breast cancer and the history of the use of oral contraceptives [48–50]. Some studies have shown no relationship [32–34, 51, 52]. However, McPherson et al. [35], Pike et al. [37], and Olsson et al. [38] found an increased risk for breast cancer in women who had taken oral contraceptives.

Our data suggest that longer lactation and shorter duration of menses, except when corrected for age, and lower body weight in postmenopausal women have statistically significant protective effects against breast cancer. Most women who have breast cancer have none of the "traditional" risk factors for this malignancy, so mammographic screening should not be omitted because of the absence of these factors. We did not find a statistically significant difference between our cancer patients and the control subjects in the use of oral contraceptives. According to our results, the age at first live birth, amount of fat in the diet, history of tobacco use, and family history of cancer including specifically breast cancer were not significantly different between cancer patients and control subjects. Our study was limited by the small number of biopsy-proved breast cancer patients (49) in our series. Also, most of our breast cancer patients were postmenopausal.

A number of possible explanations for the protective effect of lactation against breast cancer have been published. These effects range from physical changes of the breast during lactation to the hormonal effects produced by breast feeding [53].

A study of milk from the unsuckled breast of 10 lactating mothers revealed that this milk had a slightly higher pH compared with that from the suckled breast. During normal lactation, breast milk is slightly acidic with a pH range of 6.88–7.15. However, the mechanism by which the pH of breast milk favors alkalinity if the breast is unsuckled is unclear. It is known that alkalinity around epithelial cells causes hyperplasia, cell atypia, and a marked increase in mitotic activity—a prelude to neoplasia. However, the damaged epithelial cells from the alkaline milieu and the resultant hyperplasia and cell atypia and increased mitotic activity have been seen only in the gastric mucosa, colon, and lung [53]. One theory for the development of this malignant change is that the desquamated cells and degenerating secretions plus exogenous chemical substances may remain in the alveolar ductal system of the breast when lactation is not occurring, increasing the chances of epithelial damage and malignant transformation [54]. The pH thesis could explain the known features of breast cancer, including the striking predominance of left-sided breast involvement mainly in right-handed females. Most right-handed women prefer supporting the head of an infant on their right arm, and therefore nurse first on the right side, which often would lead to partial nonsuckling on the left, and thence, to alkalinity.

The hormone thesis, to which is linked the woman's age at first live birth, does not explain many epidemiologic features of breast cancer, among which is the frequent observance of a predominance of left-sided breast cancer [53, 55]. The known hormonal effects produced by breast-feeding are increased production of prolactin and decreased production of estrogen. During lactation, ovulation often ceases or is less frequent, which may also protect against breast cancer [15]. Breast-feeding in an industrialized society often spans only 3–5 months, with supplementary formula and the early introduction of solids, which is not long enough to suppress ovarian function in well-nourished women. Prolonged breast-feeding is necessary to evoke this hormonal change, which stops ovulation.

In our study, lactation occurred significantly less often among women with proved breast cancer, both when all the women were considered and when only postmenopausal women were evaluated, although the difference in the mean length of lactation was only 2 weeks. The clinical relevance of this difference in lactation is not clear. Five of our seven premenopausal women with breast cancer had never lactated. Although our data provide additional evidence that prolonged lactation protects women from some malignant changes of the breast, further investigation is needed.

We found no significant difference in the age at menarche when comparing breast cancer patients with control subjects, but the average duration of years of menstruation was significantly longer in the postmenopausal patients with breast cancer when the confounding factor of age was not removed. A significant difference in the total duration of menstruation

was seen in a 1926 study in England by Lane-Clayton in more recent publications in the United States [5, 24], and in the study of Yuan et al. [30]. This longer duration of menstruation is hormonally the opposite effect of prolonged lactation, since longer years of menstruation suggests more ovulatory cycles, whereas prolonged lactation often causes ovulation to cease.

When we compared weights between breast cancer patients and control subjects, the cancer patients were significantly heavier. In a prospective study by the American Cancer Society [46], heavy women had a higher mortality rate from breast cancer. Studies in Sweden [26] and Poland [27] also documented cancer patients as having heavier body weights, but in these two European studies, increased height was also correlated with breast cancer. A study by LeMarchand et al. [31] in the United States revealed the same relationship as ours, a relationship between increased body weight and Quetelet's index (but not height) and breast cancer only in the postmenopausal patients. The study of Yuan et al. [30] showed only a weak association of Quetelet's index with breast cancer risk, the association being strongest among women 60 years old or more. With obesity, additional biologically active estrogen is present [15] because of peripheral conversion of adrenal androgens [30].

In our study, 21% of the cancer patients had used oral contraceptives compared with 32% of the control subjects ($p = .008$); but when only the postmenopausal patients are considered, only 9% of the postmenopausal cancer patients had used contraceptive pills compared with 20% of the postmenopausal control subjects. However, the Oxford study [35, 43] and others by McPherson et al. [35], Pike et al. [37], and Olsson et al. [38] showed an increased frequency of breast cancer in patients who had taken oral contraceptives.

The study by Yuan et al. [30] suggested that the cumulative number of ovulatory cycles is directly related to breast cancer risk. Oral contraceptives decrease the number of ovulatory cycles just as a longer duration of lactation causes a substantial delay in the reestablishment of ovulation after a completed pregnancy. A lack of obesity would also fit this hypothesis of protection from breast cancer because of less estrogen in the body in these patients.

In conclusion, regarding the potential risk factors of the duration of lactation, age at menarche, total duration of menstruation, weight and height, and history of oral contraceptive use, we found the following. Lactation had a small but statistically significant protective effect against breast cancer in all the women we studied and in the subgroup of postmenopausal women. Postmenopausal cancer patients had a longer duration of menses when age was not separated out as a confounding factor, a higher mean body weight, and a resultant higher Quetelet's index. A lower percentage of postmenopausal cancer patients had been taking oral contraceptives than postmenopausal control subjects, although the results were not statistically significant. Female reproductive hormones play a key role in the development of breast cancer in postmenopausal women. The number of ovulatory cycles and the amount of biologically active estrogen are important factors in the cause of breast cancer. Our study also supported the known risk factors for breast cancer of increased age and

lower parity. Forty-two of the 49 cancer patients in our study were postmenopausal. Women who had borne no children had a 0.38 increased risk for breast cancer compared with those with two children and a 0.62 increased risk over those who had three children. Our study was limited by the small number of women with biopsy-proved breast malignancy, especially among our premenopausal patients. We used mammogram questionnaires to help identify the risk factors for breast cancer in our population; ongoing research is indicated.

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