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Cancer Detection and Prevention 26 (2002) 192–196

Cancer Detection and Prevention

www.elsevier.com/locate/cdp

Mastalgia and breast cancer: a protective association?

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Received 7 February 2002; received in revised form 29 March 2002; accepted 2 May 2002

Abstract

Breast pain (mastalgia) is a common complaint, with a potentially important relationship to breast cancer risk. We have examined the association between mastalgia and breast cancer in the patient population of the Breast Care Center of University Hospital, Syracuse, New York. Of 5463 women with complete breast cancer risk factor information, 1532 (28%) reported breast pain as an incidental complaint at their initial visit, and 861 were diagnosed with breast cancer. Forward stepwise logistic regression was used to analyze the association between breast pain and a diagnosis of breast cancer. The age-adjusted OR for breast cancer was 0.60 (95% CI 0.50–0.74). Adjustment for additional risk factors (early menarche, late first birth, late menopause, exogenous hormone use, positive family history) yielded an OR of 0.63, 95% CI 0.49–0.79. Thus, women who experienced breast pain in our patient population were less likely to be diagnosed with breast cancer than women who did not complain of breast pain, regardless of age, and of other breast cancer risk factors. Further investigation of this possible protective association is warranted.

Keywords: Mastalgia; Breast cancer; Protective association

1. Introduction

Mastalgia (breast pain) is a common complaint, which affects an estimated 10–30% of women, although accurate population based figures are not available. The etiology of breast pain remains unclear. Postulated mechanisms include altered ratios of fatty acid esters [1], higher basal prolactin levels [2], increased prolactin response to stimulation [3–5], and high dietary fat [6]. However, the biologic mechanisms leading to pain remain unknown.

Most women who present for clinical evaluation of breast pain do so because they are concerned about the possibility of a breast malignancy. Breast pain can be a presenting symptom of breast cancer, but this is rare [7]. There is some evidence in the published literature regarding the issue of mastalgia and a possible increase in breast cancer risk. This includes two case-control studies which suggest that women with a history of mastalgia are at increased risk for the development of breast cancer [8,9]. Two other studies have presented evidence that the painful breast is more likely to have a high risk mammographic pattern [10,11]. However, a study of breast biopsy findings in women who reported breast pain compared to those who denied mastalgia, found no increase in the frequency of malignant lesions in the mastalgia group [12]. Present evidence is therefore inconclusive and conflicting. However, if the painful breast is more susceptible to malignancy altered surveillance, and perhaps the management of the painful breast may be in order. The establishment of a relationship between breast pain and breast cancer would also lead to an entirely new set of etiologic hypotheses, and new avenues of biologic investigation. In view of the above considerations, we have performed a retrospective analysis of our breast symptom data base with the objective of further investigation of a possible link between breast pain and breast cancer.

2. Methods

The study population is derived from women seen at the Breast Care Center of the University Hospital in Syracuse, New York. This is a comprehensive program, where women with a variety of breast complaints are referred, or refer themselves. During the period of the study (1992–1998) an average of 1000 new patients were seen annually, and a total of 6892 women were entered into the database during this time. The database was searched to identify women over age 30, on whom and breast cancer risk factor information was complete; these totaled 5683 women. We then excluded 220

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0361-090X/02/$ – see front matter
PII: S0361-090X(02)00065-X

women who presented with a sole complaint of breast pain, because inclusion of these women would enrich the control population for women complaining of mastalgia. Thus, final study population consisted of 5463 women with complete risk factor data, over age 30, seen for some reason other than a sole complaint of mastalgia. Among these, 499 women presented with a diagnosis of breast cancer made at another institution, and 362 were subsequently diagnosed with breast cancer, for a total of 861 breast cancer cases. Of the women with benign problems, 2515 were evaluated for concern about a palpable lump, but the majority of these proved to be non-dominant masses or areas of nodularity, not requiring further intervention. A total of 991 women were seen for a mammographic abnormality, which was considered benign on further evaluation. Nipple discharge was the main complaint of 705 women, but again surgical duct excision was found to be necessary in only 84 women. The main symptom was not reported in 391 women. The majority of symptomatic women did not have abnormalities which merited biopsy, and the annual number of benign biopsies on women over 30 averaged 250.

All new patients completed a self-administered questionnaire detailing their breast symptoms and breast cancer risk factor profile, which was then reviewed by a physician or nurse. The symptom question was posed in the form: “Do you have any of the following?”, with breast pain being one of the options presented, along with breast lump, nipple discharge, etc. The patients were asked to check all responses that applied to them. A later question queried them with regard to premenstrual breast pain and tenderness. There was no attempt, in this questionnaire, to quantify the degree of pain, or to obtain information on the duration of the pain. Specific informed consent was not obtained for this retrospective analysis, but the questionnaire used to collect the data has been reviewed and approved by the Institutional Review Board of University Hospital, Syracuse. Questionnaire data were entered into a relational database. Women were designated ‘cases’ when they were diagnosed to have breast cancer (including non-invasive breast cancer). All non-cases were designated ‘controls’. Women who checked the breast pain option, or said yes to premenstrual breast pain and tenderness, were classified as suffering from mastalgia.

This database was queried as to the presence or absence of breast pain, the case or control status, and the breast cancer risk factor history (age at menarche, age at first term pregnancy, age at menopause, family history of breast cancer, and number of previous surgical breast biopsies) of the accrued population. Women under age 30 were excluded because breast cancer is rare below the age of 30. Women who presented with a sole complaint of mastalgia were also excluded, since their inclusion would bias the control population towards an over-representation of women with mastalgia. The data were analyzed using logistic regression to calculate the OR for a breast cancer diagnosis in women who reported pain, compared to those who did not. Reproductive lifespan was calculated by subtracting the age at menarche from present age for premenopausal women and age at menarche from age at menopause for postmenopausal women. Step-wise forward logistic regression was used to adjust for breast cancer risk factors, and a final adjusted OR for breast cancer in the presence of breast pain was calculated. Because younger age is associated with a greater frequency of breast pain, and a lower risk of breast cancer, a stratified analysis was also performed after dividing the population into three separate age categories.

To address the possibility that women with newly diagnosed breast cancer or a worrisome lump may have ignored the presence of breast pain when completing the self-administered survey, a subset of study subjects was given a modified short form of the McGill pain questionnaire (MPQ) [13]. This is a standardized pain instrument, which has been validated in a variety of settings. The responses to the original symptom questionnaire were then compared to the results of the MPQ to see if there were differences in concordance of these responses between cases and controls.

3. Results

We have analyzed data on 5463 women, 861 of whom were diagnosed with breast cancer, and were designated cases. The remaining 4602 women were designated controls. The mean age of the cases was older than controls (60.9 years versus 50.1 years, $P = 0.001$).

We excluded 220 women who were seen for a sole complaint of breast pain. These women were similar in characteristics to the patients who described breast pain as an incidental complaint. They tended to display a lower breast cancer risk profile than the women who denied mastalgia: 22.7% experienced early menarche, 8% had their first birth at age 30 or later, 3.3% had a family history of breast cancer (at least one affected first degree relative), and 6% had a history of breast biopsy. Of note, 43% of women who presented with mastalgia alone were alcohol users, compared to 15.8% who denied mastalgia, and 15.6% who presented with mastalgia incidentally. Of premenopausal women presenting with mastalgia alone, 38.7% were on oral contraceptives, and 43% were postmenopausal. Of these, 20% were on hormone replacement therapy. When compared with the data in Table 1, women with a sole complaint of mastalgia appear to be a lower risk population than those with incidental mastalgia, with the exception of alcohol use, which is more frequent in the mastalgia-only group.

The relation of a complaint of breast pain to menstrual and obstetrical history, family history of breast cancer, exogenous hormone use, and alcohol use is shown in Table 1. Women who were older at first full term pregnancy (FFTP), experienced later menopause, or had a family history of breast cancer, were less likely to complain of breast pain. Postmenopausal women reported breast pain much less frequently than premenopausal women (OR 0.56, $P = 0.0001$). Women who used exogenous hormones (either oral

Table 1
Characteristics of study population

	No breast pain ($n = 3931$)		With pain ($n = 1532$)		OR (for pain)	P
	n	%	n	%		
Early menarche (<12)	786	21.03	345	23.3	1.14	0.074
Late FFTP (>29)	401	13.7	136	11.2	0.80	0.030
Late menopause (>50)	844	42.1	199	35.5	0.75	0.005
Postmenopausal	2054	52.3	583	38.1	0.56	0.0001
BCP users	1196	63.7	628	66.2	1.36	0.0001
HRT users	374	18.2	140	24.0	1.40	0.002
Breast cancer FH	676	17.2	224	14.6	0.82	0.021
Hx breast biopsy	704	17.9	209	17.6	0.97	0.761
Alcohol users	626	15.8	267	15.6	1.00	0.967

FFTP: first full term pregnancy; BCP: birth control pill; HRT: hormone replacement therapy; FH: family history; Hx: history.

Table 2
Crude ORs for breast cancer

	Final study population ($n = 5463$)		Including women with only mastalgia ($n = 5683$)	
	OR	95% CI	OR	95% CI
Pain	0.45	0.37–0.55	0.42	0.35–0.51
Age	1.06	1.05–1.06	1.05	1.05–1.06
Age at menarche	0.94	0.90–0.99	0.95	0.90–0.99
Age at FFTP	1.04	1.02–1.06	1.04	1.02–1.06
Age at menopause	1.03	1.01–1.05	1.03	1.02–1.04
BCP use	0.67	0.58–0.77	0.67	0.58–0.77
HRT use	1.24	1.00–1.54	1.25	1.02–1.55
Family history	1.23	1.06–1.43	1.26	1.09–1.46
Number of breast biopsies	2.62	2.35–2.92	2.67	2.38–2.94
Alcohol users	1.04	0.96–1.12	1.05	0.97–1.14

contraceptives or postmenopausal hormones) experienced breast pain significantly more frequently than those who did not. Thus, factors which are associated with an increased risk of breast cancer were associated with a decreased frequency of breast pain, with the exception of exogenous hormone use.

Crude ORs for the established breast cancer risk factors in our data set are shown in Table 2, including and excluding the 220 patients with a sole complaint of mastalgia. There was very little difference in the odds estimates, although the impact of mastalgia on breast cancer risk was marginally stronger if the women with mastalgia as the only complaint are included. Since the more conservative approach is to exclude these women from the analysis, all subsequent data are presented without this group.

Our data set had an excess of younger control women, and we therefore, attempted to examine the differential effect of age across this population by creating three age strata with an approximately equal number of women in each. We found that among the 1807 women who were between 30 and 44 years of age (and included 92 breast cancer cases), the OR was 0.50, 95% CI 0.3–0.8. Among the 1930 women aged 45–56 years (and included 276 breast cancer cases), it was 0.60, 95% CI 0.45–0.63. And among the 1726 women over age 56 (493 breast cancer cases), it was 0.62 and 95% CI 0.5–0.8. The negative association between mastalgia and a diagnosis of breast cancer thus, appears consistent across age strata. These data are shown in Table 3.

Table 3
Age stratified analysis

Age category	Total number (with cancer)	OR (95% CI)	P
30–44 years	1807 (92)	0.50 (0.31–0.82)	0.006
45–56 years	1930 (276)	0.60 (0.45–0.63)	0.002
>56 years	1726 (493)	0.62 (0.46–0.84)	0.002

The relation between breast pain with breast cancer is shown in Table 4, with a statistically significant negative

Table 4
Adjusted ORs for breast pain and other significant risk factors

Entire population	OR	$P > \|z\|$	95% CI
Pain	0.63	0.000	0.49–0.79
Age	1.05	0.000	1.04–1.06
Age at menarche	0.93	0.002	0.88–0.99
Age at FFTP[a]	1.03	0.001	1.01–1.05
Years menstruating	1.03	0.005	1.01–1.04
Surgical biopsies	2.60	0.000	2.27–2.94

A family history of breast cancer was not significant in this model.
[a] FFTP: first full term pregnancy.

association for both premenopausal and postmenopausal women. When these data were analyzed in a forward stepwise logistic regression model, the OR for breast pain remained significantly below unity after correction for age, age at menarche, age at first term pregnancy, reproductive lifespan, and number of surgical biopsies. A family history of breast cancer and history of exogenous hormone use was no longer significant in this model, and these terms were dropped.

A detailed pain questionnaire (MPQ) was administered to a subset of 235 patients (73 cases and 162 controls). The concordance rate with the original symptom questionnaire was identical for cases and controls (75 and 74.7%), suggesting that inattention to mastalgia among the cases is not an explanation for our findings.

4. Discussion

We have performed a retrospective case-control investigation of patient reports of breast pain, related to a diagnosis of breast cancer. We find that women who report breast pain are significantly less likely to be diagnosed with breast cancer (adjusted OR 0.63, 95% CI 0.49–0.79). Our findings do not support the concept that women with mastalgia are at increased risk for breast cancer, as suggested by two published case-control studies [8,9]. On the contrary, they raise the possibility that mastalgia is not a feature of the cancer-prone breast. This apparent protective association is unlikely to be the result of an "attention bias" against breast pain on the part of the cases, as suggested by the findings of a detailed pain questionnaire administered to a subset of 235 patients, since the degree of concordance between the two instruments was identical (75%) in cases and controls. Our choice of controls was limited to women presenting to our Breast Center for routine surveillance or for evaluation of benign problems, and reported an incidental complaint of mastalgia. We excluded patients who presented with a sole complaint of mastalgia in order to reduce the bias caused by using a clinic population. These women displayed a lower breast cancer risk profile than women without mastalgia, with the exception of alcohol use, which was more prevalent in this group. It is possible that alcohol use is a risk factor for breast pain, but has not been evaluated in this regard as far as we are aware.

The problems with our study include the fact that our control population is subject to a referral bias, and women with painful breasts may be over represented, leading to the possibility of a spurious protective association between mastalgia and breast cancer diagnosis. On the other hand, it is possible that women with worrisome lesions are more attentive to the presence of breast pain, and report it more readily. Another important consideration is that of biased recall of pain, which is unlikely to apply here because we made no attempt in our questionnaire to elicit a history of pain in the past, and the question was phrased to inquire about present breast pain. Therefore, if a past history of mastalgia is relevant to the risk for breast cancer, this study does not address that possibility. However, clinical studies suggest that mastalgia tends to persist in a fluctuating manner during the premenopausal life of women who suffer from it, and that it tends to subside at menopause [14]. This postmenopausal decline in the frequency of breast pain affects both cases and controls in our population: postmenopausal controls had a 10% lower frequency of breast pain than premenopausal controls (27% compared to 37%), and postmenopausal cases showed a similar trend, (15% describing breast pain, compared to 23% of premenopausal cases), and the interaction between menopause and pain was not statistically significant ($P = 0.64$).

We do not have data on the recency of the last mammogram; and cannot relate mammographic findings to the presence and absence of pain. However, since our study population included all women with complete risk factor data who attended this comprehensive breast program during the study period, with the only exclusions being for women who presented with a sole (i.e. not an incidental complaint) of mastalgia, age under 30, and lack of risk factor information, it is unlikely that there is a bias towards excluding mastalgia patients with findings suspicious of malignancy. Nevertheless, the fact that the study population was drawn from a specialty clinic rather that from the general population is problematic, and we intend to address this in future studies.

The potential biases described above cannot be controlled for in the present study, but the large number of control subjects, and the fact that women presenting specifically with a complaint of mastalgia have been excluded, should provide some assurance that systematic reporting bias on the part of the controls is not the cause of the protective association seen in this analysis. These issues certainly need to be addressed in future studies, and we are reporting this preliminary data which conflicts with two published reports (discussed below) in an attempt to draw attention to the need for further investigation of this potentially important association.

There have been two previous reports of case-control studies examining mastalgia as a risk factor for breast cancer. The first, which also investigated the role of oral contraceptive use in relation to breast cancer risk [8], was a study of 420 premenopausal cases and controls, matched on age and age at first full term pregnancy, was designed to examine breast cancer risk in relation to oral contraceptive use and cyclical mastalgia. It is not clear from the report whether the cases were questioned about mastalgia prior to or following diagnosis. These investigators defined mastalgia as at least 6 months of bilateral cyclical breast pain lasting for 4–21 days prior to menstruation, and questioned women as to the duration of mastalgia over their lifetimes. A history of cyclical mastalgia was associated with an increased risk of breast cancer in this study (OR 2.12, 95% CI 1.3–3.4), with increasing levels of risk with increasing duration of mastalgia.

The second study of cyclical mastopathy included almost 200 premenopausal women recently diagnosed with breast cancer, and a similar number of age matched controls. The pain data were collected over a month period, and women were asked to complete breast symptom cards daily, with the cases reporting on pain in the contralateral breast. Cases and controls were found to have similar pain scores in the follicular phase, but luteal phase scores were significantly higher for the cases [9]. We have not attempted to distinguish cyclical from non-cyclical mastalgia, and have not required any minimum duration of exposure to breast pain. It remains possible that the different forms of breast pain (localized versus diffuse, cyclical versus non-cyclical) have different mechanisms, and different implications for cancer risk, but conclusions in this regard are impossible until the pain data is collected prospectively in a standardized fashion, prior to the diagnosis of cancer, with detailed information regarding cyclicity and severity.

The appropriate measurement of mastalgia is a pertinent issue in this regard, and again published data are scant. The few papers addressing the measurement of mastalgia have recommended the use of a visual analog scale and pain diaries. We have performed the first prospective study of mastalgia using a standardized pain instrument (the short form of the McGill pain Questionnaire, SF-MPQ), and find that the overall pain ratings on eleven sensory and four affective parameters are effectively captured using a few focused questions: a visual analog scale, the present pain index, and four short quality of life questions [15]. The mean pain ratings of the 271 women who participated in this pain measurement study approximated those for chronic cancer pain. These data show that breast pain is a significant pain condition, and begin to lay out a methodical approach to the efficient measurement of breast pain for use in large prospective studies.

In conclusion, our results point out again that the role of mastalgia in relation to breast cancer risk deserves to be investigated further, and is one more reason to encourage research on mastalgia, a condition which affects the quality of life of a substantial number of women.

This issue obviously needs to be investigated further, since the establishment of an association between mastalgia and breast cancer risk, whether is negative or positive, will lead to new hypotheses regarding breast cancer etiology.

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