

Short Communication

Cyclical Mastalgia and Breast Cancer Risk: Results of A French Cohort Study

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Abstract

Cyclical mastalgia is a common complaint, with a potentially important relationship to breast cancer risk. In the last decade, case-control studies have reported that cyclical mastalgia could be considered as an independent risk factor for breast cancer. The subjectivity of a retrospectively collected symptom questioned the validity of this finding. We have examined the association between cyclical mastalgia and breast cancer risk in the French cohort study of women with benign breast disease diagnosed in two breast clinics between 1976 and 1979 and followed-up until 1997. The present study was restricted to the women free of any hormonal treatment ($n = 247$). The mean follow-up was 16 ± 5 years, and a total of 22 breast cancers occurred during the follow-up. Using a Cox model with duration

of cyclical mastalgia as a time-varying variable, the adjusted relative risk of breast cancer increased with the duration of cyclical mastalgia ($P = 0.006$). The corresponding relative risk for 37 months of cyclical mastalgia was 5.31 (95% confidence interval, 1.92-14.72). We show here that the conclusion still holds when the symptom cyclical mastalgia was collected prospectively in a cohort study, bringing additional evidence that cyclical mastalgia may represent an independent and useful clinical marker of increased breast cancer risk. It might be a confounding factor when assessing the effects of hormonal treatments on breast cancer risk such as hormonal replacement therapy or oral contraceptives. (Cancer Epidemiol Biomarkers Prev 2006; 15(6):1229-31)

Introduction

Cyclical mastalgia or mastodynia is one of the most common complaints, for which women consult either their general practitioner or their gynecologist (1-3). Several authors have reported a cumulated incidence rate over the reproductive life ranging between 45% and 70%. The etiology of breast pain remains unclear. However, its recognition and individualization as a benign breast disease (BBD) is still debated, and its clinical relevance is frequently denied (2, 4, 5).

Although the etiology of cyclical mastalgia has not been established, some evidence has implicated elevated estrogen levels, low progesterone levels, or an abnormal estrogen/progesterone ratio (6). Physiologically, a direct link between breast susceptibility to the estrogen microenvironment and the occurrence of cyclical mastalgia is suggested by several observations: (a) its bilaterality and periodicity according to the different phases of the menstrual cycle; (b) its occurrence or exacerbation after exposure to estrogens contained in both oral contraceptives and hormonal replacement therapies; (c) its disappearance after surgical or chemical ovarian suppression or antiestrogen therapy.

At the present time, only two case-control studies have analyzed the relationship between cyclical mastalgia, using a strict definition, and the risk of breast cancer. Both studies have shown a significant increase in breast cancer risk in

women with cyclical mastalgia (7, 8), by showing either a direct breast cancer risk/symptom duration relationship or a direct breast cancer risk/symptom severity score relationship. However, in these two studies, the presence of cyclical mastalgia was collected retrospectively, raising questions about the importance of the recall bias. To circumvent this issue, we used the data from a cohort study of French women with BBD, in which cyclical mastalgia had been collected accurately and prospectively.

Materials and Methods

Description of the patients included in this cohort, primarily designed to analyze the relation between progestin-only treatments as commonly used in France and breast cancer risk, has been previously published (9, 10). Briefly, this study was conducted in two French hospitals in the Paris area. Patients were considered eligible for the study if they were French natives, 20 to 50 years old, premenopausal, had a diagnosis of BBD, had no personal history of breast cancer, no cancer at another site, and did not develop breast cancer within 1 year of the first visit. BBD included nodular hyperplasia, fibroadenoma, fibrocystic disease, isolated cyst, isolated cyclical mastalgia, and nipple discharge (excluding galactorrhea) as commonly defined (2, 11). The diagnosis of BBD was based on clinical symptoms, bilateral breast palpation according to classic procedure, and radiological abnormalities. Additional ultrasonography, cytology, and histologic verifications were done when necessary. All consecutive eligible women seen for the first time between 1976 and 1979 were included in the study. The inclusion periods were determined to recruit 600 patients in each center. The initial and follow-up interviews were done by specifically

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trained senior consultants, who reported all relevant information in a standardized validated questionnaire. All patients who failed to return to the clinic were contacted by mail and asked to fill in and return a similar questionnaire. In this analysis, the follow-up period started at the time of inclusion and ended in December 1997. All breast cancers were histologically confirmed.

A total of 1,150 women were included in the entire cohort. The present study was restricted to the 247 women who never used either oral or percutaneous progestin treatment, either before or after their inclusion into the cohort. Cyclical mastalgia was defined as a bilateral painful breast swelling, lasting for >4 days and up to 3 weeks, always preceding menses, and subsiding progressively during menstruation. Details of the items of the questionnaire can be found in appendix. No score scale of severity pain was used in our cohort. The presence of mastalgia was recorded if the woman herself reported pain, and if the other characteristics of cyclical mastalgia were present (see Appendix 1). This definition clearly discarded noncyclical mastalgia and Tietze's disease and was in accordance with the classification proposed by previous authors (2-4).

Statistical Analysis. Baseline distributions of certain characteristics, with respect to cyclical mastalgia status, were evaluated. χ^2 tests (for categorical variables) and *t* tests (for continuous variables) were done to determine whether these characteristics differed according to mastalgia status. Associations were examined between reported cyclical mastalgia and incident breast cancer using Cox proportional hazards regression (12). Relative risks (RR) and 95% confidence interval (95% CI) were calculated. For each analysis, the RR for a given category of duration of cyclical mastalgia was estimated by exponentiation of the proportional hazards regression coefficient. The R package was used in all analyses with the *coxph* package (13). As the choice of the time scale in the analysis of a cohort study with time-dependent covariate is known to be important (14), the present analysis was completed using the age as the time scale. In the classic approach, for each woman, the time scale is the time elapsed since the entry into the study. As the age at entry into the study varies from one woman to another and is known to be related to the incidence of breast cancer, it is incorporated into the model as a covariate. However, another approach consists in using the age reached as a time scale, allowing for comparison between patients at each event time. This approach has been shown to be less biased than the previous one and particularly adapted in cohort studies.

Results

The present study was restricted to the women free of any hormonal treatment ($n = 247$), who were classified according to the presence and the duration of cyclical mastalgia. Among

those 247 women, corresponding to a mean follow-up of 16 years (SE, 5 years) and a total of 3,860 person-years, 22 breast cancers occurred. The mean attrition rate for the women lost to follow-up in the cohort was 1.4% per year.

The presence of mastalgia was reported in 77 women. Among them, 38 women reported cyclical mastalgia only before the inclusion in this study, whereas 18 women complained of cyclical mastalgia during the follow-up period and 21 both before and after the inclusion in this cohort study.

A summary of women characteristics with or without mastalgia is shown in Table 1. No significant differences were found as far as age at inclusion, age at menopause, age at first full-term pregnancy, age at menarche, or breast biopsy. Only the occurrence of menopause during follow-up differed between the two groups ($P = 0.04$). All other risk factors for breast cancer were not different between the two groups.

Using a Cox model with duration of cyclical mastalgia as a time-varying variable, the RR of breast cancer, adjusted on age and type of associated BBD, significantly increased with the duration of cyclical mastalgia (Table 2). Overall, the presence of cyclical mastalgia was associated with a significant increase of the RR of breast cancer (RR, 3.6; 95% CI, 1.5-8.4). These results remained unchanged when other confounding factors, like parity, age at menarche, breast biopsy, familial history of breast cancer, or menopausal status (as a time-varying covariate), were taken into account in the analysis. When analyzing with age as time scale, the adjusted RR for ever versus never occurrence of mastalgia was 4.5 (95% CI, 1.8-11.1), whereas the adjusted RRs were 3.4 (95% CI, 1.2-10.2) and 6.1 (95% CI, 2.1-17.1) for 1 to 36 and ≥ 37 months versus no mastalgia, respectively ($P_{\text{trend}} = 0.00038$).

Discussion

We have done an analysis of a subgroup of a French cohort study of patients reporting BBD and free of hormonal treatment related to a diagnosis of breast cancer. A significant association of cyclical breast tenderness with breast cancer in women has been identified in this cohort study. In addition, a significant linear trend was observed with the duration of cyclical mastalgia during the reproductive life. This association was present when the breast symptom was analyzed in a univariate fashion and persisted in multivariate analyses. To our knowledge, this study is the first to report a significant increase in breast cancer risk in relation to cyclical mastalgia based on prospectively collected data, using a standardized questionnaire.

We have previously reported in a case-control study with 420 premenopausal cases and controls, matched by age and age at first full-term pregnancy, that a history of cyclical mastalgia was associated with an increased risk of breast cancer (odds ratio, 2.12; 95% CI, 1.3-3.4), with increasing levels of risk with increasing duration of cyclical mastalgia (7).

The second study of cyclical mastalgia included 200 premenopausal women recently diagnosed with breast cancer

Table 1. Characteristics of women according to the status of mastalgia

	Absence of mastalgia ($n = 170$)	Presence of mastalgia ($n = 77$)	Significance <i>P</i>
Age (y), mean \pm SE	39.7 \pm 0.6	40.0 \pm 0.9	0.78
Fibrocystic disease, <i>n</i> (%)	109 (61.6%)	40 (51.9%)	0.10
Familial history of breast cancer, <i>n</i> (%)	16 (9.4%)	6 (7.8%)	0.86
Menopause during follow-up, <i>n</i> (%)	127 (71.8%)	47 (61.0%)	0.04
Age at menopause, mean \pm SE	50.3 \pm 0.4	51.2 \pm 0.5	0.16
Age at first full-term pregnancy, mean \pm SE	25.1 \pm 0.4	24.9 \pm 0.5	0.81
Age at menarche, <i>n</i> (%)			
8-12 years	49 (28.8%)	20 (26.0%)	0.51
13 years	48 (28.2%)	18 (23.4%)	
≥ 14 years	73 (43.0%)	39 (50.6%)	
Breast biopsy, <i>n</i> (%)	46 (27%)	14 (18%)	0.13

Table 2. RR of breast cancer according to the duration of cyclical mastalgia in 247 patients with untreated BBD

Duration of mastalgia (mo)	No. women	No. breast cancer	RR ¹ (95% CI)	<i>P</i> _{trend}
0	170	9	1.0*	0.006
1-36	45	6	2.91 (1.01-8.40)	
37+	32	7	5.31 (1.92-14.72)	

NOTE: Estimated by a semiparametric proportional hazards Cox model, taking into account age at inclusion, type of BBD, parity, familial history of breast cancer, breast biopsy, and menopausal status (as a time-varying covariate).

*Reference category.

and a similar number of age-matched controls (8). The pain data were collected over a 1-month period, and women were asked to complete breast symptom cards daily, with the cases reporting on pain in the contra lateral 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 (odds ratio, 1.35; 95% CI, 1.01-1.83).

Another study has examined breast pain in all women (5,463 women) seen at the Breast Care Centre of the University Hospital in Syracuse, NY (15). The age-adjusted odds ratio for breast cancer was 0.60 (95% CI, 0.50-0.74). In this population-based study, women who experienced breast pain were less likely to be diagnosed with breast cancer than women who did not complain of breast pain. However, the authors have not attempted to distinguish cyclical from noncyclical mastalgia and have not required any minimum duration of exposure to breast pain.

The different forms of breast pain have different mechanisms and probably different implications for breast cancer risk. The fact that, in our study, cyclical mastalgia was prospectively collected in a standardized fashion before the diagnosis of breast cancer, brings additional and concordant evidence, yet of higher level, of the independent value of a simple clinical marker of the breast tissue susceptibility to its hormonal microenvironment, and justifies further investigation. The crude attributable risk in this small cohort study was 0.42. This number corresponds to the ratio of the difference between the overall breast cancer incidence in the studied population and the breast cancer incidence in the population of women who never experienced mastalgia to the overall breast cancer incidence in the studied population. Both incidences were calculated as the ratio of the number of observed cases by the corresponding total of person – months of follow-up. This estimation leads to five breast cancers for 100,000 women per year potentially attributable to this symptom. The above calculation was based on the data from our cohort and thus cannot be extrapolated to the general population.

Our results are observed in a small subgroup of the entire French cohort study of BBD. We do not believe that the association between cyclical mastalgia and breast cancer risk might be due to some bias for the following reasons. First, breast symptoms were recorded prospectively to avoid the effects of a recall bias. Second, study subjects were unaware of the study hypothesis, thereby minimizing the effects of an attention bias. Finally, we have excluded all women with hormonal treatment to avoid any induced modifications of hormonal microenvironment. No data regarding differential frequencies of mammography use during follow-up were available in women in relation to the presence of cyclical mastalgia. We cannot definitively rule out an ascertainment bias associated with a more careful and regular follow-up in women with cyclical mastalgia. However, it is not a common practice to repeat mammography especially in women with cyclical mastalgia, as it faces a high proportion of false-positive results in this age range. In addition from the clinician point of view, repeating mammography in women with breast pain is not well accepted. If we assume that each biopsy in our cohort was

preceded by a mammography, our data show that there was no statistical difference between the frequencies of biopsy in both groups (Table 1), suggesting, at least, that the frequencies of breast imaging in the mastalgia group did not lead to a higher frequency of suspicious images requesting cytology checking.

These results must be interpreted with caution considering the subjectivity of this symptom. However, under a strict clinical definition, cyclical mastalgia might represent an important confounding factor when assessing the effects of hormonal treatment on breast cancer risk, such as hormonal replacement therapy or oral contraceptives. Whether treating this symptom could decrease the individual breast cancer risk remains to be shown.

Appendix A

Practical questions asked to the study subjects to detect and characterize a cyclical mastalgia. These questions were separately recorded for the immediate period preceding the interview and the other periods of the genital life, as determined by marking events like puberty, first oral contraceptive use, first pregnancy, and so on.

- Do (did) you experience breast pain or tenderness?
- Is (was) this breast pain or tenderness bilateral?
- Is (was) the symptom isolated or associated with bilateral breast lumps or nodules?
- Is (was) this breast pain or tenderness associated with an increase in volume of your breast? To what extent? Do (did) you change your bra size? Are (were) you forced to sleep on your back? Does (did) it interfere with your social, professional, or private life?
- What is (was) the timing of the symptom: Do (did) the symptom disappear or is (was), at least, relieved the day the menstrual bleeding starts? If so, how far from the next menses does (did) it start usually? Less than 4 days or >3 weeks?
- Do (did) you experience this symptom continuously for >6 months? When and how did it disappear?

References

1. Mansel RE. ABC of breast diseases. Breast pain BMJ 1994;309:866–8.
2. Hughes LE, Mansel RE, Webster DJT. Benign disorders and diseases of the breast concepts and clinical management. 2nd ed. London: WB Saunders;2000.
3. Millet AV, Dirbas FM. Clinical management of breast pain: a review. Obstet Gynecol Surv 2002;57:451–61.
4. Wisbey J-R, Mansel R-E, Pye J-K, Kumar S, Preece RE, Hughes LE. Natural history of breast pain. Lancet 1983;ii:672–4.
5. Klimberg SV. Etiology and management of breast pain. In: Bland KL, Copeland EM, editors. The breast: comprehensive management of benign and malignant diseases. 2nd ed. Philadelphia: WB Saunders Co; 1988. pp. 247–60.
6. Wang FY, Fentiman IS. Epidemiology and endocrinology of benign breast disease. Breast Cancer Res Treat 1985;6:5–36.
7. Plu-Bureau G, Thalabard JC, Sitruk- Ware R, Asselain B, Mauvais- Jarvis PM. Cyclical mastalgia as a marker of breast cancer susceptibility: results of a case- control study among French women. Br J Cancer 1992;65:945–9.
8. Goodwin PJ, Deboer G, Clark RM. Cyclical mastopathy and premenopausal breast cancer risk: results of a case-control study. Breast Cancer Res Treat 1994;33:63–73.
9. Plu- Bureau G, Lê M, Sitruk- Ware R, Thalabard JC, Mauvais- Jarvis PM. Progesterone use and risk of breast cancer in a cohort study of premenopausal women with benign breast disease. Br J Cancer 1994;70:270–7.
10. Plu-Bureau G, Lê M, Thalabard JC, Sitruk-Ware R, Mauvais-Jarvis P. Percutaneous progesterone uses and risk of breast cancer: results from a French cohort study of premenopausal women with benign breast disease. Cancer Detect Prev 1999;23:290–6.
11. Haagensen CD. Physician's role in the detection and diagnosis of breast disease. In: Haagensen CD, editor. Diseases of the breast. Philadelphia: Saunders WB; 1971. p. 99–148.
12. Cox DR. Regression models and life tables. J R Stat Soc 1972;2:187–220.
13. R statistical package Release 2.0.0.1 <http://www.r-project.org>.
14. Thiebaut AC, Benichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Stat Med 2004;23:3803–20.
15. Khan SA, Apkarian AV. Mastalgia and breast cancer: a protective association? Cancer Detect Prev 2002;26:192–6.