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Menstrual Cycle Patterns and the Risk of Breast Disease*

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Abstract—*The relationship between menstrual cycle patterns and the risk of breast disease was evaluated using data from a hospital-based case-control study of* 288 *women with benign breast disease* (203 *chronic cystic diseases and* 85 *benign tumours*), 317 *with breast cancer and* 602 *age-matched controls with a spectrum of acute conditions unrelated to any of the established or potential risk factors for breast disease. A lifelong irregular menstrual pattern* [*defined as frequent occurrence of menstrual-like episodes of bleeding less than* 21 *or more than* 35 days *apart*) *was negatively associated with the risk of benign breast lesions* (*relative risk, RR* = 0.6, *with* 95% *confidence interval* = 0.4–1.0) *and of breast cancer* (*RR* = 0.4, *with* 95% *confidence interval* = 0.3–0.8]. *This inverse association could not be explained by any of the identified potential confounding factors, including the major risk factors for breast disease. The findings of this study, showing that a lifelong history of irregular* (*and hence more likely anovular*) *cycles was less frequent among women with benign and malignant breast diseases, support the hypothesis that frequent ovular cycles might be more carcinogenic than anovular ones.*

INTRODUCTION

THERE is a well-defined positive relation between total duration of menstrual activity and breast cancer, as the risk is reportedly greater in women with early menarche and late menopause [1]. It was originally suggested that women with early menarche and late menopause had longer duration of exposure to anovular cycles, and it was proposed that unopposed oestrogen stimulation during long and frequently anovular cycles, characterized by luteal inadequacy and decreased progesterone secretion, was the most favourable state for breast cancer induction (the so-called 'oestrogen window hypothesis') [2].

However, data from a case-control study of breast cancer in women below age 33 yr indicated that early establishment of regular cycles was associated with an elevated breast cancer risk [3], thus suggesting that endogenous progesterone levels might be positively related to the risk of breast cancer. This view was further strengthened by analyses of serum specimens of a group of healthy Finnish school-girls to determine the frequency of ovulation [4], and of urine specimens from countries with different average ages at menarche and different breast cancer risk [5]. The probability of a cycle being anovular was, in those studies, inversely and significantly related to the time elapsed since menarche and, with time since menarche held constant, positively associated with age at menarche, thus suggesting that women with early menarche have shorter, not longer, duration of exposure to anovular cycles. Furthermore, data from a retrospective study indicated that women with breast cancer reported shorter average menstrual cycle length, long cycles (>30 days) being extremely uncommon in breast cancer patients (2 vs 28% in the control group) [6]. Finally, the potential influence of progestin levels on the risk of breast cancer has recently gained widespread interest, after the report of a positive association between the use of 'high progestogen potency' combination oral

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contraceptives and breast cancer in young women [7].

The present paper further evaluates the relation between lifelong menstrual cycle pattern and the risk of breast cancer, as well as of pathologically confirmed benign breast disease, using data from a case-control study conducted in Milan.

MATERIALS AND METHODS

Since 1981 we have been conducting a case-control study of benign and malignant breast disease. Trained interviewers identified and questioned women admitted for breast disease and for a wide spectrum of other conditions to university and general hospitals of the Greater Milan area. On average, less than 2% of the eligible women (cases or controls) refused to be interviewed.

A standard questionnaire was used to obtain information on personal characteristics and habits, related medical history and history of lifetime use of female hormones for contraception or other reasons. Among several questions related to obstetrical and gynaecological variables, the subjects interviewed were simply asked whether their lifelong menstrual pattern was considered regular or irregular (frequent menstrual-like episodes of bleeding less than 21 or more than 35 days apart); no information was collected on the duration of cycles.

The present study is based on data collected before 31 December 1983. A general paper on the epidemiology of benign breast disease has been previously published [8].

The cases of benign breast disease were women with histologically confirmed benign breast lesions admitted for the first time to the Division of Medical Oncology of the National Cancer Institute of Milan to undergo breast biopsy. A total of 288 subjects aged 17-64 yr met this criterion. Among them, 85 (30%) had benign tumours (77 fibroadenomas and eight papillomas) and 203 (70%) had dysplastic lesions (21 ductal hyperplasias, 49 other dysplasias such as fibrosclerosis or adenosis, 133 mixed dysplastic lesions). All pathological material was reviewed at the Department of Pathology of the National Cancer Institute.

Only clinically relevant breast lumps, often suspected of malignancy, are referred to and biopsied at the Cancer Institute, which represents a 'second level' reference centre from a network of outpatient clinics covering the Greater Milan area for a widespread programme of screening for breast diseases.

Breast cancer cases were women below the age of 75 yr admitted, or referred for follow-up, to outpatient clinics of the National Cancer Institute and Ospedale Maggiore of Milan, with a pathologically confirmed diagnosis made within the previous year. A total of 317 women, aged 24-74 yr, were interviewed.

The control subjects were women admitted for acute conditions to university or general hospitals in Milan serving a catchment area similar to that of the hospitals where cases had been identified. They had diseases other than malignant, hormonal or gynaecological, diagnosed within the year before the interview. For each case one control was matched for age in 5-yr intervals. The two control groups (for benign and malignant breast diseases) were chosen with the same criteria but were independent, so that the same control subject could not be matched both with a patient with breast cancer and a patient with a benign lesion. Among the 285 control subjects matched with cases of benign breast diseases, 45% had musculo-skeletal diseases (trauma or other orthopaedic conditions), 14% were admitted for acute abdominal disorders that generally required operations and 42% had other illnesses, such as ear, nose and throat or dental disorders. Among the 317 controls matched with cases of breast cancer, these proportions were 59, 8 and 32% respectively.

The age distributions of cases of breast cancer, benign breast disease (further subdivided into benign tumors and dysplastic lesions) and their matched controls are given in Table 1.

Table 1. *Distribution of cases and controls according to histo-pathological classification and age, Milan, Italy,* 1981-1983

	Benign breast disease				
Age (yr)	Benign tumours	Dysplasias	Controls	Breast cancer	Controls
<30	21	17	37	6	6
30-39	29	53	80	36	36
40-49	30	98	128	90	90
50-59	5	30	35	87	87
60-69	-	5	5	66	66
70-74	-	-	-	32	32

Data analysis

Odds ratios (as estimators of relative risks, RR) [9] for benign and malignant breast disease in women with different menstrual patterns, together with their 95% approximate confidence intervals (CI) [10], were computed using an unmatched approach [9]. Adjustments for age and other factors were made using the usual Mantel-Haenszel method [11]. The relative risk estimates were adjusted, in turn, for a large number of variables (age, years of education, marital status, age at menarche, menopausal status, age at menopause, parity, age at first birth, smoking habits, body mass index and oral contraceptive use). However, since most of the adjustments did not materially change the relative risk estimates, unadjusted ones were chosen for presentation, except when indicated in the text.

All P values reported are two-sided.

RESULTS

The proportion of women reporting frequent irregular cycles was lower among the 288 cases of benign breast disease (13%) than among the 285 controls (19%), giving an overall relative risk estimate of 0.6 (95% CI = 0.4-1.0, Table 2). The negative association was statistically significant on the whole series ($\chi^2_1 = 3.85, P = 0.05$) and in the subgroup with dysplastic lesions (Mantel-Haenszel, age-adjusted $\chi^2_1 = 4.21$, $P = 0.04$), whereas it was apparently less marked (RR = 0.8), and not statistically significant, for women with benign breast tumors.

Likewise, cases of breast cancer reported a significantly lower proportion of menstrual irregularities than did controls, giving a point estimate even lower than that of benign lesions (RR = 0.4, 95% CI = 0.3-0.8, Table 3).

Post-menopausal women (or, more generally, older women) tended to recall menstrual irregularities less frequently than did younger ones, a finding which may simply reflect a less reliable recall of menstrual patterns at older age. Data in Table 4 show that the proportion of women reporting frequent menstrual irregularities was similar, below the age of 50 yr, in the control group for breast cancer (19%) and in that for benign breast disease (21%). The negative association between an irregular menstrual pattern and breast disease was evident in the various age groups considered; consequently, adjustment for age did not materially change the risk estimates.

Menstrual cycle patterns of cases and controls were also compared within strata of age at menarche and at menopause, parity, age at first birth, body mass index and oral contraceptive use (Table 4): there was no evidence that the association was confined to any particular subgroup (the differences observed between the two control groups simply reflect their disparate age distribution). Likewise, the results were practically unchanged when allowance was made for the potential confounding effect of these covariates by means of the Mantel-Haenszel procedure.

DISCUSSION

The findings of the present study show a negative association between menstrual irregularities and breast disease. The estimated protection was apparently less marked and of

Table 2. Lifelong menstrual pattern among 288 cases of benign breast disease and 285 controls, Milan, Italy, 1981-1983

Lifelong menstrual pattern	Benign breast disease		Controls	Relative risk estimate (95% CI)
	Benign tumours*	Dysplasias*		
Regular	71	177	229	1†
Irregular	14	24	55	0.6 (0.4-1.0)
Unknown	-	2	1	-

*Age-adjusted relative risks: benign tumors: 0.8 (95% CI = 0.4-1.4); dysplasias: 0.6 (95% CI = 0.3-1.0).
†Reference category.

Table 3. Lifelong menstrual pattern among 317 cases of breast cancer and 317 controls, Milan, Italy, 1981-1983

Lifelong menstrual pattern	Breast cancer	Controls	Relative risk estimate (95% CI)
Regular	296	275	1†
Irregular	19	40	0.4 (0.3-0.8)
Unknown	2	2	-

†Reference category.

Table 4. Proportions of women reporting irregular menstrual patterns among cases of breast disease and matched controls according to selected variables, Milan, Italy, 1981-1983

	Benign breast disease				Breast cancer			
	Cases		Controls		Cases		Controls	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Age (yr)								
<50	35	(14)	51	(21)	10	(8)	25	(19)
≥50	3	(8)	4	(10)	9	(5)	15	(8)
Age at menarche (yr)								
<15	35	(14)	43	(18)	15	(6)	30	(16)
≥15	3	(8)	12	(24)	4	(9)	10	(14)
Age at menopause (yr)								
Pre-menopause	35	(15)	45	(20)	9	(7)	24	(19)
<50	3	(8)	10	(17)	8	(8)	9	(9)
≥50					2	(3)	7	(7)
Parity								
0	13	(18)	17	(22)	4	(6)	13	(18)
1-2	21	(12)	30	(21)	13	(7)	17	(10)
≥3	4	(10)	8	(13)	2	(4)	10	(14)
Age at first birth (yr)								
<25	11	(11)	16	(15)	6	(4)	17	(12)
≥25	14	(12)	22	(21)	9	(8)	10	(10)
Body mass index (kg/m²)								
<25	29	(12)	41	(19)	13	(6)	21	(12)
≥25	9	(19)	14	(21)	6	(6)	19	(14)
Oral contraceptive use								
Never	22	(10)	44	(18)	12	(4)	31	(11)
Ever	16	(21)	11	(28)	7	(17)	9	(23)
Total	38	(13)	55	(19)	19	(6)	40	(13)

borderline statistical significance for benign breast lesions but more clear and highly significant for breast cancer. It is unlikely that bias explains our findings. With regard to recall bias, menstrual pattern was but one of a large number of items on which information was elicited. Furthermore, we can see no obvious reason why women with breast disease should systematically report less frequent menstrual irregularities than controls (in fact, more accurate recall in the cases might well be plausibly expected, thus leading to an underestimate of the actual differences). Likewise, selection bias appears unlikely, since 98% of eligible women participated. With regard to confounding, the results were virtually unmodified when a large number of factors were taken into account. The same type of information on menstrual pattern was collected in companion studies on ovarian and cervical cancers (unpublished data): no material difference emerged between cases and controls, the proportion of subjects reporting frequent lifelong irregular cycles ranging from 12 to 14%. In the case of endometrial cancer a positive association, as expected, was evident, with a relative risk estimate elevated for a factor of about two.

Although this finding is apparently consistent, and not affected by manifest biases, there are major limitations in the present data which produce obvious difficulties in their interpretation. The most important one is related to the type of information available, which is limited to a simple distinction between 'regular' and 'irregular' menstrual cycles (defined as frequent menstrual-like episodes less than 21 or more than 35 days apart), with no specification of duration or other factors of potential interest. Although these limitations are substantial, they do not entirely eclipse these findings. A regular menstrual pattern, of course, does not guarantee regular ovulation with luteal-phase progesterone secretion; however, women with regular cycles do have higher levels of luteal-phase progesterone than women with irregular ones (at least in the first years after menarche [12]). Consequently, irregular cycles can be reasonably assumed to be more frequently anovular. In this regard, it may also be of interest to notice that nulliparous women more frequently reported menstrual irregularities (Table 4).

Thus the results of the present study give support to the hypothesis that frequent ovular menstrual cycles might be more carcinogenic to

breast tissue than anovular ones. Previous studies on menstrual patterns in women with breast disease, mostly concentrated on the earlier post-menarche years, were generally in agreement with the present findings. Data from a case-control study of breast cancer in young women showed that early establishment of regular cycle intervals was more common among the cases [3], and analyses of longitudinally recorded menstrual and reproductive events and of serum and urine specimens indicated that women with early menarche (and hence at increased risk of breast cancer) had earlier establishment of regular [13] and ovular [4, 5] cycles. Furthermore, data from a retrospective study conducted in Sweden showed that very short (<21 days) but not long (>30 days) cycles were a feature of patients with malignant and, less frequently, benign breast disease. It is thus possible that repeated ovulation at short intervals may increase the risk of breast disease [6]. This hypothesis found further support on the observation that mitotic activity in the breast should be higher during the luteal phase of the cycle [14, 15]. There are, however, equivocal or inconclusive results as regards this. For example, MacMahon *et al.* [16] reported a frequency of anovulation of 0.14 in 94 premenopausal women with breast cancer, compared to 0.09 in 70 controls, whereas Trichopoulos *et al.* [17] showed an estimated lower proportion of ovulation among young Chinese women in low-risk areas for breast cancer (0.46), but no trend of increasing frequency from intermediate- (0.65) to high-risk areas (0.55). Finally, the relation, if confirmed, between regular ovulation and breast cancer risk, apart from its intrinsic interest, might have important implications with respect to the reported association of 'high progestogen potency' oral contraceptives with breast cancer [7]. In that case, exogenous and not endogenous progestogen levels could be the link between oral contraceptive use and the elevated risk of breast cancer.

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REFERENCES

1. Kelsey JL. A review of the epidemiology of human breast cancer. *Epidemiol Rev* 1979, **1**, 74-109.
2. Korenman SG. Oestrogen window hypothesis of the aetiology of breast cancer. *Lancet* 1980, **i**, 700-701.
3. Henderson BE, Pike MC, Casagrande JT. Breast cancer and the oestrogen window hypothesis. *Lancet* 1981, **ii**, 363-364.
4. Apter D, Vihko R. Early menarche, a risk factor breast cancer, indicates early onset of ovulatory cycles. *J Clin Endocrinol Metab* 1983, **57**, 82-86.
5. MacMahon B, Trichopoulos D, Brown J *et al.* Age at menarche, probability of ovulation and breast cancer risk. *Int J Cancer* 1982, **29**, 13-16.
6. Olsson H, Landin-Olsson M, Gullberg B. Retrospective assessment of menstrual cycle length in patients with breast cancer, in patients with benign breast disease, and in women without breast disease. *JNCI* 1983, **70**, 17-20.
7. Pike MC, Henderson BE, Krailo MD, Duke A, Roy S. Breast cancer in young women and use of oral contraceptives: possible modifying effect of formulation and age at use. *Lancet* 1983, **ii**, 926-930.
8. Parazzini F, La Vecchia C, Franceschi S *et al.* Risk factors for pathologically confirmed benign breast diseases. *Am J Epidemiol* 1984, **111**, 115-122.
9. Breslow NE, Day NE. *Statistical Methods in Cancer Research, Vol. 1. The Analysis of Case-control Studies.* Lyon, IARC, 1980.
10. Miettinen O. Estimability and estimation of case-referent studies. *Am J Epidemiol* 1976, **103**, 226-235.
11. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *JNCI* 1959, **22**, 719-748.
12. Lee PA, Xenakis T, Winer J, Matsenbaugh S. Puberty in girls: correlation of serum levels of gonadotropins, prolactin, androgens, estrogens, and progestins with physical changes. *J Clin Endocrinol Metab* 1976, **43**, 775-784.
13. Wallace RB, Sherman BM, Bean JA, Leeper JP, Treloar AE. Menstrual cycle patterns and breast cancer risk factors. *Cancer Res* 1978, **38**, 4021-4024.
14. Masters JRW, Drife JO, Scarisbrick JJ. Cyclic variation of DNA synthesis in human breast epithelium. *JNCI* 1977, **58**, 1263-1265.
15. Ferguson DJP, Anderson TJ. Morphological evaluation of cell turnover in relation to the menstrual cycle in the "resting" human breast. *Br J Cancer* 1981, **44**, 177-181.

16. MacMahon B, Cole P, Brown JB, Paffenbarger R, Trichopoulos D, Yen S. Urine estrogens, frequency of ovulation, and breast cancer risk: case-control study in premenopausal women. *JNCI* 1982, **70,** 247-250.
17. Trichopoulos D, Yen S, Brown J, Cole P, MacMahon B. The effect of westernization on urine estrogens, frequency of ovulation, and breast cancer risk. *Cancer* 1984, **53,** 187-192.