Menstrual Cycle Characteristics and Incidence of Premenopausal Breast Cancer

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Abstract

Background: **Epidemiologic studies have indicated that menstrual cycle characteristics such as age at menarche and age at menopause are associated with breast cancer risk. Anovulation, which is more common with long or irregular cycles, has been hypothesized to reduce the incidence of breast cancer.**

Methods: **We analyzed data from the Nurses' Health Study II, a cohort of 116,671 female registered nurses ages 25 to 42 years at baseline. Information on menstrual cycle characteristics was assessed in 1989 and 1993, and incident cases of premenopausal breast cancer were ascertained through 2001.**

Results: **During 1,135,496 person-years of follow-up (1989-2001), 1,163 incident cases of invasive premenopausal breast cancer were diagnosed. Overall, women with long menstrual cycles at ages 18 to 22 years (>32 days or too irregular to estimate) did not experience a significantly lower breast cancer risk compared with women with normal cycle lengths (26-31 days) at that age [covariate-adjusted hazard ratio (HR), 0.92; 95% confidence interval (95% CI), 0.79-1.06]. Among women ages <40 years, those with menstrual cycles lasting >32 days or too irregular to estimate at ages 18 to 22 years had a decreased incidence of breast cancer (covariate-adjusted HR, 0.71; 95% CI, 0.53-0.97). Current menstrual cycle characteristics were not associated with breast cancer incidence.**

Conclusion: **Overall, longer or irregular cycles at ages 18 to 22 years or in early adulthood were not associated with reduced premenopausal breast cancer risk. However, longer menstrual cycles at ages 18 to 22 years were associated with a lower incidence of premenopausal breast cancer before age 40.** (Cancer Epidemiol Biomarkers Prev 2005;14(6):1509–13)

Introduction

Epidemiologic studies have consistently found that age at menarche and age at menopause are associated with breast cancer risk (1). Both of these characteristics contribute to the number of lifetime menstrual cycles and consequently influence exposure to the ovarian hormones that accompany each cycle. It has been suggested that a reduced number of lifetime ovulatory cycles may reduce the risk of breast cancer (2).

Each menstrual cycle is divided into a follicular phase and a luteal phase. In the follicular phase, progesterone levels are low and estrogen levels increase in anticipation of ovulation. In the luteal phase, both progesterone and estrogen are elevated. The length of the luteal phase remains relatively constant, whereas the length of the follicular phase can vary dramatically (3). Therefore, women with longer menstrual cycles spend more time in the follicular phase than in women with shorter menstrual cycles.

In 1977, two groups found that breast cell proliferation is significantly higher in the luteal phase than the follicular phase (4, 5). Subsequently, epidemiologic evidence has indicated that the combination of exogenous estrogen plus progestin increases the risk of breast cancer beyond the effect of estrogen alone (6, 7). However, these studies were restricted to postmenopausal women, and whether the same exogenous hormone combinations alter premenopausal breast cancer risk is unknown.

Because estrogen and progestin together increase breast cell proliferation, women who spend a smaller proportion of their menstrual cycle in the luteal phase due to longer a follicular phase or anovulation may have a reduced risk of breast cancer.

We evaluated long or irregular menstrual cycles in relation to premenopausal breast cancer risk in the Nurses' Health Study II cohort. We have previously reported preliminary data on these associations, based on limited follow-up (8). Here we provide an updated analysis, including almost five times the number of breast cancer cases.

Materials and Methods

In 1989, 116,671 female registered nurses ages 25 to 42 years and living in one of 14 U.S. states responded to a baseline questionnaire about their medical histories and lifestyles. Women who reported cancer at enrollment (not including nonmelanoma skin cancer) were excluded. Follow-up questionnaires have been sent biennially to update information on risk factors and medical events, and the average follow-up for the cohort exceeds 90%. This study was approved by the Institutional Review Boards of the Brigham and Women's Hospital, Boston, MA and the Harvard School of Public Health, Boston, MA.

The baseline questionnaire in 1989 queried participants about the characteristics of their menstrual cycle. Information was requested on the length of their menstrual cycle from ages 18 to 22 years (<21, 21-25, 26-31, 32-39, 40-50, >50 days, or too irregular to estimate) and on the menstrual cycle pattern at ages 18 to 22 years. For the menstrual pattern question, participants were asked to exclude ''time around pregnancies or when using oral contraceptives.'' Response options for the menstrual pattern question included very regular (±3 days),

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regular, usually irregular, always irregular, and no periods. Over 99% of the participants responded to the question regarding menstrual cycle length at ages 18 to 22 years, and 97% of the participants responded to the question regarding menstrual cycle pattern at ages 18 to 22 years. Because menstrual cycle characteristics at ages 18 to 22 years may differ from other time points in adult life, we also evaluated current menstrual cycle characteristics in relation to breast cancer risk. In 1993, participants were asked to describe their current menstrual cycle length and pattern using the same categories that were offered in the baseline questionnaire, but this time, the menstrual pattern question did not ask participants to exclude time around pregnancies or oral contraceptive use. Because oral contraceptives change menstrual cycle characteristics, we excluded women who regularly used oral contraceptives (details provided in statistical analysis). On the 1993 questionnaire, 97% of premenopausal participants responded to the question about current menstrual cycle length and 87% responded to the question about current menstrual cycle pattern.

Two separate analyses were done. In the first analysis, we evaluated menstrual cycle characteristics at ages 18 to 22 years as reported on the baseline questionnaire (1989) and breast cancer incidence between 1991 and 2001. In the second analysis, we evaluated current menstrual cycle characteristics as reported in 1993 and breast cancer incidence between 1995 and 2001.

Exposure to potential confounding variables was measured at baseline and during follow-up. Participants were asked about their date of birth, age at menarche, family history of breast cancer (in mother, sister, or grandmother), weight at age 18, and height at baseline. In addition, the following variables were assessed on baseline and subsequent questionnaires: weight, history of benign breast disease, parity, age at first birth, alcohol intake, oral contraceptive use, and physical activity. Data from subsequent questionnaires were used to update information on confounding variables for each individual in each time period.

Documentation of Breast Cancer. New cases of breast cancer were identified through biennial questionnaires mailed between 1991 and 2001. Deaths were reported by family members or by the Postal Service in response to the follow-up questionnaires, and the National Death Index was searched to investigate the death of nonresponders. When a case of breast cancer was reported, we asked the participant (or next of kin for those who had died) for confirmation of the diagnosis and for permission to obtain relevant hospital records and pathology reports. We confirmed 98% of the breast cancer cases with pathology reports. Cases of carcinoma *in situ* were censored at the time of diagnosis. Breast cancer rates in the Nurses' Health Study are comparable with those reported by the national Surveillance, Epidemiology, and End Results study (9).

Statistical Analysis. Women were excluded at baseline if they had a diagnosis of breast cancer (n = 16), were postmenopausal (n = 2821), or did not report height (n = 232) or weight (n = 95). For analyses involving exposures first measured in 1993, exclusions were updated to reflect characteristics of the population in 1993, including women who died by 1993 (n = 123), had a diagnosis of breast cancer by 1993 (n = 343), were postmenopausal in 1993 (n = 5069), or did not report height (n = 229) or weight (n = 45). Women who did not answer questions regarding the main exposure of interest were excluded.

In addition, if questions regarding menstrual characteristics did not specify that only menstrual cycles occurring while not pregnant or using oral contraceptives should be considered in answering the question, then regular oral contraceptive users were excluded. In analyses of menstrual cycle characteristics at ages 18 to 22 years, we considered regular oral contraceptive use to be ≥10 months of use per year at those ages (n = 6,669), and in analyses of menstrual cycle characteristics in 1993, we considered regular oral contraceptive use to be ≥20 months of use since June 1991 (n = 7,295).

Women were censored during follow-up when they reported that they had reached menopause, developed breast cancer, or failed to report their weight in three or more questionnaires. Each participant contributed follow-up time, measured in months, from the return of the 1989 questionnaire until a diagnosis of breast cancer, death, return of the 2001 questionnaire, or last returned questionnaire if lost to follow-up. For exposures that were first assessed in 1993 (current menstrual cycle length and current menstrual pattern), analyses included follow-up between 1995 and 2001.

We used Cox proportional hazards regression models to estimate the hazard ratio (HR) of breast cancer while controlling for potential confounding variables. Covariate-adjusted models included age in months, family history of breast cancer (binary), history of benign breast disease (binary), height (continuous), current body mass index (kg/m^2; continuous), body mass index at age 18 (continuous), age at menarche (<10, 11, 12, 13, 14, >15), parity (0, 1, 2, 3, >4), age at first birth (<24, 25-30, and >30 years), oral contraceptive use (never user, past user <5 years, past user >5 years, current user <5 years, current user 5-9 years, current user >10 years), alcohol intake (0, <7.5, 7.5-15, 15-29, and >30 g/d), and physical activity (<3, 3-9, 9-17, 18-26, 27-41, and >42 mets/wk). Trend tests were done using the midpoint of the intervals.

Effect modification was assessed by creating the cross-product term between the exposure and possible effect modifier. We measured the significance of the interaction using the Wald test. Age-stratified analyses were done by assessing participants' person-time contribution and case status before and after 40 years of age separately.

Results

Among premenopausal women in the Nurses' Health Study II cohort, 1,163 incident cases of invasive breast cancer developed during 1,135,496 person-years of follow-up between 1989 and 2001.

Women with long menstrual cycles at ages 18 to 22 years (>40 days or too irregular to estimate) did not experience a significant decrease in breast cancer risk compared with women with normal cycle lengths (26-31 days) at that age [covariate-adjusted HR, 0.87; 95% confidence interval (95% CI), 0.69-1.10]. However, there was significant effect modification of the association between cycle length and breast cancer by age (<40 and ≥40 years; P = 0.02). Among women ages <40 years, women with menstrual cycles at ages 18 to 22 years that lasted 32 to 39 days had a nonsignificant decrease in breast cancer risk compared with women with normal cycles (covariate-adjusted HR, 0.73; 95% CI, 0.51-1.05). Among women ages <40 years, those with menstrual cycles at ages 18 to 22 years that lasted ≥40 days or were too irregular to estimate also had a decreased risk but the difference was not significant and power was limited (covariate-adjusted HR, 0.68; 95% CI, 0.41-1.13; Table 1). Increasing menstrual cycle length at ages 18 to 22 years was inversely related to breast cancer incidence (P = 0.07). When the top two categories were collapsed, women ages <40 years with menstrual cycles longer than 32 days or too irregular to estimate had significantly reduced breast cancer incidence compared with women with normal cycles (covariate-adjusted HR, 0.71; 95% CI, 0.53-0.97). No important associations emerged among women ages ≥40 years.

From 1993 to 2001, 910 incident cases of breast cancer were diagnosed during 739,488 person-years of follow-up. Current menstrual cycle length reported by women in 1993 was not associated with breast cancer risk (Table 2). No trend was observed with increasing length of cycle (P = 0.45).

Table 1. HRs of the association between menstrual cycle length at ages 18 to 22 years and premenopausal breast cancer incidence among participants of the Nurses' Health Study II between 1989 and 2001

Menstrual cycle length (d)	No. cases	Person-years of follow-up	Age-adjusted HR (95% CI)	Covariate-adjusted HR* (95% CI)
<26	108	114,797	0.92 (0.75-1.12)	0.91 (0.74-1.12)
26-31	743	700,241	1.00	1.00
32-39	167	165,870	0.95 (0.80-1.12)	0.94 (0.80-1.12)
>40 or too irregular to estimate	78	84,158	0.87 (0.69-1.10)	0.87 (0.69-1.10)
Total	1,096	1,065,066		
P_{trend}				0.38
Women <40 y				
<26	34	66,578	0.95 (0.66-1.37)	0.93 (0.65-1.34)
26-31	212	389,517	1.00	1.00
32-39	36	91,828	0.72 (0.50-1.02)	0.73 (0.51-1.05)
>40 or too irregular to estimate	16	46,637	0.63 (0.38-1.05)	0.68 (0.41-1.13)
P_{trend}				0.07
Women ≥40 y				
<26	74	48,219	0.90 (0.71-1.15)	0.90 (0.70-1.15)
26-31	531	310,724	1.00	1.00
32-39	131	74,042	1.04 (0.86-1.26)	1.02 (0.85-1.24)
>40 or too irregular to estimate	62	37,521	0.97 (0.74-1.26)	0.94 (0.72-1.23)
P_{trend}				0.93

NOTE: Excluding women who used oral contraceptives >10 months every year from ages 18 to 22 years and women who did not answer the question about menstrual cycle length in 1989.
*Adjusted for age, family history of breast cancer, history of benign breast disease, height, current body mass index, body mass index at age 18, age at menarche, age at first birth, parity, alcohol use, physical activity, and current and past oral contraceptive use.

Irregular menstrual cycle pattern from ages 18 to 22 years was not associated with risk of breast cancer in this population (Table 3). Similarly, current menstrual pattern, as reported in 1993, had no association with breast cancer risk (Table 4).

To exclude possible misclassification of menstrual cycle length or pattern due to pregnancy, we did a sensitivity analysis excluding women who were pregnant during the exposure period being considered. The results did not change with the exclusion of these women (data not shown).

Approximately half (55%) of the women reported the same menstrual pattern at both time points (ages 18-22 and 1993). Women who reported different menstrual cycles at the two time points were more likely to change to a more regular menstrual pattern; 55% of women who reported irregular menstrual cycles at ages 18 to 22 years later reported regular cycles in 1993, but only 10% of women who reported regular menstrual cycles at ages 18 to 22 years later reported irregular menstrual cycles in 1993.

Among women who reported consistent menstrual cycle patterns for ages 18 to 22 years and in 1993, the covariate-adjusted HR for breast cancer associated with usually irregular menstrual patterns was 1.04 (95% CI, 0.60-1.80) and with always irregular menstrual patterns or no periods was 1.35 (95% CI, 0.89-2.05) compared with women who had regular menstrual cycles. Women who reported consistently to always have irregular menstrual patterns had a higher body mass index than women with consistently regular menstrual patterns.

Discussion

Our results do not support the hypothesis that long or irregular menstrual cycles reduce the risk of breast cancer among all premenopausal women. However, among younger women, longer menstrual cycles at ages 18 to 22 years may be protective.

In an earlier analysis in our population, we observed an inverse association between breast cancer incidence and long cycle length at ages 18 to 22 years (8). The apparent attenuation of the previous association could be attributable

Table 2. HRs of the association between current menstrual cycle length (1993) and premenopausal breast cancer incidence among participants of the Nurses' Health Study II between 1993 and 2001

Current menstrual cycle length (d)	No. of cases	Person-years of follow-up	Age-adjusted HR (95% CI)	Covariate-adjusted HR* (95% CI)
<26	126	90,663	0.98 (0.80-1.19)	0.98 (0.80-1.19)
26-31	477	379,418	1.00	1.00
>31 or too Irregular to estimate	98	84,203	1.07 (0.86-1.33)	1.09 (0.88-1.37)
Total	701	554,284		
P_{trend}				0.45
Women <40 y				
<26	13	28,798	0.82 (0.46-1.48)	0.80 (0.44-1.43)
26-31	89	159,550	1.00	1.00
>31 or too irregular to estimate	25	43,104	1.05 (0.67-1.64)	1.08 (0.69-1.69)
P_{trend}				0.41
Women ≥40 y				
<26	113	61,865	1.00 (0.81-1.24)	1.00 (0.81-1.24)
26-31	388	219,868	1.00	1.00
>31 or too irregular to estimate	73	41,099	1.07 (0.83-1.38)	1.09 (0.85-1.41)
P_{trend}				0.62

NOTE: Excluding women who used oral contraceptives >20 months since 1991 and women who did not answer the question regarding menstrual cycle length in 1993.
*Adjusted for age, family history of breast cancer, history of benign breast disease, height, current body mass index, body mass index at age 18, age at menarche, age at first birth, parity, alcohol use, physical activity, current and past oral contraceptive use.

Table 3. HRs of the association between menstrual irregularities at ages 18 to 22 years and premenopausal breast cancer incidence among participants of the Nurses' Health Study between 1989 and 2001

Menstrual irregularity (ages 18-22)	No. of cases	Person-years of follow-up	Age-adjusted HR (95% CI)	Covariate-adjusted HR* (95% CI)
Regular	869	838,391	1.00	1.00
Usually irregular	140	154,806	0.89 (0.74-1.07)	0.88 (0.74-1.05)
Always irregular†	115	108,689	1.01 (0.83-1.23)	1.02 (0.84-1.25)
Total	1,123	1,101,886		
P_{trend}				0.70
Among women <40 y				
Regular	249	470,857	1.00	1.00
Usually irregular	39	88,748	0.84 (0.60-1.18)	0.86 (0.61-1.21)
Always irregular†	24	60,805	0.75 (0.49-1.14)	0.79 (0.52-1.20)
P_{trend}				0.20
Among women ≥40 y				
Regular	620	367,534	1.00	1.00
Usually irregular	101	66,058	0.91 (0.74-1.12)	0.89 (0.72-1.10)
Always irregular†	91	47,884	1.12 (0.90-1.40)	1.11 (0.88-1.38)
P_{trend}				0.75

NOTE: Question asks subject to exclude periods around pregnancies or oral contraceptive use; consequently, oral contraceptive users were included in this table. Women who did not answer the question regarding menstrual pattern in 1989 were excluded.
*Adjusted for age, family history of breast cancer, history of benign breast disease, height, current body mass index, body mass index at age 18, age at menarche, age at first birth, parity, alcohol use, physical activity, current and past oral contraceptive use.
†Women with no periods were combined with always irregular women.

to random variation or to the aging of the population. In the previous analysis, we included both premenopausal and postmenopausal women who were followed for 4 years; our updated analysis was restricted to premenopausal women followed for up to 12 years. We found that among women younger than 40 years of age, those with longer cycles at ages 18 to 22 years may have a reduced risk, whereas no association was found among older women. Because the older women have a longer latency period than the younger women, the diminishing effect may be due to increasing time since exposure.

Results from four cohort (8, 10-12) and seven case-control (13-19) studies regarding menstrual cycle length and breast cancer have been inconsistent. Some found an increased risk associated with longer menstrual cycles (11, 13, 15), several found no association (10, 12, 18, 19), and others found a decreased risk (14). In the largest of these studies, Parazzini et al. reported an increased risk among women who had menstrual cycles lasting 31 days or longer (odds ratio, 1.2; 95% CI, 0.9-1.6), but those women whose cycle was too irregular to estimate were at reduced risk (odds ratio, 0.6; 95% CI, 0.5-0.8; ref. 16).

Many of these studies focused on populations that differ from our cohort. For instance, Yuan et al. found an increased risk of breast cancer associated with irregular menstrual cycle length in a sample of Chinese women living in Shanghai (15). Yet, in another study, investigators found a decreased risk of breast cancer associated with long cycle length among Asian American women (14). Because traditional Asian populations have a much lower risk of breast cancer compared with Caucasian women, the results of the study by Yuan et al. may not apply to our study population, which is predominantly Caucasian.

In most studies, data on menstrual cycle characteristics were collected through interview, by telephone (12, 17, 18) or in person (15, 19, 20). Some investigators collected exposure data by asking subjects to keep a diary of their menstrual cycles (11, 13). Although studies that used menstrual diaries benefited from more detailed exposure information, their sample sizes were much smaller than our own. Furthermore, exposure

Table 4. HRs of the association between current menstrual irregularities in 1993 and premenopausal breast cancer incidence among participants of the Nurses' Health Study between 1993 and 2001

Current menstrual irregularity	No. of cases	Person-years of follow-up	Age-adjusted HR (95% CI)	Covariate-adjusted HR* (95% CI)
Regular	645	498,469	1.00	1.00
Usually irregular	36	32,619	0.88 (0.63-1.24)	0.89 (0.63-1.24)
Always irregular†	50	37,576	0.95 (0.71-1.26)	0.98 (0.73-1.31)
Total	731	568,664		
P_{trend}				0.70
Among women <40 y				
Regular	112	195,806	1.00	1.00
Usually irregular	11	13,870	1.48 (0.80-2.76)	1.56 (0.83-2.92)
Always irregular†	6	12,825	0.79 (0.35-1.80)	0.82 (0.36-1.87)
P_{trend}				0.89
Among women ≥40 y				
Regular	533	302,663	1.00	1.00
Usually irregular	25	18,749	0.75 (0.50-1.12)	0.75 (0.50-1.12)
Always irregular†	44	24,751	0.97 (0.71-1.32)	1.01 (0.74-1.38)
P_{trend}				0.66

NOTE: Excluding all women who used oral contraceptives >20 months since 1991 and women who did not answer the question regarding menstrual pattern in 1993.
*Adjusted for age, family history of breast cancer, history of benign breast disease, height, current body mass index, body mass index at age 18, age at menarche, age at first birth, parity, alcohol use, physical activity, current and past oral contraceptive use.
†Women with no periods were combined with always irregular women.

misclassification in our own study is unlikely to be differential between cases and non-cases due to its prospective nature.

Similar to the literature on menstrual cycle length, the results from earlier studies on the association between menstrual cycle regularity and breast cancer risk are mixed. These included two cohort (10, 12) and nine case-control studies (13-20). Most studies found an inverse association with irregular menstrual cycles (10, 13, 14, 16, 18, 20), but a few found an increased risk (12, 17, 19), and one found no association (15). Of note, one of the studies that found an increased risk was restricted to a cohort of women with a family history of breast cancer (12). These women may have a different risk profile than women with no family history. In addition, Titus-Ernstoff et al. showed that the apparent inverse association with irregular menstrual cycles was stronger among women who did not use hormonal replacement therapy (18). We were unable to evaluate this association in our population, because postmenopausal women were excluded.

Although we observed no overall association between irregular menstrual pattern and breast cancer risk, women who consistently reported irregular cycles at ages 18 to 22 years and in 1993 had a nonsignificant 35% increase in breast cancer risk. This group of women also had a higher body mass index than women with usually regular cycles which could be indicative of polycystic ovarian syndrome. Reports on polycystic ovarian syndrome and breast cancer risk have been inconsistent (21-24). Although anovulation associated with polycystic ovarian syndrome might support an inverse association with breast cancer incidence, heightened insulin sensitivity could increase the risk for breast cancer (25).

The strengths of our study include its large size and prospective design. Although some exposure information is recalled (such as menstrual cycle characteristics from ages 18-22), these data were collected before breast cancer was diagnosed. Consequently, women who developed breast cancer would not have recalled these exposures differently than those who did not. Menstrual cycle characteristics were not captured with the same detail as in those studies that included a menstrual diary recorded by subjects, but this would not have been practical in a study with over 100,000 women. Nevertheless, nondifferential misclassification might have led to an underestimation of the true association. In addition, our study is restricted to premenopausal women who may be able to more accurately report menstrual patterns from young adulthood than postmenopausal women.

In conclusion, these results do not support the hypothesis that long or irregular cycles are protective against breast cancer in all premenopausal women. However, longer menstrual cycles in young adulthood may reduce breast cancer risk in women before the age of 40.

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