Cumulative number of menstrual cycles and breast cancer risk: results from the E3N cohort study of French women.

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Abstract

Objective: To examine the relationship between breast cancer risk and the cumulative number of cycles before a first full-term pregnancy (FTP) and lifetime, taking age at menarche and at onset of regular cycling, periodicity and regularity of cycles, duration of periods of pregnancy, and lactation, oral contraceptive (OC) use, and age at menopause into account.

Methods: The data were taken from the E3N prospective cohort study of women aged 40–65 years in 1990. A total of 1718 breast cancer cases were identified during the 579,525 person-years off ollow-up.

Results: There was a highly significant linear relationship between breast cancer risk and both the cumulative number of cycles before a first FTP (p for trend < 0.0001) and lifetime (p for trend < 0.001), with multivariate relative risk (RR) of a similar magnitude for both variables. Compared to women with a lifetime number of cycles ≤402 (≤30 years), the RR for those with a lifetime total of 403–441, 442–480, 481–520, and ≥521 cycles were 0.95 (0.75–1.21), 1.21 (0.97–1.52), 1.23 (0.96–1.58), and 1.60 (1.25–2.04), respectively. Results restricted to never OC users were similar.

Conclusions: Further investigation is needed to clarify whether the underlying factor is repeated exposure to fluctuating hormones, the number of anovular/ovular cycles, or the relative importance of the follicular and luteal phases.

Key words: breast neoplasms, cohort study, menstrual cycle, menstruation, risk factor.

Introduction

A large number of epidemiological studies support the hypothesis that ovarian hormones play an important part in the development of breast cancer in women [1]. Early menarche has long been recognized as a risk factor [2], and the protective effect of early or artificial menopause has been demonstrated in earlier studies [3]. The few studies that have considered age both at menarche and age at menopause have found an increase in risk with greater lifetime menstrual activity [4–7].

In view of the breast's exposure to hormones, other factors are also relevant, such as periodicity and regularity of cycles, age at onset of regular cycling, duration of periods of pregnancy, duration of periods of lactation, and oral contraceptive (OC) use. These factors have never been considered together in the literature.

In the present study we first analyzed the relationship between breast cancer risk and exposure to each of these factors. We then considered the number of menstrual cycles, taking all hormonal events likely to influence this number into account. We studied the effect of cumulative menstrual activity before first full-term pregnancy (FTP) and during lifetime.

The data used were taken from the large sample of French women participating in the E3N cohort study.

Material and methods

E3N is a prospective cohort study on cancer risk factors, conducted in France [8]. Part of the E3N cohort (i.e.women who replied to the dietary questionnaire), are also included in the European Prospective Investigation on Cancer (EPIC) [9].

The cohort consists of around 100,000 French women who are insured with the MGEN, a national health insurance scheme primarily covering teachers. They were aged 40–65 years at inclusion. The main objective of

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the study is to investigate cancer risk factors. Participants were enrolled in the study between June 1990 and November 1991 after replying to a baseline questionnaire. Follow-up questionnaires were sent out at approximately 24-month intervals.

Menstrual and reproductive events were recorded in the two first questionnaires: age at first menstrual period (between 7 and 20, in years), age at onset of regular cycling (between 7 and 25 or older, in years, plus two additional categories: ''never'' and ''don't know''), periodicity of menstruation before 17 years of age and lifetime periodicity (five categories: ''regular, around 28 days,'' ''regular, 24 days or less,'' ''regular, 32 days or more,'' ''irregular,'' and ''don't know/never menstruated/continuously treated with OC'') and history of pregnancies (number of FTP and abortions), breastfeeding, infertility, and OC use. We took all these variables into account when computing the cumulative number of cycles, considering that irregular menstruation was the equivalent of one cycle out of two, that short cycles were of 24 days' and long cycles of 32 days' duration, that lactation resulted in an absence of cycles for a period of 1.5 months after the end of breastfeeding, and that cycles due to oral contraception were of 28 days' duration. Menopausal status was recorded in each questionnaire. Postmenopause was defined as the cessation of periods for natural reasons or due to bilateral oophorectomy. We studied the cumulative number of natural cycles from the age at which women had their first menstrual period (i) to their age at first FTP and (ii) to their age at (natural or artificial) menopause or end of follow-up.

All questionnaires asked participants whether breast cancer had been diagnosed, requesting the addresses of their physicians and permission to contact them. Deaths in the cohort were detected from reports by family members or by the postal service, and by searching the insurance company (MGEN) file, which contains information on vital status. Information on cause of death was obtained from the National Service on Causes of Deaths (INSERM). Information on non-respondents (i.e. to the questionnaire sent out after 10 years of follow-up: 14% of the initial cohort) was obtained from the MGEN file on reimbursement of hospital fees. In this case the subject's physician was contacted for diagnostic information, making it possible to find additional breast cancer cases (n = 39). Only 1815 women could not be traced in the MGEN file (names misspelled, names changed after divorce, no longer insured with the MGEN, etc.), and non-respondents in this group were considered lost to follow-up.

Follow-up time was between return of the baseline questionnaire and December 1997, the date by which most copies (92%) of the questionnaire sent out in April 1997 had been returned. The person-time of each participant was calculated up to the date of breast cancer diagnosis, date of death, date of last questionnaire returned, or December 1997 (for replies received after December 1997), whichever occurred first.

A total of 2100 breast cancer cases were reported by participants. Pathology reports were obtained for 97% (n = 2044) of cases and coded by a pathologist blinded to data on risk factors. Of the self-reported diagnoses of breast cancer 94.5% were confirmed. A total of 112 cases whose diagnosis was rejected as a result of the pathology report and 270 cases of carcinoma *in situ* were excluded. The 56 cases whose diagnosis was based on self-reporting only were included, as self-reporting proved to be extremely accurate. Women who had reported a cancer other than a basal cell carcinoma at enrollment were excluded. A total of 1718 cases of invasive breast cancer and of 579,525 person-years of follow-up between 1990 and 1997 were thus available for analysis.

Statistical analyses were performed using SAS statistical software. A proportional hazard model with age as the time scale was used, enabling the relative risks (RR) and 95% confidence intervals to be estimated. The cumulative number of cycles until menopause or end of follow-up was considered in the analysis as a timedependent variable. Personal history of benign breast disease, use of OC, use of treatments for infertility or to regulate their cycles after menarche, family history of breast cancer, body mass index, marital status, and educational level were taken into account as potential confounders, because of their possible association with characteristics of reproductive life and with breast cancer. Analyses were performed on the whole cohort and on the ''never used OC'' subgroup.

Results

At baseline the mean age (±standard deviation) of the entire cohort was 49.2 (±6.6) years, while the mean age of the cases was 50.2 (±6.4) years. Participants had a high educational level, with an average of 13.4 (±2.9) years of education for the whole cohort and 13.6 (±2.8) years among breast cancer cases. Other characteristics of the E3N population related to menstrual or reproductive events are indicated in Table 1.

Table 1. **Characteristics related to menstrual function in the E3N population (n = 91,260)**

Characteristic at inclusion	Mean (sd)	1st quartile	2nd quartile	3rd quartile
Age (years)	49.2 (6.6)	43.4	47.9	53.9
Educational level (years of education)	13.4 (2.9)	13.0	13.0	15.5
Age at menarche (years)	12.8 (1.4)	12.0	13.0	14.0
Age at onset of regular cycling[a] (years)	15.4 (3.9)	13.0	14.0	16.0
Duration of OC use[b] (years)	6.1 (5.3)	1.7	5.0	10.0
Number of FTP[c]	1.7 (1.3)	1.0	2.0	3.0
Age at first FTP[c] (years)	24.9 (4.0)	22.0	24.0	27.0
Number of abortions[d]	1.6 (1.0)	1.0	1.0	2.0
Age at menopause[e]	49.0 (4.9)	47.0	50.0	52.0

[a]A proportion of 20.9% did not answer either the questionnaire concerned or this particular question.
[b]Among those who had ever used OC; 63% had never used OC.
[c]Among parous women; 13.7% were nulliparous.
[d]Among those who had ever aborted; 50% had never aborted.
[e]Sixty percent were premenopausal; 1.21% were of unknown age at menopause.

The RR of breast cancer associated with menstrual events are shown in Table 2. The RR pertaining to different categories of age at menarche, age at onset of regular cycling, and periodicity and regularity of cycles did not differ from unity. The risk was lower for postmenopausal than for premenopausal women, whatever their menopausal status at inclusion, and increased with increasing age at menopause (*p* for trend 0.001).

Risks associated with reproductive factors are shown in Table 3. Late age at first FTP increased the risk and multiparity decreased it (for both, *p* for trend <0.0001). Overall duration of breastfeeding in excess of 3 months marginally decreased the risk (p = 5%). The risk for women who had undergone (spontaneous or induced) abortions was similar to that of those who had never aborted.

Table 4 shows the relationship between breast cancer risk and the number of cycles before a first FTP, computed for the 78,797 parous women in the study. An increasing number of cycles before a first FTP increased the risk of breast cancer (*p* for trend < 0.0001). Compared to women who had had fewer than 117 cycles before their first FTP (corresponding to 9 years with an average 13 cycles per year), the multivariate RR for those who had had between 117 and 155 (9–11 years), between 156 and 194 (12–14 years), and over 195 cycles (≥15 years) were 1.07 (95% CI 0.92–1.25), 1.19 (1.01–1.40), and 1.42 (1.20–1.67), respectively. When restricted to women who had never used OC, the results were similar.

Table 5 shows the relationship between breast cancer risk and the cumulative lifetime number of cycles. An increase in risk was apparent with an increasing number of cycles (*p* for trend = 0.001). Compared to women with a lifetime number of cycles of 402 or fewer (≤30 years), the RR for those with a lifetime total of 403–441 (equivalent to 31–34 years), 442–480 (34–37 years), 481–520 (37–40 years), and 521 or more cycles (≥40 years) were 0.95 (0.75–1.20), 1.19 (0.95–1.49), 1.20 (0.94–1.54), and 1.56 (1.22–1.99), respectively. Point estimates for the ‘‘never used OC’’ subgroup were of a similar magnitude.

Discussion

The study showed a highly significant linear relationship between breast cancer risk and both the cumulative number of cycles before a first FTP and the cumulative lifetime number of cycles. When restricted to women who had never used OC the results were similar.

The present study is the first to examine simultaneously all the menstrual and reproductive factors that play a role in determining the number of cycles. As indicated above, we considered irregular menstruations to be the equivalent of one cycle out of two. Considering that they were equivalent to one cycle out of three did not materially change our results.

Obesity and infertility are potential confounders of the relationship studied, being both related to breast cancer and to amenorrhea. They were taken into account in our analyses as adjustment factors. Due to the limited number of cases it was not possible to perform analyses among obese women, among infertile women, or even among nulliparae (a more numerous but heterogeneous subgroup, with some women nulliparous by choice, others by infertility).

Table 2. **Menstrual function and breast cancer risk; E3N cohort study, 1990–1997**

Menstrual events	No. of cases (n = 1718)	Person-years of follow-up	Multivariate RR[a] (95% CI)
Age at menarche (years)[b]			
≤11	379	118,702	1.00[c]
12	443	143,921	1.00 (0.87-1.16)
13	441	153,419	0.96 (0.82–1.12)
14	305	108,277	0.95 (0.81–1.13)
≥15	150	55,206	0.93 (0.75–1.14)
p for trend			*0.35*
Age at onset of regular cycling (years)[d]			
≤12	225	62,014	1.00[c]
13–14	340	107,883	0.83 (0.67–1.03)
15–16	168	58,985	0.76 (0.58–0.99)
17–20	80	29,122	0.72 (0.52–0.99)
≥21	87	28,021	0.81 (0.59–1.11)
p for trend			*0.47*
Cycles ever regular			
Yes	900	286,025	1.00[c]
No	109	36,078	0.91 (0.72–1.16)
Periodicity of cycles before age 17 (days)[b,e]			
<24	78	22,450	1.27 (0.97–1.67)
24–31	1114	369,617	1.00[c]
≥32	106	35,441	1.09 (0.87–1.38)
p for trend			*0.83*
Lifetime periodicity of cycles (days)[b,f]			
<24	123	44,197	0.86 (0.69–1.07)
24–31	1270	420,695	1.00[c]
≥32	110	35,428	1.06 (0.85–1.31)
p for trend			*0.22*
Menopausal status at inclusion[b]			
Premenopausal	974	344,206	1.00[c]
Postmenopausal			
Artificially	119	36,862	0.76 (0.61–0.94)
Naturally	576	183,140	0.70 (0.61–0.81)
Unknown	49	15,317	0.88 (0.65–1.18)
Age at menopause (years)[b,g]			
<40	17	9287	1.00[c]
40–44	61	22,686	1.40 (0.81–2.41)
45–49	194	65,489	1.59 (0.96–2.64)
50–54	341	104,544	1.67 (1.01–2.76)
≥55	82	17,996	2.25 (1.31–3.87)
p for trend			*0.001*

[a]Cox model with age (continuous) as time scale, including all variables, also adjusted for history of benign breast disease (Y/N), family history of breast cancer (Y/N), current body mass index (continuous variable), if ever married (Y/N), educational level (≤8, 9–12, 13–14, 15–16, ≥17 years of education), if OC ever used (Y/N), if ever treated for infertility (Y/N) or to regulate their cycles after menarche (Y/N).

[b]Missing values (n_a breast cancer cases, n_b person-years off ollow-up) were given the modal value; age menarche: $n_a = 18$, $n_b = 8{,}888$; periodicity of cycles before age 17: $n_a = 248$, $n_b = 85{,}005$; lifetime periodicity of cycles: $n_a = 122$, $n_b = 43{,}772$; menopausal status at inclusion (added to ‘‘unknown’’): $n_a = 16$, $n_b = 5{,}094$; age at menopause: $n^a = 6$, $n^b = 2{,}400$.

[c]Reference.

[d]Excluding women who reported ever having used OC, or been treated to regularize cycles before the onset of regular cycling ($n_a = 334$, $n_b = 133{,}107$), ever having irregular cycles ($n_a = 109$, $n_b = 36{,}078$), who did not know their age at onset ofregular cycling ($n_a = 266$, $n_b = 88{,}352$), who did not answer the questionnaire concerned ($n_a = 85$, $n_b = 26{,}933$), or who gave inconsistent answers ($n_a = 24$, $n_b = 9{,}030$).

[e]Excluding women with irregular cycles ($n_a = 389$, $n_b = 138{,}595$) and don’t knows ($n_a = 31$, $n_b = 13{,}422$).

[f] Excluding women with irregular cycles ($n_a = 202$, $n_b = 73{,}441$) and don’t knows ($n_a = 13$, $n_b = 5{,}764$).

[g]Among postmenopausal women.

Table 3. **Reproductive function and breast cancer risk; E3N cohort study, 1990–1997**

Reproductive events	No. ofcases (n = 1718)	Person-years of follow-up	Multivariate RRa (95% CI)
Age at first FTP[b] (among parous) (years)			
<22	232	94,468	1.00[c]
22–24	461	171,850	1.05 (0.89–1.23)
25–27	382	129,234	1.14 (0.96–1.35)
28–30	201	62,741	1.23 (1.01–1.50)
≥31	171	45,500	1.44 (1.17–1.79)
p for trend[d]			*<0.0001*
Number of FTPs[b]			
0	271	75,732	1.00[c]
1	295	92,361	0.76 (0.61–0.95)
2	705	245,718	0.72 (0.59–0.88)
3	326	121,610	0.66 (0.54–0.81)
≥4	121	44,104	0.65 (0.51–0.83)
p for trend[d]			*<0.0001*
Duration of breastfeeding[b] (among parous)			
0	440	143,654	1.00[c]
<3 months	796	282,256	0.92 (0.82–1.03)
≥3 months	211	77,883	0.84 (0.71–0.99)
p for trend[d]			*0.12*
Number of abortions[b]			
Never pregnant	218	59,626	1.05 (0.76–1.45)
Never aborted	846	290,565	1.00[c]
1	400	138,419	0.98 (0.87–1.11)
2	154	57,202	0.91 (0.76–1.08)
≥3	100	33,713	0.99 (0.80–1.22)
p for trend[d,e]			*0.76*

[a]Cox model with age (continuous) as time scale, including all variables, also adjusted for history of benign breast disease (Y/N), family history of breast cancer (Y/N), current body mass index (continuous variable), if ever married (Y/N), educational level (≤8, 9–12, 13–14, 15–16, ≥17 years of education), if OC ever used (Y/N), if ever treated for infertility (Y/N), or to regulate their cycles after menarche (Y/N).

[b]Missing values (n_a breast cancer cases, n_b person-years of follow-up) were given the modal value; number of FTP: $n_a = 20$, $n_b = 8{,}379$; duration of breastfeeding: $n_a = 78$, $n_b = 32{,}771$; number of abortions : $n_a = 2$, $n_b = 1{,}542$; age at first FTP: $n_a = 2$, $n_b = 1{,}555$.

[c]Reference.

[d]Continuous variable.

[e]Among pregnant women.

Table 4. **Cumulative number ofcycles before first FTP and breast cancer risk (parous women only); E3N cohort study, 1990–1997**

Number of cycles	All women			Excluding those who had ever used OC		
	No. of cases	Person-years of follow-up	Multivariate[a] RR (95% CI)	No. of cases	Person-years of follow-up	Multivariate[a] RR (95% CI)
<117	310	123,916	1.00[b]	184	72,026	1.00[b]
117–155	341	123,678	1.07 (0.92–1.25)	206	74,935	1.04 (0.85–1.27)
156–194	260	83,968	1.19 (1.01–1.40)	161	51,790	1.14 (0.92–1.42)
≥195	297	82,887	1.42 (1.20–1.67)	176	47,812	1.37 (1.11–1.70)
Impossible to compute	239	89,344	1.05 (0.88–1.24)[c]	142	51,619	1.03 (0.83–1.29)[d]
p for trend			<0.0001			0.003

[a]Cox model with age (continuous) as time scale, adjusted for alcohol intake (0, <p50, ≥p50), history of benign breast disease (Y/N), history of infertility (Y/N), family history of breast cancer (Y/N), body mass index (<18.5, 18.5–25, >25), if OC ever used (Y/N), if ever married (Y/N), and educational level (≤8, 9–12, 13–14, 15–16, ≥17 years of education).

[b]Reference.

[c]Reason (number ofcases/person-years): cycles always irregular (135/48,212), missing data (104/41,132).

[d]Reason (number ofcases/person-years): cycles always irregular (74/24,746), missing data (68/26,873).

Table 5. **Cumulative lifetime number of cycles and breast cancer risk. E3N cohort study, 1990–1997**

Number of cycles	All women[a]			Excluding those who had ever used OC[b]		
	No. of cases	Person-years of follow-up	Multivariate[c] RR (95% CI)	No. of cases	Person-years of follow-up	Multivariate[c] RR (95% CI)
<403	160	40,704	1.00[d]	108	29,298	1.00[d]
403–441	131	45,405	0.95 (0.75–1.20)	87	31,252	0.85 (0.64–1.14)
442–480	176	55,101	1.19 (0.95–1.49)	119	40,044	1.01 (0.77–1.32)
481–520	128	41,004	1.20 (0.94–1.54)	100	30,872	1.13 (0.85–1.51)
≥521	136	33,501	1.56 (1.22–1.99)	85	19,579	1.55 (1.15–2.10)
Impossible to compute	149	49,751	1.03 (0.81–1.30)[e]	97	35,399	0.89 (0.67–1.18)[f]
p for trend (excluding impossible to compute)			0.001			0.01

[a]Excluding (number ofcases/person-years): menopausal status unknown (106/53,273), age at menopause missing (161/76,294), age at menopause unknown because of HRT (571/184,492).
[b]Also excluding (number ofcases/person-years): menopausal status unknown (70/28,732), age at menopause missing (94/45,673), age at menopause unknown because of HRT (303/91,765).
[c]Cox model with age (continuous) as time scale, adjusted for alcohol intake (0, <p50, ≥p50), history of benign breast disease (Y/N), history of infertility (Y/N), family history of breast cancer (Y/N), body mass index (<18.5, 18.5–25, >25), if OC ever used (Y/N), if ever married (Y/N), age at first FTP (nulliparae, <22, 22–24, 25–27, ≥28 years) and educational level (≤8, 9–12, 13–14, 15–16, ≥17 years of education).
[d]Reference.
[e]Reason (number ofcases/person-years): cycles always irregular (100/32,569), missing data (49/17,182).
[f]Reason (number ofcases/person-years): cycles always irregular (62/21,934), missing data (35/13,465).

The data analyzed in the present study derive from self-administered questionnaires used as a retrospective source of information on exposure, and they are therefore potentially prone to recall errors. A study was conducted to assess the reliability of the collected data, using a subgroup of around 600 women who completed the same questionnaire twice 18 months apart: 70.7% reported an identical age at menarche on both occasions. In the same study 64.0%, 79.5%, and 78.4% of a subgroup of around 200 postmenopausal women (i.e. beyond the age at which reproductive events could occur), gave identical responses for age at first pregnancy, duration of first pregnancy, and duration of lactation, respectively. In addition, we showed in a validation study of 151 subjects on age at menopause [10] that age at menopause was accurately reported within 1 year by 69% of the subjects, on the basis of the gynecologist's medical records. Recall errors are therefore unlikely to have had a significant effect. Moreover, the prospective nature of our study means that such recall errors should be the same for cases and non-cases, thus preventing any recall bias.

There has long been growing evidence that breast cancer risk decreases with increasing age at menarche [11]. It is noteworthy that in our study the role of age at menarche was apparent only before adjustment for age at onset of regular cycling, with RR of 0.98 (0.85–1.12), 0.92 (0.80–1.05), 0.90 (0.77–1.04), and 0.86 (0.71–1.04), corresponding to menarche at 12, 13, 14, and 15 years or older, compared to those associated with menarche before age 11 (*p* for trend = 4%). Part of the protective effect of late menarche was thus due to the effect of age at onset of regular cycling. Few authors have examined the effect of age at onset of regular cycling. Their findings do not agree with one another, perhaps partly because age at onset of regular cycling is difficult for many women to recall. Indeed, in our population 20.9% of the data were missing. Some studies [12, 13] have shown evidence of increasing risk with increasing interval between menarche and onset of regular cycling. Other studies [14–17] have found virtually no variation in risk by length of time before onset of regular cycling.

The role of ovulation in breast cancer risk has long been debated [18], but research has been hampered by the difficulty of measuring it accurately. Certain studies, cited by Harlow and Ephross [19], have reported that the probability of an ovulation decreases with age, falling from 50–60% of cycles anovulatory in 10–17-year-old girls and 20–28% around 18–25 to 1–7% around 25–40, followed by a renewed increase to 12–34% in perimenopausal women. The probability of ovulation also varies with age at menarche. Earlier menarche is characterized by an earlier onset of ovulatory cycles. Several studies have shown that the prevalence of ovulatory cycles increases with an increasing interval since menarche, from 15–40% within 1 year to 75–80% after 6 years or more [20, 21]. In epidemiological studies, chronic anovulation can be evaluated using irregularity of cycles as a proxy variable. The results of such studies have been fairly consistent: women with

irregular menses had a lower risk, after adjustment for age at menarche, than those who menstruated regularly, a number of studies showing a significant reduction [13, 22–24] and others a non-significant one [14, 15, 25–27]. Some studies showed a variation in risk according to age, with lower point estimates among younger or premenopausal women [5, 17, 24].

Several explanations can be put forward to account for the effect of the usual periodicity of the cycle on breast cancer risk. It influences lifetime exposure to hormones, through the cumulative number of cycles. It can also modify the relative importance of the follicular and luteal phases: because the length of the follicular phase is more variable than that of the luteal phase, women with long lifetime menstrual activity have a relatively higher exposure to the hormones predominant in the follicular phase. The periodicity of the cycle also plays a role in determining the probability of ovulation, as both very short and very long cycles are associated with a high proportion of anovulatory cycles [28]. The results of previous studies on the relationship between breast cancer risk and length of menstrual cycle have been contradictory [6, 13–15, 23–27].

The few authors who combined these reproductive factors to replicate ovarian activity [4–7] have found an increased risk of breast cancer with an increasing lifetime number of menstrual cycles. However, the cumulative number of cycles was assessed less accurately in these studies than in the present study, and OC use was not taken into account. Nevertheless their findings, like our own, showed that the cumulative lifetime number of cycles had a greater effect on risk than did the cumulative number of cycles before a first FTP.

Our results give further confirmation that exposure to ovarian hormones is a major determinant of breast cancer. Theories proposing a relationship between menstrual function and breast cancer risk suggest that repeated exposure to fluctuating endocrine hormones may increase the risk of breast cancer through a direct effect on breast tissue. In fact with a number of estrogens, adequate evidence of carcinogenicity in animals is considered sufficient [29]. Several epidemiological studies support the hypothesis that ovarian hormones play an important role in the development of breast cancer in women, though it is not clear whether this is due to an excess of estrogens, androgens, or progesterone; to an imbalance between these hormones; or due to other growth factors. The point estimates we observed were of a lower magnitude when the cumulative number of cycles before first FTP rather than the cumulative lifetime number of cycles was considered, suggesting that the breast is not more susceptible to exposure to menstrual hormones before a first pregnancy (i.e. before differentiation of the breast cells) than afterwards. Further investigation is needed to clarify whether the underlying factor is repeated exposure to fluctuating hormones, the number of anovular/ovular cycles, or finally the relative importance of the follicular and luteal phases.

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