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Reproductive Factors and Breast Cancer Risk. Effect of Age at Diagnosis

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Abstract
The data from a French case-control study of 495 patients with breast cancer and 542 control subject, interviewed in five French public hospitals, were analyzed to assess the effect of reproductive factors (age at menarche, age at first full-term pregnancy, the time interval between these two ages, and parity) on the risk of breast cancer. Age at menarche, age at first full-term pregnancy, the time interwal between these two ages, and parity appeared to have a limited influence on breast cancer risk. However, the relationship between these factors and the risk of breast cancer varied according to the age at breast cancer diagnosis. In the youngest group of women, the most consistent effects came from factors occurring early in life (menarche, first full-term pregnancy, and consequently the time interval between these two events). These factors had a null or weak effect on the oldest group of women. The protective effect of high parity was confined to the oldest group of women.
Key words: Breast cancer, epidemiology, case-control study, risk factors, age at diagnosis, reproductive life.

Introduction

Numerous epidemiologic studies have focused on the relationship between reproductive factors and breast cancer. The protection conferred by a late age at menarche, an early age at first full-term pregnancy (FFTP), and a high parity is well established (1, 2). However, a possible interaction between these risk factors and age at the onset of disease, or menopausal status, has been suggested only recently (3-7). Low parity seems to be a risk factor for postmenopausal and older women (5, 7-15), while early menarche and a late first delivery seem to be risk factors for premenopausal and younger women (5-9, 12-26). Using the data from a French case-control study, we investigated the relationship between reproductive factors and breast cancer according to the age at which breast cancer was diagnosed.

Subjects and methods

The design of the study was described in a previous report (27). Briefly, between 1983 and 1987, 495 breast cancer patients and 542 control subjects were selected from five French public hospitals. Breast cancers had to be histologically confirmed at most 7 months before inclusion in the study; any breast cancer (except in situ carcinoma) was accepted. The age ranges were 25 to 56 years for case patients and 22 to 58 years for control subjects.

Control subjects were matched to case patients for age at the time of interview (±5 years), year of birth (± 5 years), date of interview (± 14 months), interviewer, and hospital. To be eligible, the subjects had to be white women of French nationality who were not pregnant or breastfeeding, and who had no previous malignancy. Control subjects were selected from among patients hospitalized for a nonmalignant condition or malignancies

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other than those of the colon, salivary glands, and female genital tract. Trained interviewers collected information on menstrual and reproductive factors, among other things. The description of these factors has already been reported, for case patients and control subjects (27). Less than I% of subjects refused to be interviewed. The interview took about 40 minutes; information was recorded using a structured questionnaire that covered the following characteristics: basic demographic characteristics, current and past medical history, menstrual and reproductive experience, life-style factors, familial medical history, and contraceptive history.

For statistical analysis, the GLIM computer package was used (28). Odds ratios were derived from a multivariate analysis via multiple logistic regression to simultaneously control for the potential confounders (29): hospital, educational level (primary, secondary, or higher), oral contraceptive consumption, and having a mother or sister with a history of breast cancer. Adjustments were also performed for menopausal status (premenopausal or postmenopausal), even though age at diagnosis and menopause were highly correlated. Moreover, adjustment for age (which was a matching factor) as a continuous variable was performed in the statistical analysis to allow for any residual effect. The tests of increasing risk with increasing exposure were performed on categories of the variable of exposure presented in the tables. The interactions with age at diagnosis were assessed by χ^2 tests of homogeneity of the slopes.

Resultst

Table 1 shows the effect on breast cancer risk of three factors related to reproduction: age at menarche, age at FFTP, and parity. The risk was significantly reduced for women with menarche at age 15 or later ($P< 0.005$). A 40 to 50% increase in risk was observed when the FFTP was later than age 20 compared when it was at age 20 or earlier. The breast cancer risk associated with nulliparity did not differ significantly from unity. Among parous women, the risk decreased with increasing parity ($P = 0.02$).

Table 1. **Effect of parity, age at menarche and age at first full-term pregnancy on the risk of breast cancer**

Characteristic	Cases	Controls	OR[a] (95% CI)	P (trend)[b]
Age at menarche (y)				
≤12	194	194	1.0	
13	136	118	1.2 (0.8-1.6)	$P = 0.004$
14	108	122	0.9 (0.7-1.3)	
≥ 15	57	108	0.5 (0.3-0.8)	
Age at first full-term pregnacy (y)[c]				
≤ 20	58	100	1.0	
21-25	214	224	1.4 (0.9-2.4)	
26-30	106	94	1.5 (0.9-2.4)	
≥ 31	46	39	1.4 (0.8-2.6)	NS[d]
Parity				
0	71	85	1.0	
≥1	424	457	0.8 (0.3-2.4)	
1	104	105	1.0	
2	185	164	1.1 (0.8-1.6)	$P = 0.02$
3	85	98	0.9 (0.6-1.3)	
4	31	51	0.6 (0.3-1.1)	
≥ 5	19	39	0.6 (0.3-1.2)	

[a]Odds ratio (OR) adjusted for age, hospital, menopausal status, level of education, familial history of breast cancer, oral contraceptives consumption, and other reproductive factors in the table.
[b]Categories are coded 0, 1, 2, and so on.
[c]Parous women.
[d]NS, not significant; i.e., P ≥ 0.10.

For parous women, the difference between age at menarthe and age at FFTP was calculated to analyze the time elapsed until the differentiation of breast cells due to a first pregnancy (30). The risk decreased with a decreasing time interval between menarche and the first pregnancy (Table 2); the test for trend was significant ($P < 0.002$).

The effects of these four factors were further studied in three subgroups defined by age at diagnosis: 39 years or younger, 40 to 49 years, and 50 years or older (Table 3). A decrease in risk with an increase in age at menarche was only observed among women under the age of 40 at diagnosis ($P < 0.0l$), although no heterogeneity was observed between age groups for that factor. There was no heterogeneity between age groups for either age at FFTP or nulliparity. Among parous women, the risk associated with increasing parity differed according to the age at diagnosis ($P < 0.005$). High parity only conferred a protective effect for breast cancers diagnosed at the age of 40 or later, whereas it increased risk in the youngest age group.

The effect of the time interval between age at menarche and age at FFTP, analyzed among parous women, is shown in Table 4. The risk decreased with a shorter time interval, in the youngest age group ($P < 0.0001$). The effect of this variable on risk differed across the groups ($P = 0.05$). Further adjustments on age at menarche and on age at FFTP did not alter these results.

Table 2. **Effect of the number of years between age at menarche and at first full-term pregnancy-parous women**

No. of years between age at menarche and at first full-term pregnancy	Cases	Controls	Odds ratio[a] (95% CI)	P (trend)[b]
≥12	210	160	1.0	
10-11	74	93	0.6 (0.4-0.9)	$P = 0.0015$
8-9	82	94	0.8 (0.5. 1.1)	
6-7	45	66	0.7(0.4.-1.1)	
l-5	13	44	0.3 (0.1-0.6)	

[a]Adjusted for age, hospital, menopausal status, level of education, familial history of breast cancer, oral contraceptives consumption and parity.
[b]Categories are coded 0, 1, 2, and so on.

Table 3. **Odds ratio (OR) estimates[a] by age group, for parity, age at menarche, and age at first full-term pregnancy**

	Age (y) at diagnosis						
	≤ 39		40-49		≥ 50		
Characteristic	Cases/controls	OR	Cases/controls	OR	Cases/controls	OR	Heterogeneity[b]
Age at menarche (y)							
≤12	63/66	1.0	90.82	1.0	41/46	1.0	
13	30/38	0.8	71.45	1.4	35/35	1.6	NS[c]
14	19/35	0.6	40.54	0.7	49/33	2.3	
≥ 15	9/28	0.3[d]	32/33	0.9	16/47	0.4[d]	
P value for trend[e]	0.008		NS[c]		NS[c]		
Age at first full-term pregnacy (y)[c] (among parous)							
≤ 20	10/33	1.0	25/35	1.0	23/32	1.0	
21-25	59.64	3.2[d]	97/94	1.1	58/66	0.9	NS[c]
26-30	22/27	3.4[d]	54/38	1.3	30.29	1.1	
≥ 31	4/6	3.0	26/13	1.4	16/20	0.7	
P value for trend[e]	0.07		NS[c]		NS[c]		
Parity							
0	26/37	1.0	31/34	1.0	14/14	1.0	
≥1	95/130	0.6	202/180	1.3	127/147	0.6	NS[c]
1	22/44	1.0	54/40	1.0	28/21	1.0	
2	45/57	2.0	92/60	1.2	48/47	0.5	0.004
3	26/22	3.9	33/41	0.6	26/35	0.3[d]	
4	l/4	1.5	16/19	0.7	14/28	0.2[g]	
≥ 5	l/3		7/20	0.3	11/16	0.4	
P value for trend[e,h]	0.02[i]		0.02		0.007		

[a]Odds ratio adjusted for age, hospital, menopausal status, level of education, familial history of breast cancer, oral contraceptives consumption, and other reproductive factors in the table.
[b]Test for heterogeneity in trends between age groups, χ^2 2df.
[c]NS, not significant; i.e., $P \geq 0.10$.
[d]$P < 0.05$.
[e]Categories are coded 0, 1, 2, and so on.
[f]Reference category.
[g]$P < 0.005$.
[h]Parous women.
[i]Increasing risk with higher parity.

Table 4. **Odds ratio (OR) estimates[a] by age group, for the number of years between age at menarche and age at first full-term pregnancy-parous women**

	Age (y) at diagnosis						
	≤ 39		40-49		≥ 50		
Characteristic	**Cases/controls**	**OR**	**Cases/controls**	**OR**	**Cases/controls**	**OR**	**Heterogeneity[b]**
Years between age at menarche and at first full-term pregnancy							
≥ 12	50/38	1.0	106/63	1.0	54/59	1.0	
10-11	22/28	0.4[c]	29/40	0.4[d]	23/25	1.3	0.05
8-9	13/30	0.3[d]	41/38	0.8	28/26	1.6	
6-7	9/24	0.2[d]	23/23	0.9	13/19	1.3	
l-5	l/10	0.04[d]	3/16	0.2[d]	9/18	0.9	
P value for trend[e]	<0.0001		0.09		NS[f]		

[a]Odds ratio adjusted for age, hospital, menopausal status, level of education, familial history of breast cancer, oral contraceptives consumption, and parity.
[b]Test for heterogeneity in trends between age groups, χ^2 2df.
[c]$P < 0.05$.
[d]$P < 0.01$.
[e]Categories are coded 0, 1, 2, and so on.
[f]NS, not significant; i.e., $P \geq 0.10$.

Discussion

In the present study, the effects of the reproductive factors studied appeared to be limited to some subgroups defined by age at diagnosis. A younger age at menarche and an older age at FFTP appeared to confer a protective effect for breast cancers occurring before age 40. In that subgroup, the protective effect of a short interval between these two reproductive milestones was highly significant. Multiparity had a beneficial effect on the risk of a breast cancer only when the cancer was diagnosed after age 50.

The change in the slope of the curve showing the age-specific incidence of breast cancer around the age of 50 strongly suggests an effect of age or menopause. The fact that age and menopausal status are closely related makes it difficult to separate their effects. Our study was designed to analyze the relationship between oral contraception and early breast cancer. It was restricted to women under the age of 56 in order to be certain of a risk of exposure to oral contraceptives marketed in France in the late 1970s. So, our study allowed us to analyze three subgroups that were of a different age at diagnosis, but comparable in size. However, due to a possible lack of power, our results need to be considered in light of the literature for an adequate appraisal of any heterogeneity between the subgroups.

In both this study and those of other investigators, the decrease in the risk associated with a late age at menarche mostly affected young or premenopausal women (5, 6, 8, 9, 13-18,21-24,26). Only one study suggested an increased risk with a younger age at menarche among postmenopausal women (4). Other authors found a protective effect of a late age at menarche regardless of menopausal status (25, 30, 31) or age at diagnosis (20,32). A last one found an increased risk related to late menarche confined to young women (7). To discuss the possible influence of age at menarche, error of recall of age at menarche must be kept in mind. Bean and coworkers (33) found that recall was satisfactory, whereas Apter and associates (34) did not. Errors of recall may occur more frequently among older women. In our study, due to matching, ages were similar among case patients and control subjects. For the whole group, case patients were on average 6 months older than control subjects (not significant); for the two younger subgroups, they were 5 and 3 months older (not significant); and in the older subgroup they were 8 months younger ($P < 0.01$). These slight differences are unlikely to account for our results because adjustments on age were performed. Recall of age at menarche may be more difficult for women in the oldest subgroup, which could be the reason for a lack of a relationship between case patients and control subjects observed in our results.

Several studies found a detrimental effect of a late age at FFPP that was essentially confined to the premenopausal group or to the younger women (5, 8, 12, 14-17, 19, 20, 25). In a few studies, the increase in the risk of breast cancer with an older age at FFTP appeared only among postmenopausal or older women (4, 6, 7, 9, 31), while some authors reported a similar influence whatever the age or menopausal status was at the onset of the disease (18, 30, 32, 35).

Only a few studies investigated age at menarche and age at first delivery together. Korenman (36) combined these two events in the initial estrogen window (IEW). Korenman hypothesized that the longer this period lasted, the longer the breast was exposed to the influence of potentially harmful estrogens, especially in that period of inadequate progesterone production. However, the impact of the IEW is still debated. Several authors (37-41) found that the earlier menarche occurs, the earlier the onset of ovulatory cycles, and that a late menarche is associated with a longer interval until ovulatory cycles. This implies that a long IEW is not necessarily linked to a long period of unopposed estrogen exposure (41). To our knowledge, only four studies investigated the influence of the IEW according to the age at diagnosis of breast cancer. Brignone and coworkers (18) found an effect confined to premenopausal women, while others (6, 30) found no difference according to the menopausal status. In another study (31), intervals exceeding 14 years were found to increase significantly the risk in women older than 61 years. Another report suggested that the important factor could be the number of menstrual cycles prior to the FFTP (42), but no allowance was made for the age at diagnosis of the breast cancer.

Most studies have shown a protective effect of high parity (1,2,43). When parity was studied according to menopausal status or age at diagnosis, the great majority found that the protective effect of high parity was confined to older or postmenopausal women (5, 7-15). Some authors reported an effect in both premenopausal and postmenopausal women (19, 20, 44-46), while others found no protection conferred by parity in any subgroup (4, 6, 30). In a few studies, the protection conferred by high parity was found in younger or premenopausal women (16-18, 35). However, in the study by Lipnick and colleagues (35), results were only age-adjusted. In the study by Hislop and associates (16), parity was not a significant independent risk factor on multivariate analysis. Brignone and coworkers (18) analyzed high parity in comparison with low parity and stated that women in all birth categories were at decreased risk in comparison with nulliparous women. However, confounders such as socioeconomic status were not considered in their analysis. Talamini and coauthors (17) stated that the role of parity was apparently stronger in premenopausal women, but no data were shown. Thus, there seems to be a consensus in the literature regarding the protective effect of multiparity being confined to older women. However, it should be noted that some of the youngest women may not have completed the reproductive phase of their life, whereas the oldest have.

Our results allow us to suggest that the difference in the effect of risk factors observed with age at diagnosis could be partly due to the inevitable time interval between exposure to the factors and the occurrence of the disease; this interval has been estimated to be between 10 and 20 years (47,48). The protection conferred by factors occurring early in life such as an older age at menarche, a younger age at first birth, and consequently, a short interval between these two ages would be mainly apparent for cancers occurring early in life. The protective effect of these factors would thus be limited in time. Similarly, the protective effect of a high parity, corresponding to a decreasing number of undifferentiated cells with each parity, would be preferentially observed later in life. In the same way, the protective effect of high parity would only be observed among older women because of their older age at the delivery of their last child.

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