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Original Paper

The Role of Reproductive and Menstrual Factors in Cancer of the Breast Before and After Menopause

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The aim of the study was to elucidate the role of reproductive and menstrual factors in the aetiology of breast cancer, overall and by menopausal status. A cooperative case-control study was conducted between 1991 and 1994 in six different Italian areas (including three from the centre and the south). The study included 2569 histologically confirmed incident cases of breast cancer (median age 55 years, range 23–78 years) and 2588 control women (median age 56 years, range 20–79 years) admitted to the same hospitals for a variety of acute conditions unrelated to the hypotheses in study. A trend of increasing risk with increasing age at menopause (odds ratio (OR) for age at menopause ≥53 versus <45 years = 1.8; 95% confidence interval (CI) = 1.4–2.2). High parity reduced cancer risk (OR for ≥4 versus 1 birth = 0.7; 95% CI = 0.5–0.9). Overall, nulliparous women showed a 20% lower risk than uniparous ones (OR = 0.8; 95% CI = 0.7–1.0). Late age at first birth (or pregnancy) had an independent adverse effect (OR for first birth at ≥32 versus <20 years = 1.7; 95% CI = 1.3–2.1) both before and after menopause. An approximately 2-fold elevation of breast cancer risk was evident up to 10 years after the last birth. No trend in risk was evident for induced abortions (OR = 1.2 for 1 and 1.1 for ≥2 induced abortions versus 0). Other examined menstrual and reproductive characteristics did not seem important. Multiparity, early age at first birth and early age at menopause were therefore the most important determinants of breast cancer risk. The effects of the timing of births was significantly heterogeneous in pre- and postmenopausal women because of the transient adverse effect of such events, evident only in premenopausal women.

Key words: breast cancer, reproductive factors, menstrual factors, age at diagnosis
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INTRODUCTION

THE ROLE of reproductive and menstrual factors in the epidemiology of breast cancer has long been recognised [1]. Nevertheless, some uncertainties remain about the influence of some reproductive factors, especially with respect to their independent association with aetiology [1] and their relative importance in specific strata of age at diagnosis and/or menopausal status [2–18].

As regards age at menarche, some studies [2, 5–7, 19] have found a stronger inverse relationship in women with premenopausal breast cancer than in those diagnosed after menopause. Other studies have indicated that early menarche is a weak risk factor for all age groups [8, 20, 21].

Several lines of evidence suggest that late age at menopause is an important risk factor for breast cancer [2, 20–24]. In one study [25], the increased risk associated with late age at

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natural menopause was not apparent until 65 years of age, thus suggesting a 10–20 year delay of its effect, but the time–risk relationship for age at menopause is still open. By and large, prolonged exposure to sex hormones [8, 23], as indicated by a high number of reproductive years from menarche to menopause, has been suggested to increase breast cancer risk [26, 27].

Early age at first birth has conferred, in most studies, persistent protection [2, 6, 19, 28, 29]. However, first birth after age 30, appears to be associated with a breast cancer risk higher than that in nulliparous women [6, 10, 30]. An explanation for these findings is that an early full-term pregnancy reduces the likelihood of tumour initiation, but at a later age it may promote the growth of existing tumour cells [9, 31].

Nulliparity has consistently emerged as a risk factor for breast cancer [2, 4, 6, 12, 13, 24, 29, 32]. Some studies [2, 4, 6], which considered age at cancer diagnosis, have found that the elevated risk is confined to nulliparous older women. Parous women seem to be at increased risk during the 10–15 years subsequent to a pregnancy as compared with nulliparous women [2–6, 16].

The exact time at which such a 'cross-over' effect is apparent varies from one study to another [4–7, 9, 11–14, 16–18]. Despite the convincing evidence for long-term protection of parity, pregnancy seems to be associated with a short-term increase in the risk of breast cancer [9, 18]. Along the same line of reasoning, age at subsequent births has recently attracted some attention, and it has been found positively associated with risk of breast cancer, independently of age at first birth and parity [2, 5, 32–34].

The influence of spontaneous or induced abortions on the risk of breast cancer remains unclear [2, 19, 35–37]. Some studies [23, 24, 38–40] have shown some moderate positive associations, while others have suggested no clear relationship [28, 41].

Finally, with respect to menstrual characteristics (i.e. duration of bleeding, cycle length), short or irregular menstrual cycles (a possible indicator of frequent non-ovulatory cycles) have been hypothesised to be associated with decreased risk [29, 42], but this issue is still open [27].

To further clarify the role of reproductive and menstrual factors in relation to breast cancer, overall and separately in pre- and postmenopausal women, we analysed data of a cooperative case-control study, conducted between June 1991 and February 1994 in six different areas, including three from northern, two from central and one from southern Italy.

PATIENTS AND METHODS

The data were derived from a case-control study on breast cancer [43], conducted between June 1991 and February 1994 in six Italian areas: the provinces of Pordenone and Gorizia, the urban areas of Milan and Genoa, the province of Forlì, in northern Italy, the provinces of Latina and Rome, in central Italy, and the urban area of Naples, in southern Italy. The same structured questionnaire and coding manual were used for the whole study, and all interviewers were centrally trained and tested periodically for reliability and reproducibility. Similarly centralised were the data checks for consistency and reliability. The doctors had given permission to interview their patients in all selected hospitals and wards. On average, fewer than 4% of cases and controls approached for interview refused to participate.

Cases were women with incident (i.e. diagnosed within the year before interview), histologically confirmed breast cancer, admitted to the major teaching and general hospitals in the areas under surveillance. A total of 2569 cases below 80 years (median age 55 years, range 23–78 years) were included in the present analyses.

Controls were women resident in the same geographical areas and admitted for acute conditions to the same network of hospitals where cases had been identified. The interviewers visited selected wards in these hospitals on defined days, and interviewed all eligible subjects. They were not included if admitted for gynaecological, hormonal or neoplastic diseases. A total of 2588 controls below the age of 80 years (median age 56 years, range 20–79 years) were interviewed. They were admitted to hospital for a wide spectrum of acute diseases (22% traumas, 34% other orthopaedic disorders, 17% acute surgical conditions, 14% eye disorders and 13% other diseases).

The structured questionnaire included information on personal characteristics and habits, education and other socioeconomic factors, general lifestyle habits, such as smoking, alcohol and coffee consumption, a validated food frequency consumption section, a few indicators of physical activity, menstrual and reproductive history (e.g. age at menarche, menopausal status, age at menopause, type of menopause, parity, abortions, age at first live birth and length of attempt to first pregnancy), related medical history, history of lifelong use of oral contraceptives and female hormone preparations for any other indication. Menstrual irregularity was defined as frequent menstrual-like episodes less than 21 or more than 35 days apart. Women were labelled as premenopausal if they reported having had a menstrual period within 12-month time of breast cancer diagnosis. Pregnancies of fewer than 180 days were classified as miscarriages or induced abortions, according to whether they ended spontaneously or were voluntarily interrupted. Length of attempt to first pregnancy included the number of months of unprotected intercourse before first pregnancy. This was considered '0' for unplanned pregnancies.

Multiple logistic regression was used to estimate odds ratios (OR) of breast cancer, together with their 95% confidence intervals (CI) [44], for various levels of reproductive and menstrual variables, after accounting simultaneously for potentially confounding effects [44, 45]. In addition to risk factors of interest, the regression equation included terms for area of residence, age and education and, when specified, other variables. The significance of linear trend in risk was assessed by comparing the difference between the deviance of the models with and without the variable of interest to the chi-square distribution with one degree of freedom [44]. Further, the effect of all reproductive and menstrual factors was assessed separately in pre- and postmenopausal women. Interaction tests between these two groups were carried out by means of the Wald test. Analyses by decade of age at cancer diagnosis were also carried out but not shown. Results in premenopausal women were very close to those in women below age 50 years, whereas age groups 50–59, 60–69 and 70 years or more did not show any significant or substantial heterogeneity and were thus summarised by the findings in postmenopausal women.

RESULTS

The distribution of cases and controls according to area of residence and quinquennium of age was very similar, while an

Table 1. Distribution of 2569 cases of breast cancer and 2588 controls according to menstrual and reproductive characteristics and menopausal status, Italy, 1991–1994

	Menopausal status	
	Premenopausal (n = 1832) (cases:controls)	Postmenopausal (n = 3322) (cases:controls)
Age at menarche (years)		
<12	231:184	266:305
12	287:217	339:362
13	236:209	358:359
14	163:153	320:377
≥15	72:79	291:340
Menstrual bleeding (days)		
1–3	141:119	267:310
4	277:238	476:479
5	335:281	446:425
6	98:86	131:162
≥7	138:118	256:366
Duration of menstrual cycles (days)		
<26	167:147	209:264
26–30	713:577	1209:1317
≥31	54:52	77:72
Irregular	49:65	66:75
Age at menopause (years)		
<45	0:0	232:366
45–49	0:0	408:478
50–52	0:0	547:563
≥53	0:0	384:335
Type of menopause		
Natural	0:0	1295:1328
Artificial	0:0	281:410
Parity		
Nulliparous	142:148	259:232
1	240:195	344:299
2	421:306	546:603
3	141:136	264:353
4	33:41	90:142
≥5	12:17	72:114
Miscarriage		
0	790:664	1234:1309
1	138:134	220:285
≥2	61:45	122:151

Table 1 continued overleaf

excess of individuals with higher education (i.e. ≥11 years of schooling) was seen more among cases than controls (25 and 16%, respectively) (not shown). Distributions of study subjects by various menstrual and reproductive characteristics according to menopausal status (premenopausal or postmenopausal) are shown in Table 1.

The relationship between menstrual characteristics and overall risk of breast cancer by menopausal status is shown in Table 2. Age at menarche was not associated with breast cancer risk (OR for menarche at ≥15 years compared with at <12 years = 1.0; 95% CI = 0.8–1.2). Longer periods of menstrual bleeding were associated with significant decreasing risk in postmenopausal women (OR for ≥7 days bleeding compared with ≤3 days = 0.8; 95% CI = 0.6–0.9), without a significant heterogeneity between pre- and postmenopausal women. No consistent relationship emerged between breast cancer risk and duration or regularity of menstrual cycles.

Postmenopausal women experienced a lower risk of breast cancer than premenopausal ones. Highly significant risks associated with increasing age at menopause were found (OR for menopause at ≥53 years compared with <45 years: 1.8; 95% CI = 1.4–2.2). Artificial menopause seemed to have a protective effect in comparison to natural menopause (OR = 0.8; 95% CI = 0.7–0.9), even after allowance for age at menopause (in single years).

OR according to reproductive factors are considered in Table 3. Among parous women, a significant trend of decreasing breast cancer risk with increasing number of births was seen (OR for ≥5 births compared with one birth = 0.7; 95% CI = 0.5–0.9). Such a favourable effect was not significant in

Table 1. *Continued*

	Menopausal status	
	Premenopausal (n = 1832) (cases:controls)	Postmenopausal (n = 3322) (cases: controls)
Induced abortion		
0	826:736	1427:1582
1	106:66	76:79
≥2	57:41	73:83
Age at first pregnancy (years)		
<20	59:97	77:141
20–23	264:293	362:481
24–27	341:209	465:527
28–31	124:87	270:255
≥32	83:27	170:141
Length of attempt to first pregnancy (months)		
0	422:394	688:820
1–2	182:118	250:271
3–11	155:138	243:280
≥12	99:62	140:169
Outcome of the first pregnancy		
Live birth	743:636	1186:1371
Miscarriage and stillborn	96:58	139:146
Induced abortion	33:15	18:22
Age at first birth (years)		
<20	51:90	69:128
20–23	243:280	331:463
24–27	343:213	469:527
28–31	126:85	280:252
≥32	84:27	169:143
Age at last birth (years)		
<25	122:170	130:167
25–29	321:251	366:398
30–34	260:198	436:499
35–39	120:62	287:339
≥40	20:13	97:104

Some values are missing, including menopausal status in 3 cases.

premenopausal women, but the interaction with menopausal status did not reach statistical significance (Wald test = 2.22; P = 0.14). Nulliparous women overall showed a 20% lower breast cancer risk than uniparous ones (OR = 0.8; 95% CI = 0.7–1.0). The number of miscarriages did not seem to affect breast cancer risk to any extent. With respect to induced abortions, there was a hint of an increased risk only in premenopausal women. No significant trend in risk with number of induced abortions was evident (Table 3). After allowance for other characteristics (i.e. parity, age at first and last birth, menopausal status, age at menopause, and use of oral contraceptives and hormonal replacement therapy), OR for one and two or more induced abortions became 1.3 (95% CI = 1.0–1.6) and 1.2 (95% CI = 0.9–1.6), respectively.

Age at first pregnancy and at first birth showed strong and similar inverse associations with breast cancer risk (OR for age at first birth ≥32 years compared with <20 years = 1.7; 95% CI = 1.3–2.1). At variance with the favourable effect of multiparity, delay in first pregnancy or birth exerted a significantly marked effect more in premenopausal women than in postmenopausal ones (Wald test = 10.67; P = 0.002). The reported number of months of unprotected intercourse before first pregnancy, a possible indicator of infertility, was comparable in cases and controls. Any outcome of first pregnancy other than a live birth was associated with a moderate increase in risk in premenopausal women. Miscarriage/still birth and induced abortion were in this group, associated with an OR = 1.5 (95% CI = 1.0–2.1) and OR = 1.8 (95% CI = 0.9–3.3) respectively, in premenopausal women.

Women aged 35 years or over at last birth had an OR of 1.2 (95% CI = 1.0–1.5) as compared with those who had their last birth below 25 years. Such an unfavourable effect of age at last birth showed a clear trend for risk but was restricted to premenopausal subjects (OR = 2.5; CI = 1.7–3.6 for those 35–39 years of age at last birth) (Table 3). The heterogeneity between pre- and postmenopausal women with respect to the adverse effect of late age at last birth was highly significant (Wald test = 18.12; P < 0.001).

The combined effect of parity and age at first birth was further examined in all subjects (Table 4). Multiparity and early age at first birth both retained a significant influence on breast cancer risk after allowance for mutual confounding

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) of breast cancer according to menstrual characteristics and menopausal status, Italy, 1991–1994

	Menopausal status		
	Premenopausal OR (95% CI)*	Postmenopausal OR (95% CI)*	All OR (95% CI)**
Age at menarche (years)			
<12	1†	1†	1†
12	1.1 (0.8–1.4)	1.1 (0.9–1.3)	1.1 (0.9–1.3)
13	0.9 (0.7–1.2)	1.2 (0.9–1.5)	1.1 (0.9–1.3)
14	0.9 (0.7–1.2)	1.0 (0.8–1.3)	1.0 (0.8–1.2)
≥15	0.8 (0.6–1.2)	1.1 (0.8–1.3)	1.0 (0.8–1.2)
X^2_1 (trend)	1.70; $P = 0.19$	0.03; $P = 0.85$	0.34; $P = 0.56$
Menstrual bleeding (days)			
1–3	1†	1†	1†
4	1.0 (0.8–1.4)	1.1 (0.9–1.4)	1.1 (0.9–1.3)
5	1.0 (0.8–1.4)	1.2 (1.0–1.5)	1.1 (1.0–1.4)
6	1.0 (0.7–1.4)	0.9 (0.7–1.2)	0.9 (0.7–1.2)
≥7	1.0 (0.7–1.5)	0.8 (0.6–0.9)	0.9 (0.7–1.0)
X^2_1 (trend)	0.00; $P = 0.99$	7.29; $P = 0.007$	4.50; $P = 0.03$
Duration of menstrual cycles (days)			
<26	1†	1†	1†
26–30	1.1 (0.9–1.4)	1.1 (0.9–1.3)	1.1 (1.0–1.2)
≥31	0.9 (0.6–1.5)	1.3 (0.9–1.8)	1.2 (0.9–1.5)
Irregular	0.6 (0.4–1.0)	1.1 (0.7–1.5)	0.9 (0.7–1.2)
X^2_1 (trend) (excluding irregular)	0.13; $P = 0.72$	2.17; $P = 0.14$	1.40; $P = 0.23$
Type of menopause‡			
Natural	—	1†	1†
Artificial	—	0.8 (0.6–0.9)	0.8 (0.6–0.9)
Age at menopause (years)			
<45	—	1†	
45–49	—	1.3 (1.1–1.7)	
50–52	—	1.5 (1.2–1.9)	
≥53	—	1.8 (1.4–2.2)	
X^2_1 (trend)	—	26.98; $P < 0.001$	

* Estimates from multiple logistic regression equations, including terms for area of residence, age and education. ** Estimates from multiple logistic regression equations, including terms for area of residence, age, education and menopausal status. † Reference category. ‡ Equation includes also age at menopause (year).

effect. The OR for specific combinations of these two variables suggest that the two reproductive factors do not act in a multiplicative way.

Table 5 gives the odds ratios of breast cancer according to years elapsed from last birth in premenopausal only. Postmenopausal women were not included because of the lack of recent pregnancies in that group. The first model included parity, in addition to area of residence, age and education. The second model had an additional term for age at first birth and was, thus, restricted to women with two or more children. An approximately two-fold elevation of breast cancer risk was evident up to 10 years since last birth.

DISCUSSION

This paper provides further quantitative estimates of the effects of menstrual and reproductive factors on breast cancer risk. Despite extensive research, some uncertainties remain regarding their independent association with aetiology [1], and their relative importance at different ages and before and after menopause [2–18].

No clear trend of decreasing risk with age at menarche emerged in the present data set. These results were at variance with some studies which have indicated a protective effect for late menarche [8, 20, 21]. Nevertheless, they were consistent with other studies which suggested an adverse effect of early menarche (<12 years) selectively in women below age 50 years or in premenopausal status [2, 6, 7, 15, 19]. These negative findings may partly be due to inaccuracies in establishing the beginning of ovulatory cycles or, especially in elderly women, imprecise recall of age at menarche [46].

A significant decrease of breast cancer risk with increasing duration of menstrual bleeding emerged only in postmenopausal women. By contrast, no significant association was found overall and by menopausal status according to history of menstrual irregularity. A strong trend of increasing breast cancer risk with increasing age at menopause was found. These results are in agreement with the majority of previous studies which showed that late age at menopause was an important risk factor for breast cancer [6, 15]. Artificial menopause seemed to confer some additional protection as compared to natural menopause, age at menopause being equal.

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) of breast cancer according to reproductive characteristics and menopausal status, Italy, 1991–1994

	Menopausal status		
	Premenopausal OR (95% CI)*	Postmenopausal OR (95% CI)*	All OR (95% CI)**
Parity			
Nulliparae	0.7 (0.5–0.9)	0.9 (0.7–1.1)	0.8 (0.7–1.0)
1	1†	1†	1†
2	1.4 (1.1–1.7)	0.8 (0.7–0.9)	1.0 (0.8–1.1)
3	1.0 (0.8–1.4)	0.7 (0.6–0.8)	0.8 (0.7–0.9)
4	0.8 (0.5–1.3)	0.6 (0.4–0.8)	0.7 (0.5–0.9)
⩾5	0.7 (0.3–1.6)	0.7 (0.5–0.9)	0.7 (0.5–0.9)
X^2_1 (trend) (nulliparae excluded)	2.64; $P = 0.10$	15.74; $P < 0.001$	19.04; $P < 0.001$
Miscarriage			
0	1†	1†	1†
1	0.9 (0.7–1.2)	0.8 (0.7–1.0)	0.8 (0.8–1.0)
⩾2	1.1 (0.8–1.7)	0.9 (0.7–1.2)	1.0 (0.8–1.2)
X^2_1 (trend)	0.02; $P = 0.89$	2.48; $P = 0.12$	1.72; $P = 0.18$
Induced abortion	1†	1†	1†
0	1.4 (1.0–2.0)	1.1 (0.8–1.5)	1.2 (1.0–1.5)
1	1.2 (0.8–1.9)	1.0 (0.7–1.4)	1.1 (0.8–1.4)
⩾2			
X^2_1 (trend)	3.07; $P = 0.08$	0.01; $P = 0.90$	1.42; $P = 0.23$
Age at first pregnancy (years)‡			
<20	1†	1†	1†
20–23	1.3 (1.0–1.7)	0.9 (0.7–1.1)	1.0 (0.8–1.2)
24–27	2.0 (1.6–2.7)	1.0 (0.8–1.2)	1.3 (1.1–1.5)
28–31	1.7 (1.2–2.4)	1.2 (0.9–1.5)	1.3 (1.1–1.6)
⩾32	3.6 (2.2–5.8)	1.3 (1.0–1.7)	1.7 (1.3–2.1)
X^2_1 (trend)	29.77; $P < 0.001$	18.20; $P < 0.001$	43.43; $P < 0.001$
Length of attempt to first pregnancy (months)‡			
0§	1†	1†	1†
1–2	1.5 (1.2–2.1)	1.0 (0.8–1.2)	1.1 (1.0–1.4)
3–11	1.2 (0.9–1.5)	1.0 (0.8–1.1)	1.0 (0.9–1.2)
⩾12	1.5 (1.1–2.2)	0.9 (0.7–1.2)	1.1 (0.9–1.3)
X^2_1 (trend)	2.97; $P = 0.08$	0.00; $P = 0.97$	1.19; $P = 0.27$
Outcome of first pregnancy‡			
Live birth	1†	1†	1†
Miscarriage and stillbirth	1.5 (1.0–2.1)	1.1 (0.8–1.4)	1.2 (1.0–1.5)
Induced abortion	1.8 (0.9–3.3)	0.9 (0.5–1.7)	1.3 (0.8–2.0)
Age at first birth (years)‡			
<20	1†	1†	1†
20–23	1.2 (0.9–1.6)	0.8 (0.7–1.0)	0.9 (0.8–1.1)
24–27	2.0 (1.5–2.6)	1.0 (0.8–1.2)	1.3 (1.1–1.5)
28–31	1.7 (1.2–2.4)	1.2 (1.0–1.5)	1.4 (1.1–1.7)
⩾32	3.6 (2.2–5.8)	1.3 (1.0–1.7)	1.7 (1.3–2.1)
X^2_1 (trend)	34.82; $P < 0.001$	21.90; $P < 0.001$	52.09; $P < 0.001$
Age at last birth (years)§			
<25	1†	1†	1†
25–29	1.7 (1.3–2.1)	1.0 (0.8–1.2)	1.2 (1.0–1.4)
30–34	1.6 (1.2–2.1)	0.9 (0.8–1.1)	1.1 (1.0–1.3)
35–39	2.5 (1.7–3.6)	0.9 (0.7–1.1)	1.2 (1.0–1.5)
⩾40	1.8 (0.8–3.7)	1.0 (0.8–1.4)	1.2 (0.9–1.6)
X^2_1 (trend)	17.25; $P < 0.001$	0.15; $P = 0.69$	6.34; $P = 0.01$

* Estimates from multiple logistic regression equations, including terms for area of residence, age and education. ** Estimates from multiple logistic regression equations, including terms for area of residence, age, education and menopausal status. † Reference category. ‡ Nulligravidae or nulliparae excluded. § Includes unplanned pregnancies.

Table 4. Combined effect of parity and age at first birth on breast cancer risk, Italy, 1991–1994*

	Age at first birth (years)						
	≤23		24–27		≥28		All
Parity	Cases:controls	OR (95% CI)	Cases:controls	OR (95% CI)	Cases:controls	OR (95% CI)	OR (95% CI)
≥4	111:183	1†	66:88	1.2 (0.8–1.7)	21:26	1.2 (0.6–2.2)	1*
3	165:248	1.0 (0.7–1.4)	156:170	1.3 (0.9–1.8)	76:71	1.6 (1.3–2.3)	1.1 (0.8–1.3)
2	306:376	1.2 (0.9–1.6)	389:327	1.7 (1.2–2.2)	275:203	1.9 (1.4–2.6)	1.3 (1.1–1.6)
1	108:148	1.1 (0.7–1.5)	196:153	1.7 (1.2–2.4)	281:207	1.9 (1.4–2.6)	1.3 (1.0–2.6)
							X^2_1 (trend) 6.87; $P = 0.009$
All		1†		1.4 (1.2–1.6)		1.6 (1.3–1.9)	X^2_1 (trend) 32.25; $P < 0.001$

* Risk estimates from multiple logistic regression equations, including terms for area of residence, age, education, parity and age at first birth, as appropriate. † Reference category. OR, odds ratio; CI, confidence interval.

Table 5. Odds ratio (OR) and 95% confidence intervals (CI) of breast cancer according to years elapsed from last birth in premenopausal cases and controls, Italy, 1991–1994

	All parae		Parae ≥2	
Years elapsed from last birth	Cases:controls	OR_1 (95% CI)	Cases:controls	OR_2 (95% CI)
≥15	288:265	1*	183:182	1*
10–14	147:134	1.2 (0.9–1.7)	110:104	1.0 (0.7–1.5)
5–9	140:88	2.3 (1.5–3.3)	105:65	1.8 (1.1–2.9)
<5	76:54	2.4 (1.4–3.9)	49:34	1.8 (0.9–3.4)
X^2_1 (trend)		18.23; $P < 0.001$		5.13; $P = 0.02$

* Reference category.
OR_1, all parous women; estimates from multiple logistic regression equations, including terms for area of residence, age, education and parity.
OR_2, only women with two or more children; estimates from multiple logistic regression equations, including terms for area of residence, age, education, parity and age at first birth.

High parity reduced the risk of breast cancer, in agreement with most previous studies [1]. This favourable effect of pregnancy has been related either to changes in breast tissue that render the tissue less susceptible to carcinogenic agents, or to long-lasting modifications in the hormonal milieu subsequent to a first full-term pregnancy [1]. Such a protective effect seemed stronger in postmenopausal than in premenopausal women, possibly on account of the confounding effect of time since last birth in younger ones. As in previous studies [18], nulliparous women were not at increased risk as compared to all parous ones. Furthermore, premenopausal women with two or more births had a higher risk of breast cancer than nulliparae. Age at first birth and number of births did have an independent effect on the risk of breast cancer.

The hypothesised dual effect on parity on breast cancer risk receives further support. Premenopausal women who gave birth to their last child at age 30 years or over showed an approximately 50% elevated risk. The pattern of breast cancer risk across different times after last birth in premenopausal women with two or more births (where allowance for all three reproductive factors is possible), provides evidence that the immediate effect of a full-term pregnancy is an approximately 2-fold risk increase. Biologically, the large increases in oestradiol and progesterone, specific for pregnancy, might exert a short-term adverse effect, which, after a 10-year period, is replaced by a long-term beneficial effect of pregnancy [9]. Some parallel exists with the short-term risk elevation subsequent to the use of oral contraceptives [47].

A few studies [23, 37, 40, 48] have suggested that first-trimester induced abortions were associated with moderately increased breast cancer risk, especially if the abortion occurred before a first full-term pregnancy. Based on animal models, it has been proposed that an interrupted pregnancy may not confer any benefit or even be detrimental if it causes proliferation of breast cells without the protective effect of subsequent differentiation [49]. The present data did not show a significant risk elevation in women who underwent spontaneous or induced abortions. Although increases of breast cancer risk around 20% were seen for history of one induced abortion, no trend in risk was apparent.

In conclusion, the present data confirm that early age at menopause, multiparity and early age at first birth affect breast cancer risk favourably and independently. Because of the large size study, it was possible to consider risk patterns by menopausal status which helped to elucidate the dual effect of full-term pregnancies and, especially, the length of time (possibly up to 10 years) of breast cancer increase following pregnancy. Results with respect to interrupted pregnancies are reassuring, but they indicate the need of additional studies, especially in respect to new abortion modalities.

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