Risk of breast cancer in relation to the interval since last full term pregnancy

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Abstract

***Objective*—To examine whether the risk of breast cancer is increased by a recent term pregnancy.**

***Design*—Population based case-control study.**

***Setting*—Eight areas in the United States.**

***Subjects*—Cases were 2279 multiparous women residents of the eight areas aged 25-49 who were diagnosed as having breast cancer during 1980-2. Controls were 2357 multiparous women selected from the same areas by random digit dialling.**

***Main outcome measure*—Relative risk of developing breast cancer according to the time interval since last full term pregnancy.**

***Results*—The distribution of intervals since the last term pregnancy was similar in cases and controls. Adjusted for age, parity, and age at first term pregnancy, the odds ratios observed for categories of years since the last full term pregnancy were: 0-2 years, odds ratio 1·16 (95% confidence interval 0·84 to 1·59); 3-6 years, odds ratio 1·21 (0·95 to 1·54); 7-9 years, odds ratio 1·04 (0·84 to 1·38); ≥10 years, odds ratio 1·00 (reference).**

***Conclusions*—Among multiparous women aged 25-49 years there was no association between the risk of breast cancer and the time interval since the last full term pregnancy.**

Introduction

Though it is generally agreed that a woman's risk of breast cancer is reduced by a history of pregnancy,[1,2] some studies suggest this effect may be modified by age.[3,4] Forty years ago Logan noted that married, parous women aged 35 or over had a lower breast cancer mortality than married nulliparous women or single women of corresponding age.[3] However, below the age of 35 the direction of this association was reversed. A possible explanation is that pregnancy has two effects on breast tissue.[1] Firstly, there is a short term deleterious effect, which increases the risk of cancer; and, secondly, there is a long term protective effect. To test this, several studies have examined the risk of breast cancer in relation to the time interval since the last term pregnancy, with conflicting findings.[5-8] Because the question is unsettled we analysed data to test the hypothesis that a recent term pregnancy is associated with an increased risk of breast cancer.

Subjects and methods

We used data from the cancer and steroid hormone study, a large population based case-control study of risk factors for breast cancer.[9-12] Cases were women aged 20-54 years who had primary breast cancer diagnosed during 1980-2. They were identified by eight population based tumour registries in the United States. Controls were women selected during the same time period from the same regions by random digit dialling. Controls were frequency matched to the age distribution of the cases. Study participants were interviewed in the home. Further details have been published.[9-13]

A total of 5896 cases and 5698 controls were identified, of whom 4742 (80·4%) and 4754 (83·4%) respectively were interviewed.[13] Twelve cases were removed from the data file because it was unknown if they had used oral contraceptives, and 66 controls were removed because they had a history of breast cancer. We excluded women under the age of 25 because there were only 16 cases in this age group and therefore reliable estimates of risk would not be possible. To allow direct comparison of our results with previous studies[5,6] women aged over 49 were excluded. Only 32 women aged over 49 (12 cases, 20 controls) had reported a term pregnancy in the previous 10 years. Nulliparous women provide no information about the risk associated with recency of term pregnancies, so they were excluded. A term pregnancy was defined as any pregnancy which lasted over six months. Women with no pregnancy lasting over six months, with any pregnancy for which the length was unknown, and with unknown age at first term pregnancy were excluded (table I).

TABLE I—*Reasons for excluding interviewed study subjects*

Reasons for exclusion	No (%) of cases (total interviewed=4742)	No (%) of controls (total interviewed=4754)
Unknown if used oral contraceptives	12 (0·3)	0
Previous breast cancer	0	66 (1·4)
Age <25 years	16 (0·3)	106 (2·2)
Age ≥50 years	1395 (29·4)	1400 (29·4)
Never pregnant	431 (9·1)	287 (6·0)
No pregnancy lasting >6 months	123 (2·6)	118 (2·5)
Any pregnancy of unknown length	14 (0·3)	18 (0·4)
Parity=1	446 (9·4)	363 (7·6)
Age at first term pregnancy unknown	26 (0·5)	39 (0·8)
Total remaining	2279 (48·1)	2357 (49·6)

Age and age at first term pregnancy affect the risk of breast cancer,[1,2] and adjustment was made for those variables. For primiparous women, current age minus age at first term pregnancy equals the time since last pregnancy, so that the effect of time since last term pregnancy cannot be assessed independently. For example, if a woman had her first and only term pregnancy at age 30 and developed breast cancer at age 35 the time since her last pregnancy is five years. Within each stratum of age and age at first term pregnancy there is no variation in years to last term pregnancy for primiparous women. Therefore, primiparous women were excluded.

Analysis—Logistic regression was used to control for confounding by other exposures.[14] Time since last pregnancy was categorised as <3, 3-6, 7-9, and ≥10 years to conform to previous reports.[5,6] Other variables examined included those listed in table II, as well as months of breast feeding, age at menarche, menopausal status, family history of breast cancer, body mass index, marital status, race, education, income, geographic region, history of benign breast disease, number of spontaneous and induced abortions, past use of oral contraceptives, duration of oral contraceptive use, history of using oestrogens, past sterilising surgery, smoking history, and current pregnancy.

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TABLE II—*Distribution of multiparous cases and controls according to selected reproductive variables*

Characteristic	No (%) of cases (total=2279)	No (%) of controls (total=2357)
Years since last term pregnancy:		
<1	45 (2·0)	56 (2·4)
1	56 (2·5)	55 (2·3)
2	61 (2·7)	50 (2·1)
3-6	285 (12·5)	253 (10·7)
7-9	272 (11·9)	277 (11·8)
≥10	1560 (68·5)	1666 (70·7)
Parity:		
2	951 (41·7)	841 (35·7)
3	699 (30·7)	716 (30·4)
4	342 (15·0)	404 (17·1)
5	152 (6·7)	191 (8·1)
≥6	135 (5·9)	205 (8·7)
Age at first term pregnancy (years):		
<19	331 (14·5)	411 (17·4)
19-	496 (21·8)	570 (24·2)
21-	473 (20·8)	505 (21·4)
23-	529 (23·2)	533 (22·6)
>25	450 (19·7)	338 (14·3)

Results

The distribution of years since last term pregnancy was similar in cases and controls (table II). The adjusted relative risk estimates for breast cancer in multiparous women differed little with time since last term pregnancy (table III). When time since last term pregnancy was treated as a continuous linear variable the relative risk estimate for each additional year since last term pregnancy was 0·9968 (95% confidence interval 0·9774 to 1·017). These estimates were adjusted for age, age squared, parity (classified as 2, 3, 4, 5, and ≥6), and age at first term pregnancy (linear). Further adjustment for other variables (described above) had no important influence on these estimates.

There was no important association between time since last term pregnancy and breast cancer incidence within individual categories of parity or age at first term pregnancy. The relative risk estimates related to comparatively recent time intervals since last pregnancy were slightly higher for younger than for older women (table IV).

The first three years after the most recent term pregnancy were subdivided and adjusted relative risk estimates calculated (retaining ≥10 years as the reference category). Results were: <1 year, odds ratio 0·91 (95% confidence interval 0·57 to 1·47); 1 year, odds ratio 1·17 (0·76 to 1·81); 2 years, odds ratio 1·36 (0·88 to 2·09). Thus there was no appreciably increased risk in any of the first three years after a term pregnancy.

TABLE III—*Relative risk estimates for breast cancer in multiparous women aged 25-49 stratified by years since last term pregnancy*

Years since last term pregnancy	Odds ratio*	95% Confidence interval
0-2	1·16	0·84 to 1·59
3-6	1·21	0·95 to 1·54
7-9	1·04	0·84 to 1·38
≥10	1·00 (reference)	
χ^2_1 For trend		P=0·18

*Adjusted for age, parity, and age at first term pregnancy.

TABLE IV—*Relative risk estimates for breast cancer in multiparous women stratified by years since last term pregnancy and age at diagnosis (cases) or interview (controls)*

	Age (years)					
	25-34 (272 cases; 302 controls)		35-44 (1112 cases, 1062 controls)		45-49 (895 cases, 993 controls)	
Years since last term pregnancy	Odds ratio*	95% Confidence interval	Odds ratio*	95% Confidence interval	Odds ratio*	95% Confidence interval
0-2	1·25	0·80 to 1·96	1·17	0·79 to 1·74	1·10	0·50 to 2·43
3-6	1·38	0·92 to 2·07	1·19	0·93 to 1·53	1·03	0·64 to 1·65
7-9	1·08	0·73 to 1·62	1·05	0·85 to 1·30	1·02	0·71 to 1·47
≥10	1·00 (reference)		1·00 (reference)		1·00 (reference)	

*Adjusted for age, parity, and age at first term pregnancy.

Discussion

Among multiparous women aged 25-49 there was no evidence that a woman who had had a recent term pregnancy was at increased risk of breast cancer as compared with a woman of the same parity whose last delivery had occurred earlier in life. A limitation of our analysis was that the association between breast cancer and the time interval since last pregnancy could not fully be separated from other measures of pregnancy and time, such as age at first term pregnancy. If the risk of breast cancer is related to a recent first term pregnancy our analysis was unable to detect it. No analysis can separate the effect of a first pregnancy from the joint effects of age and age at the time of the pregnancy.

The data we used were population based and response rates were high, reducing the likelihood of selection bias. Nevertheless, response rates could have differed with interval since last term pregnancy. Possibly women with a recent pregnancy might be more likely to be at home compared with other women and would be overrepresented among controls contacted by telephone. This bias would tend to lower the relative risk estimates associated with recent pregnancy. This bias, if present, was probably small in our series because the study called all telephone numbers on at least five occasions and at different times both on weekdays and at weekends.[13]

Our failure to find an association between the risk of breast cancer and the interval after pregnancy agrees with the results of two population based case-control studies. A Scandinavian group found no association between years since last pregnancy and the risk of breast cancer.[7] Using nulliparous women as the reference population, the group obtained a relative risk of 0·6 (95% confidence interval 0·2 to 2·0) for the first year, 0·9 (0·4 to 2·0) for 1-4 years, and 0·8 (0·4 to 1·5) for ≥5 years. Similar results were reported from Norway: the relative risk was 1·2 (95% confidence interval 0·9 to 1·5) for ≤5 years since last pregnancy, 1·0 (0·8 to 1·2) for 6-10 years, and 1·0 (reference group) for 11-15 years.[8] Though both studies included nulliparous and primiparous women, making it harder to interpret results, it seems unlikely that these inclusions could have masked a raised relative risk in the period soon after delivery.

Our findings conflict with two reports of hospital based case-control studies. An Italian study of 573 multiparous women with breast cancer diagnosed before the age of 50 reported an association between time since last pregnancy and the risk of breast cancer.[5] The relative risk for 0-2 years was 2·7 (95% confidence interval 1·3 to 5·4), for 3-6 years 1·8 (1·1 to 2·9), for 7-9 years 1·4 (1·0 to 1·9), and for ≥10 years 1·0 (reference group). Similar results were reported by British workers, who analysed data from 422 multiparous women with breast cancer diagnosed before the age of 50.[6] They found a relative risk for 0-2 years after the last pregnancy of 2·9 (95% confidence interval 1·3 to 6·5), for 3-6 years 1·4 (0·8 to 2·6), for 7-9 years 0·8 (0·5 to 1·3), and for ≥10 years 1·0 (reference).

Further subdividing the three years immediately after the last term pregnancy, the British group noted that the relative risk during the first year was 20·5, which fell to 1·4 during the next two years.[6] The authors suggested that women with a recent pregnancy might avoid attending hospital and therefore be underrepresented in the control group. If their suggestion is correct this selection bias might explain why the

Epidemiological implications

- The risk of breast cancer is thought to be reduced by a past history of pregnancy
- Previous evidence suggests that a recent pregnancy (within three years) may transiently increase the risk of breast cancer
- A controlled study of over 2000 multiparous women aged 25-49 with newly diagnosed breast cancer has found no association between risk of breast cancer and time since last pregnancy

hospital based studies seem to show a transient increase in the relative risk of breast cancer related to a recent term pregnancy while the three population based studies found virtually no association.

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Comparability and validity of two clinical scores in the early differential diagnosis of acute stroke

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Abstract

***Objective*—To compare two available clinical scores for the differential diagnosis of cerebral ischaemia and haemorrhage in acute stroke patients.**

***Design*—Prospective, multicentre study of acute stroke patients evaluated with computed tomography and Allen and Siriraj scores; the scores were tested for comparability (kappa statistic) and validity (sensitivity, specificity, positive and negative predictive values, diagnostic gain). The effect of a policy of using Allen and Siriraj scores to determine pathological type of stroke before computed tomography was calculated.**

***Setting*—Three hospitals in Italy, all participating in the international stroke trial, with different access facilities to computed tomography.**

***Subjects*—231 consecutive patients who were screened in the three hospitals for possible inclusion in the international stroke trial from 1 November 1991 to 31 May 1993.**

***Results*—The prevalence of haemorrhage (diagnosed with computed tomography) was 14·7% (95% confidence interval 10·1% to 19·3%). Allen scores were "uncertain" in 44 cases and Siriraj scores in 38 cases; in the 164 cases with both the scores in the range of "certainty" kappa was 0·72. Sensitivity, specificity, positive and negative predictive values, and diagnostic gain for haemorrhage were 0·38, 0·98, 0·71, 0·91, and 0·58 for Allen scores and 0·61, 0·94, 0·63, 0·93, and 0·48 for Siriraj scores; positive predictive values for infarction were 91% for Allen scores and 93% for Siriraj scores. According to these data, of 1000 patients with acute stroke, 680 would be correctly and 70 wrongly diagnosed as "ischaemic" with the Allen score; the figures would be 671 and 48 with Siriraj score.**

***Conclusion*—When computed tomography is not immediately available and the clinician wishes to start antithrombotic treatment (or randomise patients in a clinical trial), the Siriraj score (and possibly the Allen score) can be useful to identify patients at low risk of intracerebral haemorrhage.**

Introduction

Haemorrhagic and ischaemic stroke cannot be distinguished clinically with a simple clinical evaluation, and it is virtually impossible for all stroke patients to have a computed tomography scan immediately after admission. Thus, in small district hospitals as well as in large university centres a weighted clinical score may offer some advantages to physicians who are involved in stroke management and need to distinguish between haemorrhage and ischaemia for the purpose of treat-