

# Fertility problems and breast cancer risk in young women: a case-control study in the United States

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**Objectives:** Late age at first birth and nulliparity are established risk factors for breast cancer, yet the extent to which fertility problems contribute to these associations remains largely unexplored. Here, we examine self-reported fertility problems as a risk factor for breast cancer in young women.

**Methods:** We used a population-based case-control study of 2,173 cases and 1,990 controls aged 20 to 54 years in the United States. Structured in-person interviews were used to elicit detailed information on established and potential breast cancer risk factors. Information was collected on pregnancy details, including difficulties becoming pregnant or maintaining a pregnancy.

**Results:** Self-reported difficulty in becoming pregnant or maintaining a pregnancy was reported by 450 cases and 377 controls. Overall, there was little association between these fertility problems and risk of breast cancer (odds ratio [OR] = 1.05). Parity was associated with a decreased risk of breast cancer in women both with (OR = 0.71) and without (OR = 0.79) fertility problems. There was little evidence of an increased risk of breast cancer with later age at first full-term birth among women without fertility problems ( $OR_{\text{age } 35+ : \text{age } <20} = 1.13$ , 95 percent confidence interval [CI] = 0.7-1.9), but a relatively strong association among women with fertility problems ( $OR_{\text{age } 35+ : \text{age } <20} = 2.96$ , CI = 1.3-7.0). Among women with a first full-term birth at age 35 or older, fertility problems were associated with a twofold risk of breast cancer. Analyses of duration of unprotected sexual intercourse prior to first pregnancy as an alternative estimate of infertility produced similar results.

**Conclusions:** Our study suggests that the association between late age at first birth and breast cancer is stronger among women with self-reported fertility problems than among women with no fertility problems. *Cancer Causes and Control* 1998, 9, 331-339

**Key words:** Breast cancer, infertility, pregnancy, United States.

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## Introduction

Infertility, as defined by failure to conceive after 12 months of intercourse without contraception, is estimated to affect 8.5 percent of married couples with wives aged 15 to 44 years.<sup>1</sup> Couples with fertility problems may be more likely to remain nulliparous or to have their first child at an older age.<sup>1</sup> Both nulliparity and late age at first birth are associated with an increased risk of breast cancer.<sup>2</sup> Several studies have examined the risk of breast cancer associated with a history of infertility and all but one<sup>3</sup> have found little evidence of a relationship.<sup>4-14</sup> Few studies have examined the effect of fertility problems on risk of breast cancer among nulliparous women, and these have found little association.<sup>10,11</sup> Also, few studies have examined whether the increased risk associated with a late age at first birth is related to fertility problems. One cohort study of postmenopausal women<sup>12</sup> revealed an increased risk of breast cancer among infertile women with both a late age at first birth and a family history of breast cancer. No association of breast cancer and infertility was seen unless both these factors were present. One case-control study<sup>6</sup> indicated that the increased risk of breast cancer associated with older age at first birth was largely attributable to a later age at onset of regular sexual intercourse, and not to fertility problems. Another case-control study<sup>11</sup> also tested for effect modification of the relationship between infertility and breast cancer by age at first birth and menopausal status, and found no effect.

To examine the effect of fertility problems in the development of breast cancer, stratified by parity and age at first birth, we used data from a large, population-based case-control study of women under 54 years of age.<sup>15</sup>

## Materials and methods

This case-control study was conducted in three areas of the United States covered by cancer registries – Atlanta (Georgia), Seattle/Puget Sound (Washington), and five counties in central New Jersey. Details have been published elsewhere.<sup>15</sup> The present analyses include all women aged 20 to 44 years in Seattle and New Jersey, and aged 20 to 54 years in Atlanta, who were newly diagnosed with *in situ* or invasive breast cancer during the period 1 May 1990 through 31 December 1992. Cases were identified through rapid ascertainment systems. Controls were chosen through random digit dialing and were frequency matched by geographic area and age to the expected distribution of cases. A 90.5 percent response rate to the telephone screener was obtained from 16,254 telephone numbers.

Structured in-person interviews were carried out, and completed interviews were obtained from 2,202 of the 2,551 eligible cases (86.3 percent) and 1,990 of the 2,552 eligible controls (78.0 percent). The interview elicited detailed information on demographic factors, reproductive and menstrual history, contraceptive behavior, screening history, smoking habits, and alcohol consumption. Information on risk factors was truncated at the reference date (*i.e.*, the date of diagnosis for cases or the date of completion of the telephone screener for controls). Women were defined as postmenopausal if they had undergone either a natural menopause or surgery to remove both ovaries. Women with unknown ovarian function who were older than 51 years (assumed to be the median age of menopause among women in the US) were also defined as postmenopausal. In order for the cases and controls to be comparable, the 29 cases without residential telephones were excluded from the analyses. The study population consisted of the remaining 2,173 cases and 1,990 controls.

Subjects were queried about each of their pregnancies, including the outcome (*e.g.*, livebirth, stillbirth, miscarriage, abortion, ectopic). In addition, they were asked about visits to a doctor, clinic, or hospital because of difficulties in either becoming pregnant or maintaining a pregnancy, the cause of such difficulties (if known) and any treatments used to help in conceiving or maintaining a pregnancy. The principal measure of infertility in this study is a self-reported difficulty in either becoming pregnant or maintaining a pregnancy. However, a calendar was used during the interview to record details of reproductive history and contraceptive use throughout a subject's life, and the duration of contraceptive-free sexual intercourse prior to first pregnancy calculated from this calendar was used as an additional measure of infertility.

The distribution of established or suspected breast-cancer risk factors among controls with and without a history of fertility problems respectively, were age-standardized, using the controls without a history of fertility problems as the standard population.<sup>16</sup> Odds ratios (OR) and 95 percent confidence intervals (CI) were calculated as estimates of the relative risk using multiple logistic regression. Adjustment was made for age at reference date as a continuous variable, and geographic site (Atlanta, New Jersey, Seattle), years of oral contraceptive (OC) use (less than six months, six months to less than five years, five to less than 10 years, and 10 or more years), and level of education (high school or less, technical school, some college, college graduate, postgraduate work) as categorical variables. The latter two variables were included as they were

strongly associated with a history of fertility problems among controls ( $P < 0.01$ ). Analyses of parous women were further adjusted for number of full-term births and age at first full-term birth where appropriate.

## Results

A total of 451 cases (21 percent) and 377 controls (19 percent) responded that they had experienced difficulties in either becoming pregnant or maintaining a pregnancy. The majority of these women (264 cases and 205 controls) reported difficulty in becoming pregnant only. Of the remaining women, 123 cases and 117 controls reported difficulty in maintaining a pregnancy only, and 64 cases and 55 controls reported both problems.

The age-standardized distributions of breast cancer risk factors among controls with and without a history of fertility problems are shown in Table 1. The proportion of controls who were nulliparous was similar in both groups. Among parous controls, those with fertility problems were more likely to have a late age at first full-term birth, and further analyses showed that this association was restricted to those women reporting difficulty becoming pregnant rather than those reporting difficulty maintaining a pregnancy. Controls with fertility problems were less likely to have used OC for at least one year, and more likely to have received postgraduate education. Among gravid controls, women with fertility problems were less likely to have had an induced abortion.

The ORs associated with fertility problems in the study population overall and among the subgroups of nulligravid and parous women are shown in Table 2. Risk estimates for women who were gravid and nulliparous (181 cases and 145 controls) are not presented as these women had only an interrupted pregnancy (due either to an induced or spontaneous abortion), and there is no clearly suitable baseline group for assessing the effect of fertility problems on their breast cancer risk. There was little overall association between fertility problems and risk of breast cancer ( $OR = 1.05$ ), and results were largely similar among nulligravid and parous women separately. The OR was greatest for parous women who reported difficulty both in becoming pregnant and maintaining a pregnancy, compared with parous women with no fertility problems ( $OR = 1.22$ ,  $CI = 0.8-1.8$ ).

Parous women were at a lower risk of breast cancer than nulligravid women ( $OR = 0.79$ ,  $CI = 0.7-0.9$ , adjusted for age at reference date, site, years of OC use, and education level). The reduction in risk was similar for women with ( $OR = 0.71$ ) and without ( $OR = 0.79$ ) fertility problems. Among parous women without

fertility problems, increasing parity was associated with a reduced risk of breast cancer ( $OR_{4 \text{ births}:1 \text{ birth}} = 0.63$ ,  $CI = 0.5-0.8$ ; Table 3). There was little effect of further adjustment for age at first full-term birth. In contrast, among women with fertility problems, there was little evidence of a reduction in risk of breast cancer with increasing parity after adjusting for age at first full-term birth ( $OR_{4 \text{ births}:1 \text{ birth}} = 0.85$ ,  $CI = 0.5-1.6$ ; Table 3).

Time since last pregnancy has been shown in some studies<sup>2</sup> to confer a transient increased risk of breast cancer. In this study, the majority of women both with (52 percent) and without (58 percent) fertility problems had had their last pregnancy at least 10 years before the reference date, and there was no evidence of an association between shorter time since last pregnancy and risk of breast cancer. Adjustment for time since last pregnancy had little effect on the interaction between age at first birth and fertility problems (results not shown).

Table 4 shows the effects of age at first full-term birth on risk of breast cancer among women with and without fertility problems. There was little effect of age at first birth on risk of breast cancer among women with no fertility problems ( $P \text{ trend} = 0.16$ ). In contrast, among women with fertility problems, the trend with age at first birth was significantly stronger, rising to a threefold risk for women with a first full-term birth at age 35 years or older compared with age at first birth of less than 20 years ( $OR_{\text{age} \geq 35:\text{age} < 20} = 2.96$ ,  $CI = 1.3-7.0$ ;  $P \text{ trend} < 0.001$ ). The interaction between age at first birth and presence or absence of fertility problems was statistically significant ( $P = 0.02$ ). Further adjustment for the other breast cancer risk factors in Table 1 had little effect on the results. Additional analyses were carried out to investigate this effect further. Similar results to those in Table 4 were found when the definition of fertility problems was restricted to primary infertility (*i.e.*, women who experienced fertility problems before a first livebirth), or by analyzing age at first pregnancy instead of age at first full-term birth. It is likely that there is some misclassification of fertility problems due to women who have never attempted to become pregnant, and hence would be unaware of any fertility problems. In an attempt to minimize this misclassification, analyses in Table 4 were repeated among women aged 40 to 55 only, and results changed little (results not shown). A previous study<sup>12</sup> found an interaction between age at first birth and infertility only among women with a family history of breast cancer. However, stratification by family history in our data showed that the risk of breast cancer was increased with age at first birth only among women with fertility problems, regardless of family history (results not shown).

**Table 1.** Distribution of breast cancer risk factors among controls with and without self-reported fertility problems;<sup>a</sup> USA

Risk factor	Controls with fertility problems ( <i>n</i> = 377) No. (%) <sup>b</sup>	Controls with no fertility problems ( <i>n</i> = 1,612) No. (%) <sup>b</sup>
Age (yrs) at reference date		
< 35	21 (6%)	269 (17%)
35-39	81 (21%)	393 (24%)
40-44	160 (42%)	576 (36%)
45-50	61 (16%)	195 (12%)
50-54	54 (14%)	179 (11%)
Race		
White	301 (79%)	1,253 (78%)
Black	55 (15%)	268 (17%)
Other	21 (6%)	91 (6%)
Family history of breast cancer		
No	350 (94%)	1,516 (94%)
Yes	27 (6%)	96 (6%)
Previous breast biopsy		
No	335 (90%)	1,481 (92%)
Yes	42 (10%)	131 (8%)
Parity		
Nulliparous	68 (21%)	324 (20%)
Parous	309 (79%)	1,288 (80%)
Age (yrs) at first full-term birth <sup>c</sup>		
< 20	52 (17%)	323 (25%)
20-24	116 (36%)	458 (36%)
25-29	79 (25%)	327 (25%)
30+	62 (21%)	179 (14%)
Menopausal status		
Premenopausal	320 (87%)	1,423 (88%)
Postmenopausal	56 (12%)	181 (11%)
Age (yrs) at menarche		
14+	91 (23%)	327 (20%)
13	103 (25%)	481 (30%)
12	101 (28%)	421 (26%)
<12	81 (24%)	379 (24%)
Duration of OC <sup>d</sup> use		
Never or < 6 mo.	117 (31%)	478 (30%)
6 mo - 1 yr	167 (45%)	565 (35%)
1-4 yrs	64 (16%)	349 (22%)
5+ yrs	29 (8%)	220 (14%)
Cigarette smoker		
Never or irregular	192 (52%)	811 (50%)
Ex-smoker	106 (27%)	449 (28%)
Current smoker	78 (21%)	351 (22%)
Level of education		
High school or less	104 (25%)	481 (30%)
Technical school	24 (7%)	138 (9%)
Some college	99 (29%)	410 (25%)
College graduate	80 (21%)	387 (24%)
Postgraduate work	70 (18%)	196 (12%)
Body mass index (kg/m <sup>2</sup> )		
< 22	93 (25%)	365 (23%)
22-24.59	91 (24%)	386 (24%)
24.6-29.02	101 (27%)	405 (25%)
29.03+	87 (23%)	427 (26%)
Alcohol consumption (lifetime average drinks per week)		
0	175 (48%)	817 (51%)
<1-6.9	186 (47%)	739 (46%)
7+	14 (5%)	54 (3%)
Number of induced abortions <sup>e</sup>		
0	283 (81%)	1,054 (76%)
1+	64 (19%)	324 (23%)

<sup>a</sup> A woman is defined as having a history of infertility if she reported difficulty in either becoming pregnant or in maintaining a pregnancy. One woman did not answer the question about difficulty in maintaining a pregnancy and is excluded from this table.

<sup>b</sup> Percentages are age-standardized using women without infertility problems as the standard population.

<sup>c</sup> Among parous women.

<sup>d</sup> OC = oral contraceptive.

<sup>e</sup> Among gravid women.

Table 5 shows the risk of breast cancer by fertility problems within strata of age at first full-term birth. No effect of fertility problems was seen among women with a first full-term birth at age 29 years or younger. Among women whose first full-term birth occurred at age 30 years or older, however, fertility problems were associated with elevated risks of breast cancer (at age 30-34, OR = 1.46; at age ≥ 35, OR = 1.95). Results were similar for self-reported difficulty becoming pregnant and difficulty maintaining a pregnancy (results not shown). Further analyses stratified by age at first pregnancy rather than age at first full-term birth indicated an increased risk of breast cancer associated with fertility problems in each age group from 25 years or older at first pregnancy (results not shown), compared with women aged less than 25 at first pregnancy.

As an additional estimate of infertility, we examined the risk of breast cancer by duration of unprotected sexual intercourse prior to first pregnancy. There was some suggestion of an increased risk of breast cancer with increasing months of unprotected intercourse prior to first pregnancy (OR<sub>12-17 months</sub> = 0.87; OR<sub>18-23 months</sub> = 1.10; OR<sub>≥ 24 months</sub> = 1.31; *P* trend = 0.05; risks are relative to less than 12 months of unprotected intercourse, adjusted for age at reference date, site, years of

OC use, education level, age at first birth and number of births). Table 6 shows the risk of breast cancer by age at first birth, stratified by duration of unprotected sexual intercourse prior to first pregnancy. Among women with less than 12 months of unprotected intercourse, the risk increased slightly with age at first birth, to 1.31 among women with a first full-term birth at age 35 years or older compared with women with a first birth at age less than 20 years. Among women with at least 12 months of unprotected intercourse prior to first pregnancy, a first birth at age 35 years or older was associated with a twofold increase in risk.

Persistence of infertility was estimated by the duration from the first visit to a doctor for fertility problems until first full-term birth. There was no evidence of an increased risk of breast cancer with increasing length of this interval. The increase in risk of breast cancer among women with older age at first full-term birth was similar for women with less than two years' duration (OR<sub>35+ years : <25 years</sub> = 2.67, CI = 0.7-9.6) and for those with 2 or more years duration (OR<sub>35+ : years: <25 years</sub> = 3.22, CI = 1.0-10).

The majority of women who reported difficulty becoming pregnant said that they had been given an explanation by their doctor (71 percent of cases and 69

**Table 2.** Odds ratios (OR) and 95% confidence intervals (CI) of breast cancer associated with self-reported fertility problems; USA

	Cases	Controls	OR <sup>a</sup>	(CI)
All women <sup>b</sup>				
No fertility problems	1,722	1,612 <sup>c</sup>	1.00	—
Fertility problems	451	377	1.05	(0.9-1.2)
Nulligravid women				
No fertility problems	264	216	1.00	—
Difficulty becoming pregnant	50	31	1.04	(0.6-1.7)
Parous women <sup>b</sup>				
No fertility problems	1,307	1,288	1.00	—
Fertility problems	370	309	1.10	(0.9-1.3)
Difficulty becoming pregnant	191	156	1.09	(0.9-1.4)
Difficulty maintaining a pregnancy	119	110	1.08	(0.8-1.4)
Both difficulties	60	43	1.22	(0.8-1.8)

<sup>a</sup> All odds ratios are adjusted for age at reference date, site, years of oral contraceptive use and education level.

<sup>b</sup> Analyses involving parous women are further adjusted for age at first full-term birth and number of full-term births.

<sup>c</sup> One control had missing information on difficulty maintaining a pregnancy.

**Table 3.** Odds ratios (OR) and 95 percent confidence intervals (CI) of breast cancer associated with number of full-term births among parous women, by self-reported fertility status; USA

Number of full-term births	No fertility problems						Fertility problems					
	Cases	Controls	OR <sup>a</sup>	(CI)	OR <sup>b</sup>	(CI)	Cases	Controls	OR <sup>a</sup>	(CI)	OR <sup>b</sup>	(CI)
1	323	293	1.00	—	1.00	—	96	68	1.00	—	1.00	—
2	589	524	1.00	(0.8-1.2)	1.01	(0.8-1.3)	182	121	1.11	(0.8-1.7)	1.32	(0.9-2.0)
3	270	296	0.81	(0.6-1.0)	0.84	(0.7-1.1)	60	73	0.62	(0.4-1.0)	0.86	(0.4-1.4)
4+	125	175	0.63	(0.5-0.8)	0.66	(0.5-0.9)	32	47	0.56	(0.3-1.0)	0.85	(0.5-1.6)

<sup>a</sup> Adjusted for: age at reference date, site, years of oral contraceptive use, and education level.

<sup>b</sup> Additionally adjusted for age at first full-term birth.

**Table 4.** Odds ratios (OR) and 95 percent confidence intervals (CI) of breast cancer associated with age at first full-term birth among parous women, by self-reported fertility status; USA

Age at first full-term birth (yrs)	No fertility problems				Fertility problems			
	Cases	Controls	OR	(CI)	Cases	Controls	OR	(CI)
< 20	277	323	1.00	—	38	52	1.00	—
20-24	463	458	1.08	(0.9-1.3)	99	116	1.00	(0.6-1.7)
25-29	354	327	1.11	(0.9-1.4)	108	79	1.47	(0.8-2.6)
30-34	164	139	1.18	(0.9-1.6)	90	49	1.98	(1.1-3.7)
35+	48	40	1.13	(0.7-1.9)	35	13	2.96	(1.3-7.0)

<sup>a</sup> Adjusted for: age at reference date, site, years of oral contraceptive use, education level, and number of full-term births.

**Table 5.** Odds ratios (OR) and 95 percent confidence intervals (CI) of breast cancer with self-reported fertility status, stratified by age at first full-term birth, among parous women; USA

	Cases	Controls	OR <sup>a</sup>	(CI)
Age at first full-term birth < 20 yrs				
No fertility problems	277	323	1.00	—
Fertility problems	38	52	0.88	(0.6-1.4)
Age at first full-term birth 20-25 yrs				
No fertility problems	463	458	1.00	—
Fertility problems	99	116	0.84	(0.6-1.1)
Age at first full-term birth 25-29 yrs				
No fertility problems	354	327	1.00	—
Fertility problems	108	79	1.18	(0.8-1.7)
Age at first full-term birth 30-34 yrs				
No fertility problems	164	139	1.00	—
Fertility problems	90	49	1.46	(0.9-2.3)
Age at first full-term birth 35+ yrs				
No fertility problems	48	40	1.00	—
Fertility problems	35	13	1.95	(0.9-4.4)

<sup>a</sup> Adjusted for age at reference date, site, years of oral contraceptive use, education level, and number of full-term births.

percent of controls). The 25 cases and 17 controls reporting hormone-related fertility problems had a significantly older mean age at first birth than those reporting non-hormonal problems (30.2 years *cf* 27.3 years,  $P < 0.001$ ). However, there is likely to be substantial misclassification in diagnosis and reporting of type of fertility problem (*e.g.*, hormonal factor, cervical factor, tubal factor, male factor), especially in the absence of clinical fertility records, and hence detailed analyses on risks associated with types of infertility were not carried out. Exclusion of the 49 cases (11 percent) and 32 controls (eight percent) of women with fertility problems who reported that a male factor was the cause of their fertility problems made little difference to the overall results or the interaction between fertility problems and age at first birth (results not shown).

Over half of all women with fertility problems (59 percent of cases and 61 percent of controls) did not report taking any medication to assist with becoming pregnant or maintaining a pregnancy. For the remaining

women, the most commonly used medication was clomiphene citrate, which was reported by 88 cases and 56 controls. There was little association of use of clomiphene citrate (OR = 1.01) or other medication (OR = 0.87) with risk of breast cancer among women with difficulty becoming pregnant (after adjusting for age at reference date, race, site, and the combination variable of number of full-term births and age at first full-term birth). Similarly, no association between medication use and breast cancer was seen among women who reported difficulty maintaining a pregnancy (OR = 1.02). Information on duration of usage of these medications was not available.

## Discussion

Strengths of the present study include the size – which enabled the joint analyses of infertility by parity and age at first birth – and the detailed information on potential confounding factors. There are, however, several reasons for caution in interpreting these data. First, it is likely

**Table 6.** Odds ratio (ORs) and 95 percent confidence intervals (CI) of breast cancer associated with age at first full-term birth, by time of unprotected intercourse before first pregnancy among parous women; USA

Age at first full-term birth	Period of unprotected intercourse prior to first pregnancy							
	< 12 months				12 + months			
	Cases	Controls	OR <sup>a</sup>	(CI)	Cases	Controls	OR <sup>a</sup>	(CI)
< 20 <sup>b</sup>	269	328	1.00	—	46	47	1.00	—
20-24	464	469	1.09	(0.9-1.4)	98	105	0.98	(0.6-1.6)
25-29	364	319	1.21	(0.9-1.6)	98	87	1.06	(0.6-1.8)
30-34	175	140	1.30	(1.0-1.8)	79	49	1.46	(0.8-2.7)
35+	51	39	1.31	(0.8-2.1)	32	14	2.06	(0.9-4.7)

<sup>a</sup> Adjusted for age at reference date, site, years of oral contraceptive use, education level, and number of births.

<sup>b</sup> ORs relative to < 25 years at first birth: < 12 months: 1.14, 1.23, 1.23; 12+ months: 1.07, 1.48, 2.09.

that self-reported fertility problems and use of fertility drugs are subject to error, and the data are further limited by lack of validation by clinical records. Women who reported no difficulty becoming pregnant because they have never attempted to become pregnant are classified as having no fertility problems. Further, perception of fertility problems may vary with age. Women may seek evaluation or treatment for fertility problems more readily if attempting pregnancy at a late age; conversely, women with fertility problems may delay evaluation for a longer time-period if their pregnancy attempts occur at a relatively young age. However, this would not explain the study findings unless this tendency occurred to varying extents in cases and controls. Also, the similar results found when analyzing duration of unprotected intercourse before the first pregnancy as a measure of infertility argue against differences in perception of fertility problems in women with varying ages at first birth as an explanation of the study findings.

As the oldest age-at-first-birth group was open-ended (35 years or older), it is possible that the increase in risk in women with fertility problems and a late age at first birth may be partly attributable to residual confounding by age at first birth in this group. The small numbers of women in this category meant it was not possible to stratify further within this age group. However, the distribution of age at first birth among women in this category was similar for cases and controls (infertile cases, median = 36.4 years, range 35-42; infertile controls, median = 38.2 years, range 35-43), indicating that such residual confounding does not explain our results.

Fertility problems did not appear to be a major reason for nulliparity in this study, as similar proportions of controls with and without fertility problems were nulliparous, and our results show that fertility problems did not seem to affect the increased breast cancer risk among nulligravid women. In contrast, our data suggest that fertility problems are an effect-modifier on risk of breast cancer among parous women. Among women

with no fertility problems, an increasing number of full-term births is associated with a further reduction in risk of breast cancer, while in women with fertility problems, there is no clear reduction in risk with increasing number of births beyond the first, after adjusting for age at first birth. However, the numbers of women with fertility problems in each age group is small, and this result may be due to chance.

There was no overall association between risk of breast cancer and self-reported fertility problems in this study, but an increased risk was observed for women with fertility problems who had a first birth at age 30 to 35 years and 35 or more years. These results suggest that the established increased risk of breast cancer among women with a late age at first birth may be partly attributable to fertility problems occurring in these women. Few previous studies have examined associations between infertility and age at first birth on risk of breast cancer.<sup>3,9,11</sup> In one of these,<sup>3</sup> the risk of breast cancer in a cohort of infertile women was greater among those with an older age at first birth (30 years), although the study was limited by its small sample size and the difference was not statistically significant. In two larger studies,<sup>9,11</sup> no overall association was found between breast cancer and infertility, and no effect modification when data were stratified by age at first birth. In contrast, a prospective cohort study,<sup>12</sup> which included 620 cases of postmenopausal breast cancer, found an interaction of infertility and age at first birth among women with a family history of breast cancer. No interaction was found among women with no family history.

In our study, the increased risk with age at first birth was apparent only among women with fertility problems, with no effect modification by a family history of breast cancer. A case-control study of 575 parous breast cancer cases<sup>6</sup> found that the older age at first birth among the cases was due primarily to older age at onset of regular sexual intercourse. In contrast to our results, the authors found no effect of duration of unprotected

intercourse prior to first pregnancy, and concluded that the late age at first birth among cases was not attributable to fertility problems.

Infertility may be related to breast cancer through its association with ovarian hormones, which are suspected to play an important role both in breast carcinogenesis,<sup>17</sup> and in many causes of infertility.<sup>1</sup> If there is an association between fertility problems and breast cancer, then the increased risk associated with fertility problems among women with an older age at first birth may be due to a more severe form of infertility among these women (hence the delayed childbirth). However, the increase in risk of breast cancer was similar among women with a short *of* long interval between visit to a doctor for fertility problems and first birth, indicating no strong effect of severity of fertility problems, although this is a relatively crude measure of persistence of infertility. We also adjusted the analyses in Table 4 for duration of unprotected intercourse before first pregnancy, and this made little difference to the results.

Another possible explanation for the restriction of increased risk to women with both fertility problems and a late age at first birth in this study is that risk of breast cancer may be increased through a joint effect of these factors. One suggested reason for the increasing risk of breast cancer in women with a later age at first birth is the accelerated growth of breast cells during pregnancy, possibly causing progression of occult tumors in women with an older age at first pregnancy.<sup>2</sup> It is possible that fertility problems in women with a late age at first birth may be related to factors which increase the likelihood of occult tumors or enhance their progression, thus resulting in the joint effect.

Also, different reasons for infertility between women with a younger *of* older age at first birth may explain the restriction of increased risk of breast cancer to women who had both fertility problems and a late age at first birth. The occurrence of an age-related decline in fertility is well-documented, although the precise mechanisms of this effect are unclear.<sup>18</sup> In this study, there was some evidence that hormonal reasons underlying fertility problems were more common among women with an older age at first birth. It may be that hormonal fertility problems contribute to the observed association between risk of breast cancer and older age at first birth. However, the increased risk of breast cancer with older age at first birth was still observed among women who did not report hormonal fertility problems (results not shown). Further work in this area, with detailed assessment of reasons for fertility problems is needed.

Medications used to treat infertility may influence cancer risk. However, in this study, the majority of women with fertility problems did not report use of fertility drugs. Our null result for risk of breast cancer

associated with use of clomiphene citrate contrasts with results from a recent study,<sup>14</sup> which assessed the risk of breast cancer associated with use of ovulation-inducing agents in a cohort of infertile women. In that study, although there was no overall effect of infertility on breast cancer risk, women who had been treated with clomiphene citrate were at half the risk of breast cancer, as were infertile women who had not used the drug (OR = 0.5, CI = 0.2-1.2). Clomiphene is structurally similar to tamoxifen, and has been observed to exert anti-proliferative effects on human mammary cancer cells *in vitro*. There is also limited evidence in one study<sup>19</sup> of tumor regression following treatment with clomiphene for advanced breast cancer.

To conclude, this study found little overall association between self-reported fertility problems and breast cancer. However, there appeared to be a joint effect of fertility problems and older age at first birth on risk of breast cancer. Among women with a first birth at age 35 or older, women with fertility problems were at twice the risk of breast cancer as women with no reported fertility problems. As this is the first study to show such an effect, further work in this area is necessary.

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