

Parental Age in Relation to Risk of Breast Cancer¹

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Abstract

Data from a population-based case-control study were analyzed to evaluate risk of breast cancer among women according to parental age at the time of subject birth. Between 1988–91, breast cancer cases ($n = 1,253$) were obtained from the statewide tumor registry in Wisconsin. Concurrently, population controls ($n = 1,121$) were randomly selected from driver's license lists (if under age 65) and Medicare beneficiary files (if 65–74 years). Information regarding parents' ages and breast cancer risk factors was obtained by telephone interview. Relative risk estimates were very slightly elevated with increasing maternal age, although no consistent trend of increasing risk was observed (P for trend = 0.38). No association between paternal age and breast cancer risk was observed (P for trend = 0.98). Older maternal or paternal age was not associated with risk among any of the subgroups examined, except for daughters who had late age at first birth. These findings are consistent with the majority of studies that have found little or no association between parental age and breast cancer risk.

Introduction

There is some evidence that prenatal exposures may be involved in the development of breast cancer. Among *in utero* exposures, older parental age has been hypothesized to increase risk in later born daughters because of higher levels of endogenous estrogen concentrations in older pregnant women (1–3), or germ cell mutations at older paternal and maternal ages (4, 5). While several investigators have reported a modestly increased risk—about 25%—in women born to older mothers (6–11) or older fathers (9), few of these studies were able to rule out chance as an explanation. Other studies failed to observe a positive association (12–17). In this report we analyze data from a population based case-control study in order to evaluate both maternal and paternal age in relation to breast cancer risk.

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Materials and Methods

Details of the larger collaborative case-control study from which these data were derived has been reported previously (18). Briefly, all female residents of Wisconsin with a new diagnosis of invasive breast cancer who were under 75 years were identified from the statewide cancer registry from April 1988 through December 1991. According to an institutionally approved protocol, the physician for each eligible case was contacted for permission to approach the patient. Eligibility was limited to cases with a driver's license if less than 65 years of age and to those with a Medicare card (if over age 65). Controls were randomly selected from the Wisconsin population using two sampling frames: those under 65 years of age were selected from lists of licensed drivers; subjects over age 65 through 74 years of age were selected from a roster of Medicare beneficiaries provided by the Health Care Financing Administration. Since the interview was conducted over the telephone, eligibility of case and controls was restricted to those with a listed telephone number. The 25 minute telephone interview elicited the age of the subject's mother and father at the time of birth, in addition to a complete reproductive history, use of exogenous hormones, early life physical activity, alcohol consumption, selected dietary intake, personal and family medical history, and demographic factors. Information about the women's personal and family history of breast cancer was obtained at the end of the interview to maintain blinding; the interviewers reported that for 78% of cases and 90% of controls they were unaware of the women's disease status until the end of the interview.

Of the 4563 eligible breast cancer cases, physicians refused participation for 380 (8.3%), 271 (5.9%) had died, 11 (0.2%) could not be located, and 112 (2.5%) declined to participate. Thus, 3789 women participated from Wisconsin, for an overall response rate of 83.0%. Of the 4445 eligible controls, 49 (1.1%) had died, 21 (0.5%) could not be located, and 376 (8.5%) declined to participate for an overall response rate of 90.0%. Questions on parental age were included in the interview from September 1990 to June 1991. Of the 1311 cases participating during this period, 62 could not report their mother's age and 96 could not report their father's age. Similarly, of the 1158 control subjects in this time, 38 could not report their mother's age and 73 could not report their father's age. Therefore, after exclusion of subjects with missing parental age, 1253 case subjects and 1121 control subjects were available for analysis (38 cases/36 controls knew mother's age but not father's; 4 cases/1 control knew father's age but not mother's; these subjects were included in appropriate analyses.)

A reference age was defined for cases as the age at diagnosis; for comparability the control subjects were assigned a reference age equal to the age at interview minus the average time from diagnosis to interview for the cases, about 12 months. Age was defined as the reference age. Odds ratios and 95% confidence intervals from unconditional logistic regression models were used to evaluate relative risks (19). Subjects with unknown values for variables in the multivariate models were

incorporated as a separate category. Tests for trend and interactions (as product terms) were evaluated using a continuous scale where appropriate.

As compared with the controls, the women with breast cancer had a younger age at menarche, were older at the delivery of their first child, had lower parity, were more likely to have a family history of benign breast disease, consumed higher levels of alcohol, and had a higher body mass [if postmenopausal (18)]. These factors were considered to be potential confounders of the relationship between parental age and breast cancer risk and were included in multivariate models.

Results

The mean maternal age at the time of subject's birth (after age adjustment) was similar in cases, 28.4 years, and controls, 28.1 years. After adjustment for age and other breast cancer risk factors, no consistent association was observed between increasing maternal age and breast cancer risk in the daughter (Table 1). Compared to maternal age at birth below age 20, the relative risk for maternal age over 40 years was 0.92 (95% confidence interval (0.62–1.37), and there was no suggestion of a trend ($P = 0.38$). After adjustment for subject's age, the mean paternal age for cases (31.9 years) and controls (31.8 years) were similar. Compared to paternal age at birth below 24 years, paternal age over 40 years was not associated with an increase of breast cancer (relative risk, 0.92; 95% confidence interval, 0.68–1.24) with no trend evident (P trend = 0.98). These estimates differed only slightly from estimates obtained after adjustment only for age.

Because initiating prenatal events associated with parental age, both maternal and paternal, might result in earlier ages of breast cancer onset, we examined specific risks with respect to age, family history, and reproductive characteristics (Tables 2 and 3). In general, relative risks among women with higher maternal ages were greater in magnitude than the estimates for women with younger ages; however, these differences were not statistically significant at the 5% level. Higher maternal age appeared to be associated with risk only among women with late age at first birth (relative risk, 1.81; 95% confidence interval, 1.05–3.13; P for interaction = 0.03). Risk elevations were not present according to increasing paternal ages among any levels of the selected breast cancer risk factors.

Discussion

Overall, parental age was not associated with the risk of breast cancer. Older maternal age was associated with some increases in risk among daughters with later ages at first birth and perhaps among women with late menarche or nulliparity. These modest increases in risk, however, could have occurred by chance, particularly in light of the large number of associations evaluated.

These results are consistent with most studies that have evaluated this relationship (12–17). The positive association between maternal age and breast cancer risk was first described by Standfast in 1967 (5); however, because this study included only women who died of breast cancer at ages 40–44 years and there was inadequate control for other potentially confounding variables, the interpretation of these results was unclear. Subsequently, a number of studies have evaluated this association including approaches less susceptible to bias such as prospective (11, 12, 16) or record linkage (15) designs. None of these studies found the relationship to be strong, and only a few demonstrated a statistically significant increased risk despite

Table 1 Relative risk (RR) of breast cancer among daughters according to parental age at birth

	Cases	Controls	Multivariate ^a RR (95% CI)
Maternal age at daughter's birth			
≤20	136	119	1
21–24	261	270	0.84 (0.62–1.14)
25–29	348	302	1.02 (0.76–1.37)
30–34	250	226	0.93 (0.68–1.28)
35–39	165	121	1.16 (0.82–1.65)
≥40	89	82	0.92 (0.62–1.37)
P trend (continuous per year)			$P = 0.38$ 1.01 (0.99–1.02)
Paternal age			
≥24	190	166	1
25–29	328	296	0.97 (0.74–1.27)
30–34	301	261	1.01 (0.77–1.33)
35–39	197	184	0.93 (0.69–1.25)
≥40	199	178	0.92 (0.68–1.24)
P trend (continuous per year)			$P = 0.98$ 1.00 (0.99–1.01)

^a Adjusted for age in 5-year intervals, menopausal status, age at menarche, parity, age at first birth, body mass index, family history of breast cancer, personal history of benign breast disease, and recent alcohol intake. CI, confidence interval.

the considerable statistical power of some (7, 12, 13, 16). Previous studies have not corroborated our finding of an increased risk among women in the subgroup born to older mothers with a late age at first birth. Although some studies observed that the association between maternal age and breast cancer risk was greater among nulliparous women (11, 12), another study found the risk elevated only among parous women (10). Other risk factors, such as benign breast disease, body mass, and others, have not been consistently related to risk among women with older mothers (10–12). Studies of paternal age and breast cancer risk among daughters have also been equivocal (6, 8, 9, 11, 12, 16) with only one report demonstrating a statistically significant positive association (9). The interpretation of this latter study is limited by the use of hospital controls.

Some limitations should be considered in interpreting our results. The response rates for this study were high, which suggests that selection bias, if any, was limited (18). Missing information on maternal age was low for both cases (4.7%) and controls (3.3%). Although we were unable to validate maternal and paternal ages, the validity of self-reported paternal age was found to be high ($r = 0.78$) in a substudy of Wisconsin census participants (21). Any misclassification with respect to parental age is likely to be nondifferential and would thus attenuate any association. Confounding was unlikely to have introduced substantial bias, because the fully adjusted models differed only slightly from estimates obtained after adjustment only for age; however, other unmeasured aspects of socioeconomic status may be relevant. Information was not collected on other factors that may be more directly related to prenatal and perinatal exposure, such as family size or sibling age, extreme weight gain, prematurity, toxemia, and neonatal jaundice, characteristics that have been found to reflect pregnancy estrogens (2, 3, 5, 22–24).

Although we did not generally observe an association between parental age and breast cancer risk, the use of this surrogate measure of relevant perinatal exposures is likely too crude to be informative. Further evidence for the importance of perinatal factors will most meaningfully come from the direct

Table 2 Relative risk (RR) of breast cancer in daughter according to maternal age and selected breast cancer risk factors^a

	≤24 ^b		25–34		≥35		P interaction
	Cases/ Controls	RR (95% CI)	Cases/ Controls	RR (95% CI)	Cases/ Controls	RR (95% CI)	
All subjects	397/389	1	598/528	1.11(0.92–1.34)	254/203	1.19(0.94–1.51)	
Age at diagnosis							
<40	29/28	1	52/41	1.29(0.63–2.64)	10/8	1.21(0.39–3.73)	
40–49	79/100	1	115/133	1.07(0.72–1.58)	37/41	1.14(0.66–1.96)	
50–59	78/69	1	125/98	1.18(0.76–1.83)	54/40	1.30(0.75–2.27)	
60–69	142/141	1	210/181	1.16(0.84–1.59)	102/80	1.25(0.85–1.84)	
≥70	69/51	1	96/75	1.03(0.61–1.72)	51/34	1.34(0.73–2.48)	P = 0.76
Menopausal status							
Pre	91/109	1	151/152	1.24(0.85–1.80)	49/43	1.37(0.82–2.29)	
Post	290/262	1	423/354	1.08(0.86–1.36)	196/152	1.17(0.89–1.55)	P = 0.27
Family history of breast cancer							
Positive	72/46	1	103/63	1.07(0.63–1.81)	57/28	1.22(0.64–2.32)	
Negative	314/338	1	489/460	1.13(0.92–1.38)	191/171	1.19(0.92–1.55)	
Unknown	11/5	1	6/5	0.80(0.09–6.92)	6/4	0.81(0.08–7.88)	P = 0.57
Age at menarche							
≤12	161/151	1	231/196	1.15(0.85–1.56)	82/80	1.02(0.69–1.51)	
13–14	185/180	1	290/261	1.06(0.81–1.39)	131/94	1.27(0.90–1.79)	
>14	45/55	1	69/66	1.38(0.77–2.45)	38/24	1.98(0.98–3.98)	P = 0.54
Parity							
Nulliparous	44/39	1	71/72	0.85(0.47–1.52)	45/23	1.71(0.84–3.49)	
Parous	353/350	1	527/456	1.15(0.94–1.40)	209/180	1.11(0.86–1.44)	P = 0.22
Age at first birth							
<25	261/253	1	316/286	1.07(0.84–1.37)	120/116	1.00(0.73–1.38)	
25–29	63/70	1	153/130	1.42(0.92–2.20)	56/48	1.25(0.73–2.13)	
≥30	73/66	1	129/112	1.05(0.67–1.63)	78/39	1.81(1.05–3.13)	P = 0.03

^a When appropriate, models were adjusted for age in 5-year intervals, menopausal status, age at menarche, parity, age at first birth, body mass index, family history of breast cancer, personal history of benign breast disease, and recent alcohol intake. CI, confidence interval.

^b Referent group.

Table 3 Relative risk (RR) of breast cancer in daughter according to paternal age and selected breast cancer risk factors^a

	≤24 ^b		25–34		≥35		P interaction
	Cases/ Controls	RR (95% CI)	Cases/ Controls	RR (95% CI)	Cases/ Controls	RR (95% CI)	
All subjects	190/166	1	629/557	0.99(0.78–1.26)	396/362	0.92(0.71–1.19)	
Age at diagnosis							
<40	15/18	1	54/39	1.57(0.66–3.75)	20/20	1.18(0.43–3.21)	
40–49	38/45	1	132/140	1.05(0.64–1.75)	57/81	0.78(0.45–1.37)	
50–59	33/25	1	127/106	0.88(0.48–1.62)	92/72	0.98(0.52–1.86)	
60–69	72/58	1	221/198	0.94(0.63–1.41)	149/130	0.93(0.61–1.44)	
≥70	32/20	1	95/74	0.95(0.47–1.92)	78/59	1.03(0.50–2.10)	P = 0.98
Menopausal status							
Pre	44/54	1	158/153	1.35(0.84–2.17)	80/89	1.10(0.65–1.85)	
Post	140/103	1	444/379	0.87(0.64–1.17)	301/259	0.87(0.63–1.19)	P = 0.45
Family history of breast cancer							
Positive	31/22	1	105/71	0.92(0.47–1.81)	87/43	1.24(0.60–2.56)	
Negative	154/140	1	514/483	0.95(0.73–1.24)	302/313	0.85(0.64–1.13)	
Unknown	5/4	1	10/3	5.32(0.35–81.13)	7/6	0.85(0.09–7.81)	P = 0.10
Age at menarche							
≤12	80/61	1	254/220	0.92(0.62–1.36)	127/131	0.74(0.48–1.14)	
13–14	84/76	1	294/267	0.96(0.67–1.38)	210/176	1.01(0.69–1.47)	
>14	25/26	1	73/67	1.17(0.58–2.34)	53/51	1.07(0.52–2.21)	P = 0.73
Parity							
Nulliparous	18/19	1	80/67	1.26(0.59–2.69)	57/47	1.21(0.54–2.69)	
Parous	172/147	1	549/490	0.97(0.75–1.26)	339/315	0.89(0.67–1.17)	P = 0.78
Age at first birth							
<25	133/106	1	344/325	0.87(0.64–1.18)	196/201	0.77(0.56–1.08)	
25–29	26/27	1	151/129	1.21(0.65–2.25)	94/84	1.11(0.58–2.12)	
≥30	31/33	1	134/103	1.39(0.78–2.49)	106/77	1.38(0.76–2.53)	P = 0.10

^a When appropriate, models were adjusted for age in 5-year intervals, menopausal status, age at menarche, parity, age at first birth, body mass index, family history of breast cancer, personal history of benign breast disease, and recent alcohol intake. CI, confidence interval.

^b Referent group.

evaluation of specific maternal and infant pregnancy experiences that may reflect high estrogen or other hormone levels.

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