Induced Abortion, Miscarriage, and Breast Cancer Risk of Young Women[1]

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Abstract

Early studies of breast cancer raised substantial concern regarding risk associated with induced abortion and miscarriage. Literature reviews suggest that study findings depend heavily on the comparison group and that the use of parous women as a reference group for nulliparous women may artificially inflate risk. To examine the individual effects of induced abortion and miscarriage on breast cancer risk of parous and nulliparous women, 744 patients ≤40 years of age and diagnosed from 1983–1988 were matched by parity, age, and race with controls living in the same neighborhood in Los Angeles County. In-person interviews were conducted to obtain a detailed reproductive history. Risk estimates were obtained by conditional logistic regression using nulligravid women as the reference group for nulliparous women with a history of incomplete pregnancy and parous women with no incomplete pregnancies as the reference group for parous women with a history of incomplete pregnancy. Breast cancer risk of parous women was unrelated to a history of miscarriage or induced abortion. Breast cancer risk was reduced among nulliparous women with a history of induced abortion relative to nulligravid women, although the risk estimate was imprecise. Risk declined as the number of induced abortions increased ($P = 0.04$). Our results do not support the hypothesis that induced abortion or miscarriage increase the breast cancer risk of young women.

Introduction

A report by Pike *et al.* (1) published in 1981 raised substantial concerns that incomplete pregnancies increased the breast cancer risk of young women. Their population-based case-control study of women ≤32 years of age, conducted in Los Angeles, CA, showed a 2.4-fold increase in risk among women who had previously had either an induced abortion or a spontaneous abortion (*i.e.,* miscarriage). With continued subject accrual, in which the upper age limit was extended from age 32 years to 37 years, these effects were diminished (2). Separating the effects on breast cancer risk of an induced abortion from those of a miscarriage is critically important (3, 4). The hormonal milieu in which a miscarriage occurs may differ substantially from that of an induced abortion (5, 6). Some early reports did not consider the separate effects of induced abortion and miscarriage (*e.g.*, Refs. 7, 8). Among studies evaluating the effects of induced abortion and miscarriage separately, the multicentered case-control study of women ≤45 years of age reported by Daling *et al.* (9) heightened concern that induced abortions increased the risk of breast cancer. Other studies of young women have not shown an increased risk of breast cancer among women with a history of induced abortion (10–13). Rookus and van Leeuwen (14) pointed out the potential effects of reporting bias in case-control studies of this association. The study of Melbye *et al.* (11), a cohort study that overcame this potential bias through record linkage of surveillance data for induced abortion and breast cancer, found no effect of induced abortion on breast cancer risk.

Two epidemiological reviews of studies on the effects of induced abortion and breast cancer risk have pointed out that study findings depend heavily on the reference group, and that it is most appropriate to compare parous women with a history of induced abortion (or miscarriage) to parous women with no history of incomplete pregnancy, and to compare nulliparous women with a history of induced abortion (or miscarriage) to nulligravid women (3, 4). Including parous women in the reference group for nulliparous women (*i.e.,* conducting analyses among gravid women) may result in an increase in breast cancer risk for young women who have not had a full-term pregnancy that results from their nulliparity and not the exposure of an incomplete pregnancy. Lipworth *et al.* (15) have demonstrated how estimates of risk in parous women change depending on the choice of the reference group.

We conducted a population-based case-control study of risk factors for breast cancer among women ≤40 years of age in Los Angeles County. A unique design element of this study is that nulliparous controls were individually matched to nulliparous cases and parous controls to parous cases. Results of our analyses of these factors are presented in this report.

Materials and Methods

The design of this study has been described in detail previously (16–18). Female residents of Los Angeles County diagnosed with *in situ* or invasive breast cancer between July 1, 1983 and December 31, 1988 were included in the study if they were ≤40 years of age at diagnosis, white (including Latina whites), and

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Table 1 Characteristics of 744 young women with breast cancer and their matched controls

Characteristic	Number of cases (%)	Number of controls (%)
Age at reference date[a] (years)		
20–24	17 (2.3)	15 (2.0)
25–29	55 (7.4)	78 (10.5)
30–34	224 (30.1)	219 (29.4)
≥35	448 (60.2)	432 (58.1)
Age at menarche (years)		
≤11	209 (28.1)	167 (22.5)
12	214 (28.8)	217 (29.2)
13	210 (28.2)	210 (28.2)
≥14	111 (14.9)	150 (20.2)
Age at first full-term pregnancy (years)		
≤19	106 (14.3)	119 (16.0)
20–24	164 (22.0)	180 (24.2)
25–29	133 (17.9)	107 (14.4)
30–34	51 (6.9)	51 (6.9)
≥35	16 (2.2)	13 (1.8)
No full-term pregnancy	274 (36.8)	274 (36.8)
Number of full-term pregnancies (parous women)		
1	146 (31.1)	134 (28.5)
2	213 (45.3)	198 (42.1)
3	72 (15.3)	98 (20.9)
≥4	39 (8.3)	40 (8.5)
Months of lactation (parous women)		
None	202 (43.0)	189 (40.2)
1–6	134 (28.5)	112 (23.8)
7–15	84 (17.9)	91 (19.4)
≥16	50 (10.6)	78 (16.6)
Family history of breast cancer		
No	627 (84.3)	682 (91.7)
Yes	104 (14.0)	48 (6.5)
Adopted	10 (1.3)	10 (1.3)
Unknown	3 (0.4)	4 (0.5)
Average hours per week of exercise from menarche to reference date		
None	194 (26.1)	154 (20.7)
0.1–0.7	103 (13.8)	90 (12.1)
0.8–1.6	84 (11.3)	102 (13.7)
1.7–3.7	103 (13.8)	100 (13.4)
≥3.8	61 (8.2)	99 (13.3)
Not available[b]	199 (26.8)	199 (26.8)
Months of oral contraceptive use		
None	124 (16.7)	116 (15.6)
1–48	326 (43.8)	325 (43.7)
49–96	159 (21.4)	183 (24.6)
97–144	83 (11.2)	89 (12.0)
≥145	52 (7.0)	31 (4.2)
History of hCG use		
None, BMI[c] ≤27.4	552 (74.2)	525 (70.6)
None, BMI[c] ≥27.5	147 (19.8)	154 (20.7)
Yes, BMI[c] ≤27.4	12 (1.6)	29 (3.9)
Yes, BMI[c] ≥27.5	33 (4.4)	36 (4.8)

[a] Reference date was defined as the month and year that was 12 months before the date of the case patient's diagnosis (for a case and her matched control).
[b] Data on lifetime activity were available only for 545 cases and their matched controls (16).
[c] Body mass index (BMI) is based on a woman's maximum nonpregnancy weight (kg)/height $(m)^2$.

born in the United States, Canada, or Europe. Patients were identified by the University of Southern California Cancer Surveillance Program, the population-based cancer registry for Los Angeles County. Women diagnosed previously with breast cancer were ineligible. In all, 969 eligible patients were identified. Of these, 20 (2.1%) died before interview, 172 could not be interviewed because of physician (5.6%) or patient (11.5%) refusal, or illness (0.7%), and 33 (3.4%) had moved outside Los Angeles County or were lost to follow-up. Interviews were conducted with 744 patients (76.8%); 68 of these had a diagnosis of *in situ* breast cancer.

Each interviewed patient was matched individually to a control subject on birth date (within 36 months), race (white), parity (nulliparous *versus* parous), and neighborhood of residence. Control subject eligibility was also limited to women born in the United States, Canada, or Europe who had no prior history of breast cancer. To identify each neighborhood control subject, we established a predefined walk pattern for the neighborhood where the case patient lived at the time of her diagnosis. Detailed records were maintained to determine the number of housing units contacted, eligibility of residents, and participation rates. We contacted a median number of 32 housing units to interview a matched control subject for each case patient. For 592 case patients, the first eligible control subject participated. For 124 case patients, 1 eligible person refused before the recruitment of a matched control subject. For the remaining 28 case patients, the number of refusals in the walk pattern ranged from 2 (for 18 case patients) to 6 (for 2 case patients).

In-person interviews were conducted with all of the subjects by the same female nurse-interviewer. Recall was facilitated by the creation of a lifetime calendar of key events in the history of the participant including all of the pregnancies (start and stop dates), methods and dates of contraception, and changes, if any, in sexual partners. We recorded details about induced abortions and miscarriages (spontaneous abortions) including the reason for an induced abortion (medical or other), whether a physician documented the occurrence of a miscarriage, whether a dilation and curettage procedure was done subsequent to the miscarriage, and the length of each pregnancy. We also obtained complete information on other reproductive factors, oral contraceptive and other hormone use, physical exercise activities up to the date of the case's diagnosis for both cases and controls, and imposed time restrictions on these variables during statistical analyses. A reference date, defined as the month and year that was 12 months before the date of the case's diagnosis, was assigned to both the case and her matched control. This date was used as the cutoff date for information used in these analyses. No pregnancies were included in our analyses if they occurred after this reference date. Women with a positive family history of breast cancer had a mother or sister who had been diagnosed with breast cancer. Women who were not adopted and did not know their family history of breast cancer were considered to have a negative family history (3 cases/4 controls).

Signed, informed consent was obtained from each subject. Study procedures were approved by the University of Southern California Research Committee, in accordance with assurances approved by the United States Department of Health and Human Services.

Statistical models were created and compared using Epilog, and statistical power calculations used Power (both from Epicenter Software, Pasadena, CA). Separate sets of statistical analyses were conducted for parous women and for nulliparous women using univariate and multivariate conditional logistic regression methods for individually matched case-control studies (19) to obtain ORs[3] and their 95% CIs. Nulligravid women served as the reference group

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval; hCG, human chorionic gonadotropin.

Table 2 Risk of breast cancer related to pregnancy outcomes among nulliparous women ≤40 years of age (274 case/control pairs)

Pregnancy characteristic	Cases/controls	Univariate OR (95% CI)	Multivariate[a] OR (95% CI)	Trend *P*	Homogeneity test *P*
Never pregnant	178/165	1.00	1.00		
Any history of induced abortion	74/94	0.71 (0.49–1.02)	0.69 (0.46–1.04)		
Number of induced abortions					
1	53/60	0.82 (0.54–1.26)	0.84 (0.52–1.35)		
≥2	21/34	0.57 (0.31–1.04)	0.54 (0.28–1.04)	0.04	
Any history of miscarriage	21/15	1.45 (0.74–2.83)	1.33 (0.64–2.77)		
Number of miscarriages					
1	8/11	0.76 (0.30–1.92)	0.59 (0.22–1.63)		
≥2	13/4	3.15 (1.01–9.77)	3.47 (1.03–11.66)	0.17	
Any other pregnancy outcome					
Current pregnancy	9/6	1.45 (0.52–4.09)	1.91 (0.61–5.99)		
Ectopic pregnancy	1/6	0.15 (0.02–1.27)	0.16 (0.02–1.67)		
Gestation length of first induced abortion					
≤8 weeks	44/74	0.56 (0.36–0.86)	0.55 (0.34–0.89)		
>8 weeks	30/20	1.34 (0.74–2.43)	1.27 (0.67–2.40)		0.02
Calendar era of first induced abortion: pre/post Roe *vs.* Wade decision					
Before 1973	24/27	0.86 (0.48–1.54)	0.86 (0.46–1.63)		
1973 or later	50/67	0.68 (0.45–1.04)	0.67 (0.41–1.07)		0.48
Age at first induced abortion					
<20 years	20/12	1.68 (0.76–3.75)	1.95 (0.80–4.71)		
≥20 years	54/82	0.63 (0.43–0.94)	0.60 (0.38–0.93)		0.01

[a] For each type of pregnancy outcome, multivariate models include adjustment for first degree family history of breast cancer, age at menarche, months of oral contraceptive use, average hours per week of exercise activity since menarche, use of hCG among women with low and high body mass index, and other pregnancy outcomes.

for nulliparous women with a history of incomplete pregnancy. Women who had experienced only full-term pregnancies served as the reference group for parous women with a history of incomplete pregnancy. In all of the analyses, we included a term for incomplete pregnancy outcomes other than the pregnancy outcome of interest in the statistical model. For example, for those women with a history of induced abortion, an indicator variable was also included to denote whether an individual had a history of any other incomplete pregnancy outcome (miscarriage, molar pregnancy, ectopic pregnancy, or currently pregnant on the reference date).

Multivariate models included the following covariates: age at menarche (<12, 12, 13, or ≥14 years); first degree family history of breast cancer (no, yes, or adopted); total months of oral contraceptive use (none, 1–48, 49–96, 97–144, or ≥145; Ref. 18); use of hCG (never or ever) among women with high (≥27.5 kg/m^2) and lower (<27.5 kg/m^2) body mass index (17); and average hours per week of exercise during reproductive years (none, 0.1–0.7, 0.8–1.6, 1.7–3.7, or ≥3.8; Ref. 16). Because complete histories of exercise activity were collected for only 545 case-control pairs (16), the remaining 199 matched pairs were included in the multivariate analyses by coding their exercise activity the same (arbitrarily chosen to be the baseline category); this effectively eliminated their contribution to estimating an exercise effect. Multivariate models assessing breast cancer risk in parous women also included covariates representing age at first full-term pregnancy (20–24, 25–29, 30–34, or ≥35 years), total number of full-term pregnancies (≤2, 3, or ≥4), and total months of breast feeding (1–6, 7–15, or ≥16).

Tests for linear trend were calculated across ordinal categories of increasing exposure. To determine whether the OR estimate for one subgroup of women differed from that of another subgroup (whether the OR estimate for a first pregnancy outcome of induced abortion differed for women whose induced abortion occurred by the 8th week of pregnancy *versus* later, before 1973 *versus* 1973 or later, or <20 years of age *versus* ≥20 years of age), we constructed a likelihood ratio test (test for homogeneity) to determine whether a model that fit a variable separately for each category fit the data significantly better than a model that fit a single variable for induced abortion. All of the significance levels reported (*P*s) are two-sided. We report results from multivariate models in the text.

Results

The distributions of reference age for cases and controls are similar reflecting that controls were individually matched to cases within 3 years of age, and controls were assigned the reference date that was 1 year before the date of diagnosis of the case (Table 1). We provide the distributions of other variables considered as covariates in our logistic regression models in Table 1.

Nearly all of the nulliparous women in our study who reported a history of induced abortion reported this as the outcome of their first pregnancy (71 of 74 cases and 93 of 94 controls). Breast cancer risk was reduced 30% among nulliparous women who had a history of induced abortion relative to nulligravid women (OR, 0.69; 95% CI, 0.46–1.04; Table 2). As the number of induced abortions increased, breast cancer risk declined among nulliparous women (trend $P = 0.04$). The reduction in risk for nulliparous women associated with an induced abortion was limited to women whose induced abortion occurred within the first 8 weeks of pregnancy (OR, 0.55; 95% CI, 0.34–0.89; homogeneity $P = 0.02$). Breast cancer risk did not vary according to whether the induced abortion occurred before 1973 or later (homogeneity $P = 0.48$). Breast cancer risk varied with the age of the woman at the time of her first induced abortion among nulliparous women with those whose abortion occurred at ≥20 years of age at reduced risk (OR, 0.60; 95% CI, 0.38–0.93) and those whose abortion

Table 3 Risk of breast cancer related to pregnancy outcomes among parous women ≤40 years of age (470 case/control pairs)

Pregnancy characteristic	Cases/controls	Univariate OR (95% CI)	Multivariate[a] OR (95% CI)	Trend *P*	Homogeneity test *P*
Full-term pregnancy only	255/252	1.00	1.00		
Any history of induced abortion	118/109	1.07 (0.79–1.46)	1.05 (0.75–1.48)		
Number of induced abortions					
1	78/73	1.09 (0.77–1.54)	1.03 (0.70–1.50)		
≥2	40/36	1.12 (0.70–1.81)	1.19 (0.69–2.04)	0.59	
Any history of miscarriage	117/118	0.98 (0.72–1.33)	1.00 (0.71–1.41)		
Number of miscarriages					
1	91/80	1.13 (0.81–1.58)	1.13 (0.78–1.65)		
≥2	26/38	0.69 (0.42–1.15)	0.76 (0.44–1.34)	0.69	
Any other pregnancy outcome					
Current pregnancy	15/11	1.34 (0.61–2.93)	1.47 (0.60–3.61)		
Ectopic pregnancy	12/4	2.93 (0.94–9.11)	2.69 (0.79–9.18)		
Molar pregnancy	1/1	—	—		
Outcome of first pregnancy					
Induced abortion	54/48	1.11 (0.71–1.72)	0.98 (0.60–1.61)		
Miscarriage	55/48	1.13 (0.73–1.75)	1.17 (0.72–1.89)		
Other pregnancy outcome[b]	5/1	4.69 (0.55–40.31)	2.34 (0.25–22.15)		
Full-term, but later incomplete	101/121	0.82 (0.60–1.13)	0.87 (0.61–1.25)		
Induced abortion as the outcome of first pregnancy					
Gestation length					
≤8 weeks	38/31	1.21 (0.72–2.02)	1.01 (0.56–1.82)		
>8 weeks	16/17	0.94 (0.47–1.89)	0.93 (0.42–2.02)		0.48
Calendar era of induced abortion					
Before 1973	30/23	1.30 (0.73–2.31)	1.19 (0.62–2.27)		
1973 or later	24/25	0.96 (0.52–1.76)	0.78 (0.39–1.55)		0.35
Age					
<20 years	22/20	1.11 (0.57–2.15)	0.99 (0.47–2.06)		
≥20 years	32/28	1.14 (0.66–1.97)	0.97 (0.52–1.79)		1.00

[a] For each type of pregnancy outcome, multivariate models include adjustment for first degree family history of breast cancer, age at menarche, months of oral contraceptive use, average hours per week of exercise activity since menarche, use of hCG among women with low and high body mass index, age at first full-term pregnancy, number of full-term pregnancies, months of breast feeding, and other pregnancy outcomes.
[b] Other pregnancy outcomes include ectopic (5 cases) and molar (1 control) pregnancies.

occurred before 20 years of age at somewhat greater risk (OR, 1.95; 95% CI, 0.80–4.71; homogeneity $P = 0.01$; Table 2). Although breast cancer risk was unrelated to a history of miscarriage among nulliparous women (OR, 1.33; 95% CI, 0.64–2.77), risk was elevated among those with a history of two or more miscarriages (OR, 3.47; 95% CI, 1.03–11.66).

Breast cancer risk among parous women with a history of induced abortion was similar to that of parous women who had only full-term pregnancies (OR, 1.05; 95% CI, 0.75–1.48; Table 3). Risk did not vary according to the number of induced abortions and was unrelated to a history of miscarriage. Breast cancer risk also was not associated with a history of miscarriage or induced abortion as the outcome of the woman's first pregnancy among parous women.

Discussion

The design of this case-control study permitted separate evaluation of the effects of induced abortion and miscarriage on breast cancer risk by parity status. Our sample size of 274 nulliparous case-control pairs is sufficient (80% statistical power) to detect as statistically significant (0.05 significance, 2-sided hypothesis) a relative odds of breast cancer associated with a history of induced abortion that is ≥1.66 or <0.58. Similarly, our sample size of 470 parous case-control pairs is sufficient to detect as statistically significant a relative odds of breast cancer associated with a history of induced abortion that is ≥1.53 or <0.62. Overall, we find no evidence that induced abortions are associated with increased breast cancer risk among young women.

Controversial results have been reported in both case-control and cohort studies with respect to a young woman's risk for breast cancer and her history of abortion (3, 4). Some studies reflect an increase in risk associated with induced abortion (9, 20), whereas others report no increase in risk overall (12, 21), or among either parous (10, 13, 22, 23) or nulliparous women (10, 13, 22, 24). Similarly, one study has shown increased breast cancer risk for young women with a history of miscarriage (20), whereas others show no effect on risk overall (9, 12, 21), or among either parous (22, 23) or nulliparous women (22, 24).

Disparities in study findings have been attributed to differences in the accuracy of reporting these reproductive events. For miscarriages, recall is more accurate for longer duration pregnancies (25). Early miscarriages may go undetected (26). Induced abortions may be more accurately reported with respect to gestational length but are still vulnerable to underreporting because of the personal and sensitive nature of the procedure (14, 27, 28). The possibility of differential recall leading to biased estimates of risk has been posited as problematic in case-control studies, because breast cancer cases may be more likely or willing to recall health-related events than women who have been comparatively healthy (11, 14, 27, 28). Our study is subject to these same limitations. In our questionnaire we asked for details of any of the incomplete pregnancies reported, querying whether the woman had an induced abortion

for medical or for other reasons to reduce the possibility of a perceived stigma associated with having an induced abortion. We also recorded whether miscarriages had been diagnosed by a physician, and whether the woman had undergone dilation and curettage. The sole interviewer for the study was a nurse-epidemiologist.

Although surveillance of legally induced abortions has been conducted by the Centers for Disease Control and Prevention using a voluntary reporting system (29), population-based data on the prevalence of a positive history of induced abortion among young women (whose average age is 36 years as in this study) are not available in published statistics. The prevalence estimates of induced abortion among women in our study were 25.1% for parous cases, 27.0% for nulliparous cases, 23.2% for parous controls, and 34.3% for nulliparous controls. The study by Daling *et al.* (9) focused on women similar in age to our participants and was conducted during approximately the same time frame. Their reported prevalence of induced abortion (based on all of the women) was 24.9% for cases and 20.9% for controls. Our overall case prevalence (25.8%) is consistent with theirs. However, the prevalence of induced abortion among our controls (27.3%) is higher than theirs. Nevertheless, we cannot rule out underreporting in our participants.

On the basis of the assumption that women in the United States would be more likely to report an induced abortion if it occurred after the legalization of that procedure in 1973, we investigated whether first pregnancy outcomes of induced abortion varied by time period. The estimated risk for developing breast cancer was (nonsignificantly) reduced in nulliparous women whose first pregnancy outcome was an induced abortion before 1973 (*versus* women who had never been pregnant). This reduction in risk was slightly more pronounced, but still nonsignificant, for those nulliparous women whose first pregnancy outcome was an induced abortion during or after 1973. Therefore, it is possible that nulliparous controls were less likely than cases to report induced abortions occurring before 1973. A similar but less remarkable effect was seen in parous women.

Socioeconomic factors or access to medical care could confound the association between abortion and breast cancer. Use of neighborhood controls in our study is a means for reducing the variation between cases and controls on socioeconomic factors such as income, education, housing density, and access to medical care.

Early hypotheses regarding breast cancer risk subsequent to induced abortion focused on interrupted gestation during the first trimester (10, 30–32). We compared parous women who had an induced abortion during the first 8 weeks of their first pregnancy with those who had one after week 8 of their first pregnancy. For these women, an induced abortion as the outcome of first pregnancy was unrelated to breast cancer risk, regardless of when the abortion occurred (Table 3). Although we saw an apparent reduction in risk among nulliparous women reporting an early (≤8-week gestation) induced abortion, risk was not reduced with longer gestational age (Table 2). Therefore, we interpret this finding with caution. Although we found an increased risk for breast cancer associated with two or more miscarriages among nulliparous women, we found no other studies that confirm this finding.

In conclusion, we find no increased risk for breast cancer associated with induced abortion in young women, regardless of parity. Future studies to address the effect of incomplete pregnancies should be designed in a manner that permits separate analyses for nulliparous and parous women with adequate statistical power for both sets of analyses.

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