

# Induced and Spontaneous Abortion and Incidence of Breast Cancer Among Young Women

## A Prospective Cohort Study

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**Background:** Induced abortion has been inconsistently associated with breast cancer risk in case-control studies. Retrospective cohort studies using registry information in Scandinavia have not suggested an increase in the incidence of breast cancer, although data on individual reproductive factors were not accounted for.

**Methods:** We examined the association between induced and spontaneous abortion and the incidence of breast cancer in a prospective cohort of young women, the Nurses' Health Study II. The study included 105 716 women 29 to 46 years old at the start of follow-up in 1993. Information on induced or spontaneous abortions was collected in 1993 and updated biennially. During 973 437 person-years of follow-up between 1993 and 2003, 1458 newly diagnosed cases of invasive breast cancer were ascertained.

**Results:** A total of 16 118 participants (15%) reported a history of induced abortion, and 21 753 (21%) re-

ported a history of spontaneous abortions. The hazard ratio for breast cancer among women who had 1 or more induced abortions was 1.01 (95% confidence interval, 0.88-1.17) after adjustment for established breast cancer risk factors; among women with 1 or more spontaneous abortions, the covariate-adjusted hazard ratio was 0.89 (95% confidence interval, 0.78-1.01). The relation between induced abortion and the incidence of breast cancer did not differ materially by number of abortions ( $P$  for trend = .98), age at abortion ( $P$  for trend = .68), parity ( $P$  for interaction = .54), or timing of abortion with respect to a full-term pregnancy ( $P$  for interaction = .10).

**Conclusion:** Among this predominantly premenopausal population, neither induced nor spontaneous abortion was associated with the incidence of breast cancer.

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**A** FULL-TERM PREGNANCY BEFORE the age of 35 years reduces lifetime risk of breast cancer,<sup>1</sup> possibly by accelerating breast-cell differentiation. An incomplete pregnancy may not result in sufficient differentiation to counter the high levels of pregnancy hormones that may foster proliferation.<sup>2</sup> However, these biological mechanisms are uncertain, and a prematurely terminated pregnancy may not affect breast cancer risk at all.

Induced abortion has been associated with an increased risk of breast cancer in some retrospective case-control studies, whereas no association has been found in studies with information on abortion recorded prospectively.<sup>3,4</sup> Most epidemiologic studies<sup>3</sup> of spontaneous abortion (miscarriage) and breast cancer have indicated no association. Most epidemiologic evidence on the relation between induced abortion and breast cancer is from retrospective case-control studies, the data on abortion having been gathered from women with breast cancer and healthy controls.

Given the personal and sensitive nature of information on abortion, reporting bias may be different for cases and controls, with case patients being more likely to volunteer this information, leaving case-control studies difficult to interpret.<sup>3</sup>

In 2 retrospective cohort studies with prospectively recorded abortion data, registries available in Scandinavian countries were used, and registry data on induced abortion were linked with cancer registry information. In a Swedish study by Lindfors-Harris et al,<sup>5</sup> induced abortion was associated with a reduced risk of breast cancer. In a study<sup>4</sup> that included 1.5 million Danish women, no association was found between induced abortion and breast cancer incidence. Similarly, in 3 prospective case-control studies that used registry information on induced abortion assessed before breast cancer developed, no association or an inverse association between induced abortion and the risk of breast cancer was observed.<sup>6-8</sup> Registry studies, however, generally do not capture the entire reproductive history of all women included

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and are unable to control for several breast cancer risk factors, such as age at menarche, menopausal status, body mass index, and alcohol intake. In the 3 prospective cohort studies on postmenopausal women conducted to date, the Iowa Women's Study,<sup>9</sup> the Shanghai Textile Workers Study,<sup>10</sup> and the European Prospective Investigation Into Cancer and Nutrition,<sup>11</sup> information on induced abortion was obtained directly from the participants, and no association between induced abortion and breast cancer incidence was found in these studies. In prospective cohort studies in which abortion information is obtained from the women directly, reproductive history is generally assessed retrospectively at baseline among disease-free women, and participants are followed up prospectively until they develop the outcome of interest. This approach may underestimate abortions, and this nondifferential misclassification may bias the effect estimate toward the null. Furthermore, in all 3 cohorts, information on abortion was assessed only once, at baseline, and was not updated during follow-up, which may add misclassification.

We examined the associations between induced and spontaneous abortion and the incidence of breast cancer among the participants in the Nurses' Health Study II (NHSII). In this cohort, information on induced and spontaneous abortion was updated throughout follow-up.

## METHODS

### STUDY POPULATION

The NHSII is an ongoing prospective cohort study designed to examine associations between lifestyle factors, reproductive factors, and the occurrence of breast cancer and other major illnesses. In 1989, a total of 116 671 female registered nurses 25 to 42 years of age who were free of cancer (except nonmelanoma skin cancer) and living in 1 of 14 US states responded to a baseline questionnaire. Follow-up questionnaires were mailed biennially, updating information on reproductive factors, lifestyle factors, and newly diagnosed diseases. In 1993, information on induced and spontaneous abortion was first assessed, which represented the baseline for the present analysis. Excluding women who had been diagnosed as having cancer (n=4065), who did not answer the question on abortion (n=958), or who did not respond in 1993 (n=8955) left a total of 105 716 women to be included. Of these women, 92% were non-Hispanic white. During follow-up, we censored women who were newly diagnosed as having breast cancer, had died, or were lost to follow-up. Women who skipped questionnaires or did not respond to the questions on induced or spontaneous abortion in any given cycle were censored only for those periods. The response rate of our study population in 2003 was 95%. The protocol of this study was approved by the Human Subjects Research Committees of the Brigham and Women's Hospital and the Harvard School of Public Health.

### ASCERTAINMENT OF ABORTION

On the 1993 questionnaire, we ascertained spontaneous and induced abortion separately by including the question, "Have you ever had a spontaneous or induced abortion before the sixth month of pregnancy?" The response options, which were separate for spontaneous and induced abortions, included "no," "yes" and, if "yes," at what age(s): younger than 18 years, 18 to 20 years, 21 to 23 years, 24 to 26 years, 27 to 29 years, 30 to 34

years, and 35 years or older. On each subsequent biennial questionnaire, participants were asked whether they had been pregnant in the previous 2-year period and, if they had, whether pregnancies that lasted less than 6 months resulted in miscarriages or induced abortions. Response options provided allowed participants to report miscarriages and induced abortions for each calendar year since the previous questionnaire was sent (questionnaires are mailed in June); response options did not include "no."

Of the 107 721 study participants who returned the 1993 questionnaire, 106 804 (99.1%) answered the question on spontaneous and induced abortion; 16 359 (15.2%) of them reported that they had experienced 1 or more induced abortions, and 22 236 (20.6%) reported 1 or more spontaneous abortions. Among the 105 716 women included in the present analysis, 16 118 (15.2%) reported 1 or more induced abortions and 21 753 (20.6%) reported 1 or more spontaneous abortions. Among all 116 671 women in the NHSII, 115 754 provided information on abortion or miscarriage at least once in follow-up questionnaires between 1993 and 2003. Among them, 16 916 (14.6%) reported ever having had an induced abortion and 25 837 (22.3%) reported ever having had a miscarriage.

### RISK FACTORS FOR BREAST CANCER

Data on established or suspected risk factors for breast cancer used for the present analyses were collected in 1989 and on biennial questionnaires through 2003. Date of birth, height, family history of breast cancer, age at menarche, and alcohol consumption were reported on the 1989 questionnaire. Information on weight, history of benign breast cancer, parity, age at first birth, and menopausal status was reported in 1989 and updated with every biennial questionnaire.

### ASCERTAINMENT OF BREAST CANCER

At each follow-up cycle, we ask whether breast cancer has been diagnosed and, if so, the date of diagnosis. We routinely search the National Death Index for women who did not respond to the questionnaires. We ask all women who reported breast cancer (or the next of kin for those who have died) for permission to review the relevant medical records and confirm the diagnosis. Self-reported breast cancer was histologically confirmed for 99% of women whose medical records could be obtained. Because the accuracy of participants' reports was extremely high among those whose records were obtained, we included self-reported breast cancer for those whose medical records were not available. We censored cases of carcinoma in situ (n=399) from the primary analyses, but results including in situ cases were comparable to those for invasive cases only.

### STATISTICAL ANALYSIS

Our analyses included all women who answered the questions on abortion throughout follow-up between 1993 and 2003. In 1993, some women responded only to the question on induced abortion but omitted the spontaneous abortion question and vice versa. Of the 105 716 women included in this analysis, 28 392 did not answer the question on induced abortion but answered the question on spontaneous abortion; 13 652 of these women indicated that they had a spontaneous abortion. We assumed that the women who answered only half of the question did not answer the other question because of an oversight or because they felt that the question did not apply to them; we thus coded the missing response as "no induced abortion." Similarly, 22 768 women did not answer the question on spontaneous abortion in 1993; of these, 9167 answered that they had an induced abor-

**Table 1. Age-Standardized Distribution of Breast Cancer Risk Factors Throughout Follow-up Among 105 716 Participants in the Nurses' Health Study II According to History of Induced or Spontaneous Abortion\***

Characteristic	Induced Abortion		Spontaneous Abortion	
	Yes	No	Yes	No
Person-years	152 386	821 051	221 408	752 029
Mean age, y	42.1	42.3	42.3	42.2
Family history of breast cancer, %	20.9	20.0	20.9	19.9
History of benign breast disease, %	14.9	15.9	15.9	15.8
Mean height, m	1.65	1.65	1.65	1.65
Mean body mass index†	25.6	26.0	25.9	25.9
Mean age at menarche, y	12.4	12.4	12.4	12.4
Parity				
Nulliparous, %	22.0	18.0	8.4	21.5
Mean (SD) parity‡	1.6 (1.2)	1.9 (1.2)	2.2 (1.2)	1.7 (1.2)
Mean age at first birth, y‡	27.3	26.2	26.9	26.2
Use of oral contraceptives, %§				
Never	7.3	14.0	12.3	13.2
Past	83.5	76.6	80.7	76.8
Current	9.0	8.3	6.7	8.9
Menopausal status, %§				
Premenopausal	84.6	81.9	83.0	82.1
Postmenopausal	9.6	11.0	10.5	10.9
Alcohol consumption, %§				
Never	27.4	35.2	37.2	33.0
<10 g/d	46.5	37.2	40.9	37.9
≥10 g/d	13.2	7.1	8.0	8.1

\*Proportions are age-standardized to the age distribution of the study population.

†Calculated as weight in kilograms divided by height in meters squared.

‡Among parous women.

§Percentages pertain to women for whom information on the characteristic was available. Percentages do not always total 100 because of missing values and/or rounding errors.

tion. We again coded the nonresponses as “no spontaneous abortion.” Information on induced and spontaneous abortion was updated biennially; since a response option of “no” was not provided on subsequent questionnaires, a response of “no” was coded for either abortion if “yes” was not marked. We conducted sensitivity analyses of our approach. Results did not change when we excluded nonresponses to half of the 1993 question from the analyses or coded a missing response as “no” only if the other part of the question was answered with “yes.”

Hazard ratios (HRs) were calculated using a Cox proportional hazards regression model as the incidence rate of breast cancer among women who had an abortion before the diagnosis of breast cancer relative to the incidence rate of breast cancer among women who did not have an abortion, based on 2-year follow-up cycles.<sup>12</sup> The HRs were adjusted for age (in months), height (continuous in meters), body mass index (BMI) at the age of 18 years (continuous; calculated as weight in kilograms divided by height in meters squared), current BMI (continuous; calculated as weight in kilograms divided by the square of height in meters), family history of breast cancer (binary), history of benign breast disease (binary), age at menarche (<11, 11, 12, 13, 14, ≥15 years), use of oral contraceptives (never, past and <5 years, past and ≥5 years, current and <5 years, current and 5-9 years, current and ≥10 years), parity (nulliparous, 1, 2, 3, ≥4 live births), age at first birth (≤24, 25-30, ≥31 years), alcohol consumption (none, <7.5, 7.5-14.9, 15-29.9, ≥30 g/d), physical activity (<3, 3-8, 9-17, 18-26, 27-41, ≥42 metabolic equivalents per week), menopausal status (premenopausal or postmenopausal), age at menopause (continuous in years), and postmenopausal hormone use (never, past, or current). Analyses were conducted examining the number of abortions, the age at first abortion, and the timing of abortion with

respect to a full-term pregnancy. Trend tests were performed using the midpoints of intervals. Analyses were also stratified by parity. Effect modification was assessed by creating the cross-product terms between indicator variables of abortion categories and each potential effect modifier. We measured the significance of statistical interaction using the likelihood ratio test, comparing a model that included the cross-products that represented interaction terms and the nested model that did not include these terms. Separate analyses were performed for estrogen receptor-positive (ER+) and estrogen receptor-negative (ER-) and for progesterone receptor-positive (PR+) and progesterone receptor-negative (PR-) breast cancer. We used polychotomous logistic regression with 3 outcome categories (ER+ breast cancer, ER- breast cancer, and no breast cancer or PR+ breast cancer, PR- breast cancer, and no breast cancer) to evaluate the association between induced and spontaneous abortion and breast cancer subtypes defined by ER and PR status. Likelihood ratio tests with 1 *df* were used to compare a model with different slopes for each outcome with a model with a common slope. We used  $\chi^2$  tests to obtain 2-sided *P* values for the likelihood ratio statistics.<sup>13</sup>

## RESULTS

This study included 105 716 women 29 to 46 years old at the start of follow-up in 1993. The distribution of risk factors for breast cancer throughout follow-up of the study population according to history of induced or spontaneous abortion is presented in **Table 1**. At baseline in 1993, 93% of the study population was premenopausal,

**Table 2. History of Induced or Spontaneous Abortion and Hazard Ratios of Invasive Breast Cancer Among 105 716 Participants in the Nurses' Health Study II Between 1993 and 2003**

Abortion History	Induced Abortion				Spontaneous Abortion			
	No. of Breast Cancer Cases	No. of Person-Years	Age-Adjusted HR (95% CI)	Covariate-Adjusted HR (95% CI)*	No. of Breast Cancer Cases	No. of Person-Years	Age-Adjusted HR (95% CI)	Covariate-Adjusted HR (95% CI)*
No	1225	821 051	1 [Reference]	1 [Reference]	1156	752 029	1 [Reference]	1 [Reference]
Yes	233	152 386	1.05 (0.91-1.20)	1.01 (0.88-1.17)	302	221 408	0.88 (0.78-1.00)	0.89 (0.78-1.01)
1 Abortion	195	126 519	1.06 (0.91-1.23)	1.02 (0.88-1.19)	249	179 387	0.90 (0.78-1.03)	0.90 (0.79-1.04)
≥2 Abortions	38	25 867	0.99 (0.72-1.37)	0.95 (0.68-1.31)	53	42 020	0.82 (0.62-1.08)	0.82 (0.62-1.08)
<i>P</i> value for trend			.64	.98			.04	.06
Age at first abortion, y†								
≤19	72	54 817	1.06 (0.84-1.35)	1.15 (0.76-1.74)	13	19 344	0.41 (0.24-0.72)	0.50 (0.27-0.92)
20-24	41	35 253	0.81 (0.60-1.11)	0.84 (0.54-1.32)	39	27 803	0.83 (0.60-1.14)	1.02 (0.67-1.56)
25-29	70	37 007	1.17 (0.92-1.49)	1.22 (0.82-1.81)	115	82 766	0.93 (0.77-1.12)	1.06 (0.77-1.46)
≥30	50	25 309	1.12 (0.84-1.48)	1.18 (0.78-1.78)	135	91 496	0.97 (0.81-1.15)	1.03 (0.75-1.41)
<i>P</i> value for trend			.37	.41			.31	.27

Abbreviations: CI, confidence interval; HR, hazard ratio.

\*Adjusted for age, birth weight, premature birth, family history of breast cancer, history of benign breast disease, height, body mass index at the age of 18 years and current body mass index (calculated as weight in kilograms divided by height in meters squared), age at menarche, oral contraceptive use, parity, age at first birth, alcohol consumption, physical activity, menopausal status, age at menopause, and postmenopausal hormone use.

†Covariate-adjusted analyses additionally adjusted for number of induced or spontaneous abortions.

and 66% of our study population remained premenopausal throughout follow-up. Women who reported spontaneous abortions were less likely to be nulliparous and had more children than women who did not report spontaneous abortions. Women who reported at least 1 induced abortion were slightly more likely to be nulliparous, to be older at first birth, to have used more oral contraceptives, and to have consumed more alcohol than women without a history of induced abortion.

During 973 437 person-years of follow-up, 1458 newly diagnosed cases of invasive breast cancer were reported. The age-adjusted HR for breast cancer among women who had 1 or more induced abortions was 1.05 (95% confidence interval [CI], 0.91-1.20). Adjustment for birth weight, premature birth, family history of breast cancer, history of benign breast disease, height, BMI at the age of 18 years, current BMI, age at menarche, use of oral contraceptives, parity, age at first birth, alcohol consumption, physical activity, menopausal status, age at menopause, and postmenopausal hormone use did not materially alter the HR (induced abortion: covariate-adjusted HR, 1.01; 95% CI, 0.88-1.17). No trend was observed with the increasing number of induced abortions or with age at first induced abortion (**Table 2**). Among women with 1 or more spontaneous abortions, the covariate-adjusted HR was 0.89 (95% CI, 0.78-1.01; *P* for trend = .06 with increasing number of spontaneous abortions) (Table 2). The incidence of breast cancer was lower among women who experienced a first spontaneous abortion before the age of 20 years than among women who had never had a miscarriage, but results were based on small numbers (13 cases of breast cancer among women with spontaneous abortion before the age of 20 years), and no trend emerged for age at first spontaneous abortion (*P* for trend = .27).

The association between a history of pregnancy termination and breast cancer did not differ by parity sta-

tus (*P* for interaction = .54); no association was found among either nulliparous or parous women (**Table 3**). Among parous women, more women had an induced abortion before (n = 80 333 person-years) than after (n = 31 962 person-years) their first birth. The incidence of breast cancer did not differ appreciably among women who had an induced abortion before their first birth, had an induced abortion after their first birth, or had no abortion (*P* for interaction = .10) (Table 3). Similarly, the association between spontaneous abortion and breast cancer did not differ by parity status (*P* for interaction = .10). Few nulliparous women reported a spontaneous abortion. Parous women who reported a spontaneous abortion were twice as likely to experience it after their first birth than before their first birth.

Although the association between induced abortion and ER+ and ER- breast cancer was similar (*P* for heterogeneity = .30), a difference was found in the association between induced abortion and PR+ and PR- breast cancer (*P* for heterogeneity = .03). Among parous women, the HRs were 1.58 (95% CI, 1.13-2.20) for PR- breast cancer and 0.80 (95% CI, 0.60-1.05) for PR+ breast cancer (*P* for heterogeneity = .002) among women with induced abortion. No other difference was found in the association of induced or spontaneous abortion with breast cancer subtype defined by ER or PR status among nulliparous or parous women (**Table 4**).

#### COMMENT

A full-term pregnancy before the age of 35 years reduces long-term risk of breast cancer,<sup>1,14</sup> possibly by inducing breast-cell differentiation.<sup>15</sup> Russo and Russo<sup>2</sup> observed that, in rats, interruption of pregnancy negated the protection pregnancy confers from mammary tu-

**Table 3. History of Induced and Spontaneous Abortion and Hazard Ratios of Invasive Breast Cancer Among 105 716 Participants in the Nurses' Health Study II Between 1993 and 2003 Stratified by Parity Status**

Parity*	No. of Breast Cancer Cases	No. of Person-Years	Age-Adjusted HR (95% CI)	Covariate-Adjusted HR (95% CI)†
<b>Induced abortion</b>				
Nulliparous				
No induced abortion	243	159 290	1 [Reference]	1 [Reference]
Induced abortion	68	34 833	1.26 (0.96-1.65)	1.19 (0.90-1.58)
1 Abortion	56	28 347	1.28 (0.95-1.71)	1.21 (0.89-1.64)
≥2 Abortions	12	6485	1.18 (0.66-2.13)	1.12 (0.62-2.02)
<i>P</i> value for trend			.14	.29
Parous				
No induced abortion	962	642 741	1 [Reference]	1 [Reference]
Induced abortion	157	112 295	0.96 (0.81-1.13)	0.93 (0.79-1.11)
1 Abortion	133	93 953	0.98 (0.81-1.17)	0.95 (0.79-1.15)
≥2 Abortions	24	18 342	0.87 (0.58-1.30)	0.84 (0.56-1.26)
<i>P</i> value for trend			.51	.35
Induced abortion before first birth‡	99	80 333	0.92 (0.75-1.13)	0.85 (0.68-1.05)
Induced abortion after first birth‡	58	31 962	1.03 (0.79-1.34)	1.12 (0.85-1.46)
<b>Spontaneous abortion</b>				
Nulliparous				
No spontaneous abortion	283	174 423	1 [Reference]	1 [Reference]
Spontaneous abortion§	28	19 699	0.82 (0.55-1.21)	0.82 (0.55-1.21)
Parous				
No spontaneous abortion	856	560 996	1 [Reference]	1 [Reference]
Spontaneous abortion	263	194 040	0.89 (0.78-1.03)	0.87 (0.76-1.01)
1 Miscarriage	216	158 248	0.90 (0.77-1.04)	0.88 (0.76-1.03)
≥2 Miscarriages	47	35 792	0.87 (0.65-1.17)	0.84 (0.62-1.12)
<i>P</i> value for trend			.12	.06
Spontaneous abortion before first birth‡	101	68 440	0.97 (0.79-1.20)	0.92 (0.75-1.14)
Spontaneous abortion after first birth‡	162	125 601	0.85 (0.72-1.00)	0.85 (0.72-1.00)

Abbreviations: CI, confidence interval; HR, hazard ratio.

\*Parity status was updated in the regression analysis at every 2-year interval. Women who did not provide information on parity were excluded from this analysis.

†The HRs and 95% CIs among nulliparous women were adjusted for age, birth weight, premature birth, family history of breast cancer, history of benign breast disease, height, body mass index at the age of 18 years and current body mass index (calculated as weight in kilograms divided by height in meters squared), age at menarche, oral contraceptive use, alcohol consumption, physical activity, menopausal status, age at menopause, and postmenopausal hormone use. The HRs and 95% CIs among parous women were adjusted for the same covariates as among nulliparous women and in addition for parity and age at first birth.

‡Not mutually exclusive (women who had abortions before and after first birth contributed information to both strata).

§There were too few spontaneous abortions among nulliparous women to stratify by number of spontaneous abortions.

morigenesis, resulting in a risk comparable to that of virgin rats. Russo and Russo hypothesized that the differentiation process during the first trimester might be insufficient to outweigh the effects of increased levels of pregnancy hormones, such as estrogen and progesterone, that enhance breast-cell division. More recently, Russo and colleagues<sup>16,17</sup> found that placental human chorionic gonadotropin, a hormone that is an important regulator of cellular differentiation and proliferation and that may activate apoptosis, induces the synthesis of inhibin by the mammary epithelium. Bernstein et al<sup>18</sup> observed a reduced risk of breast cancer among women who had received human chorionic gonadotropin injection as part of a weight loss regimen or as a component of infertility treatment. Because levels of human chorionic gonadotropin rise in the early stages of human pregnancy, an incomplete pregnancy of short duration might impart the benefits of a full-term pregnancy and thus reduce the risk of breast cancer.

In this cohort study of young women, we found no association between induced abortion and breast cancer incidence and a suggestion of an inverse association between spontaneous abortion and breast cancer inci-

dence during 10 years of follow-up. We observed associations in 2 subgroups, an association between induced abortion and PR- breast cancer and an inverse association between spontaneous abortion before the age of 20 years and breast cancer incidence. Subgroup analyses have to be interpreted cautiously, especially if the strata are small. No obvious mechanisms can be provided for these subgroup findings; thus, chance has to be considered as a possible explanation.

The association between abortion and breast cancer has previously been considered in numerous studies, most of which had a case-control design.<sup>3</sup> Among studies in which induced abortions were considered separately from spontaneous abortions, no association was found in approximately half, and in half an increased risk of breast cancer was observed.<sup>3</sup> No association was found for spontaneous abortion in most studies, including both cohort and case-control studies.<sup>3</sup>

When a sensitive personal issue such as induced abortion is studied, underreporting is probable, especially for abortions that occurred before 1973, when abortions were illegal in the United States. Even after the *Roe v Wade* decision, induced abortions are still stigmatized. Healthy

**Table 4. History of Induced and Spontaneous Abortion and Hazard Ratios of Invasive Receptor-Specific Breast Cancer Among 105 716 Nulliparous and Parous Participants in the Nurses' Health Study II**

Parity*	No. of Breast Cancer Cases†	No. of Person-Years	Age-Adjusted HR (95% CI)	Covariate-Adjusted HR (95% CI)‡	P Value for the Test of Heterogeneity
Induced abortion					
Nulliparous					
No induced abortion	243§	159 290	1 [Reference]	1 [Reference]	
Abortion					
ER+	42	34 862	1.27 (0.90-1.79)	1.25 (0.87-1.78)	.65
ER-	14	34 884	1.45 (0.79-2.68)	1.35 (0.71-2.58)	
PR+	33	34 865	1.49 (1.00-2.22)	1.39 (0.92-2.11)	.73
PR-	12	34 889	1.25 (0.65-2.40)	0.97 (0.49-1.93)	
Parous					
No induced abortion	962	642 741	1 [Reference]	1 [Reference]	
Abortion					
ER+	99	112 347	0.99 (0.80-1.23)	0.95 (0.77-1.18)	.40
ER-	35	112 405	1.17 (0.81-1.69)	1.20 (0.83-1.74)	
PR+	59	112 382	0.84 (0.64-1.11)	0.80 (0.60-1.05)	.002
PR-	47	112 393	1.62 (1.17-2.23)	1.58 (1.13-2.20)	
Spontaneous abortion					
Parous					
No spontaneous abortion	856	560 996	1 [Reference]	1 [Reference]	
Spontaneous abortion					
ER+	165	194 122	0.92 (0.77-1.10)	0.90 (0.75-1.07)	.81
ER-	52	194 228	0.96 (0.70-1.32)	0.94 (0.69-1.30)	
PR+	110	194 162	0.89 (0.72-1.10)	0.86 (0.69-1.07)	.88
PR-	50	194 232	0.86 (0.63-1.19)	0.81 (0.58-1.11)	

Abbreviations: CI, confidence interval; ER+, estrogen receptor positive; ER-, estrogen receptor negative; HR, hazard ratio; PR+, progesterone receptor positive; PR-, progesterone receptor negative.

\*Parity status was updated in the regression analysis at every 2-year interval. The number of women who were nulliparous and reported spontaneous abortions was too small to calculate reasonably stable estimates.

†Cases with ER information and cases with PR information may overlap.

‡The HRs and 95% CIs among nulliparous women were adjusted for age, birth weight, premature birth, family history of breast cancer, history of benign breast disease, height, body mass index at the age of 18 years and current body mass index (calculated as weight in kilograms divided by height in meters squared), age at menarche, oral contraceptive use, alcohol consumption, physical activity, menopausal status, age at menopause, and postmenopausal hormone use. The HRs and 95% CIs among parous women were adjusted for the same covariates as the HRs and 95% CIs among nulliparous women and in addition for parity and age at first birth.

§Total number of cases, including 149 ER+ and 42 ER- (a total of 191 cases with known ER status), and 99 PR+ and 41 PR- (a total of 140 cases with known PR status) cases. The incidence of breast cancer with corresponding ER/PR status was used when calculating HRs of ER+, ER-, PR+, and PR- breast cancer.

||Total number of cases, including 586 ER+ and 174 ER- (a total of 760 cases with known ER status), and 413 PR+ and 172 PR- (a total of 585 cases with known PR status) cases. The incidence of breast cancer with corresponding ER/PR status was used when calculating HRs of ER+, ER-, PR+, and PR- breast cancer.

¶Total number of cases, including 520 ER+ and 157 ER- (a total of 677 cases with known ER status), and 362 PR+ and 169 PR- (a total of 531 cases with known PR status) cases. The incidence of breast cancer with corresponding ER/PR status was used when calculating HRs of ER+, ER-, PR+, and PR- breast cancer.

women interviewed as controls in case-control studies may thus be reluctant to reveal such intimate information in an epidemiologic study, whereas women with breast cancer may be more likely to reveal a history of abortion in a study that is searching for the cause of their illness. Because such differential retrospective reporting would produce a spurious association, retrospective case-control studies that address the issue of induced abortion and breast cancer are problematic. Conversely, a cohort study with data on abortion collected before the diagnosis of cancer might be affected by nondifferential misclassification because of general underreporting of abortion, which would bias the observed effect estimate toward the null. Abortion registry studies might draw from the most objective source of information on induced abortion, but few countries have such registries, and data on potential confounding variables are often unavailable. Moreover, registry studies are usually restricted to a limited period of follow-up and therefore do not capture the entire reproductive his-

tory of the women included. For example, a large Danish study included 1.5 million women born between 1935 and 1978, but access to information on induced abortions was limited to the period between 1973 and 1992, and cancer follow-up spanned 1968 to 1992.<sup>4</sup> The complete history of induced abortions might not have been captured for most of the women included, possibly introducing nondifferential misclassification.

A general underreporting of induced abortion in a cohort study would most likely lead to an underestimation of the true association. The reported frequency of induced abortion (percentage of women who reported any induced abortion) of 15% among our study participants is similar to that in the European Prospective Investigation Into Cancer and Nutrition (16%)<sup>11</sup> and in the Danish registry study (19%).<sup>4</sup> None of these studies, however, included all reproductive years of the women participating, thus leaving room for misclassification. In our study population, 66% of women were still premeno-

pausal at the end of follow-up in 2003; therefore, their reproductive history may still have been incomplete. Women in our cohort were born between 1946 and 1964; therefore, most of their reproductive years were after 1973, when induced abortion was legalized in the United States. However, the oldest members of our cohort were 27 years of age in 1973; thus, pregnancy termination was illegal during part of their reproductive years. Participants in the Iowa Women's Study were aged 42 to 51 years in 1973, and only 1.8% of participants reported an induced abortion.<sup>9</sup> Although comparisons with national figures of abortion are difficult because they are usually generated using a life table approach, the Alan Guttmacher Institute estimates that 1 of 4 US women younger than 45 years has had at least 1 induced abortion.<sup>19</sup> The nurses in our cohort may not be representative of the social classes most likely to use abortion services. Some misclassification, however, cannot be ruled out.

Breast cancer cases in our study population were almost exclusively premenopausal; therefore, our results may not be generalizable to postmenopausal women. However, the positive association previously reported from case-control studies was largely restricted to premenopausal women.<sup>3</sup> The lack of association observed in the large Danish study was consistent across all ages of diagnosis of breast cancer.<sup>2</sup> Although our data are not compatible with any substantial overall relation between induced abortion and breast cancer, we cannot exclude a modest association in subgroups defined by known breast cancer risk factors, timing of abortion, or parity.

In 2003, the National Cancer Institute convened an international expert panel to review and assess the existing evidence on reproductive events and the risk of breast cancer. The summary report of the Early Reproductive Events and Breast Cancer Workshop concluded that according to the existing evidence, induced abortion is not associated with an increase in breast cancer risk.<sup>20</sup> The data from the NHSII provide further evidence of a lack of an important overall association between induced or spontaneous abortions and risk of breast cancer.

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## REFERENCES

- Rosner B, Colditz GA, Willett WC. Reproductive risk factors in a prospective study of breast cancer: the Nurses' Health Study. *Am J Epidemiol.* 1994;139:819-835.
- Russo J, Russo IH. Susceptibility of the mammary gland to carcinogenesis. II: pregnancy interruption as a risk factor in tumor incidence. *Am J Pathol.* 1980;100:497-512.
- Michels KB, Willett WC. Does induced or spontaneous abortion affect the risk of breast cancer? *Epidemiology.* 1996;7:521-528.
- Melbye M, Wohlfahrt J, Olsen JH, et al. Induced abortion and the risk of breast cancer. *N Engl J Med.* 1997;336:81-85.
- Lindfors-Harris BM, Edklund G, Meirik O, Rutqvist LE, Wiklund K. Risk of cancer of the breast after legal abortion during first trimester: a Swedish register study. *BMJ.* 1989;299:1430-1432.
- Goldacre MJ, Kurina LM, Seagroatt V, Yeates D. Abortion and breast cancer: a case-control record linkage study. *J Epidemiol Community Health.* 2001;55:336-337.
- Erlandsson G, Montgomery SM, Cnattingius S, Ekblom A. Abortions and breast cancer: record-based case-control study. *Int J Cancer.* 2003;103:676-679.
- Tang MT, Weiss NS, Malone KE. Induced abortion in relation to breast cancer among parous women: a birth certificate registry study. *Epidemiology.* 2000;11:177-180.
- Lazovich D, Thompson JA, Mink PJ, Sellers TA, Anderson KE. Induced abortion and breast cancer risk. *Epidemiology.* 2000;11:76-80.
- Ye Z, Gao DL, Qin Q, Ray RM, Thomas DB. Breast cancer in relation to induced abortions in a cohort of Chinese women. *Br J Cancer.* 2002;87:977-981.
- Reeves GK, Kan SW, Key T, et al. Breast cancer risk in relation to abortion: results from the EPIC study. *Int J Cancer.* 2006;119:1741-1745.
- Cox D. Regression models and life-tables. *J R Stat Soc [Ser B].* 1972;34:187-220.
- Marshall RJ, Chisholm EM. Hypothesis testing in the polychotomous logistic model with an application to detecting gastrointestinal cancer. *Stat Med.* 1985;4:337-344.
- MacMahon B, Cole P, Lin TM, et al. Age at first birth and breast cancer risk. *Bull World Health Organ.* 1970;43:209-221.
- Russo J, Tay LK, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. *Breast Cancer Res Treat.* 1982;2:5-73.
- Alvarado MV, Alvarado NE, Russo J, Russo IH. Human chorionic gonadotropin inhibits proliferation and induces expression of inhibin in human breast epithelial cells in vitro. *In Vitro Cell Dev Biol Anim.* 1994;30A:4-8.
- Russo IH, Koszalka M, Russo J. Effect of human chorionic gonadotropin on mammary gland differentiation and carcinogenesis. *Carcinogenesis.* 1990;11:1849-1855.
- Bernstein L, Hanisch R, Sullivan-Halley J, Ross RK. Treatment with human chorionic gonadotropin and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev.* 1995;4:437-440.
- Daling JR, Malone KE, Voigt LF, White E, Weiss NS. Risk of breast cancer among young women: relationship to induced abortion. *J Natl Cancer Inst.* 1994;86:1584-1592.
- Summary Report: Early Reproductive Events and Breast Cancer Workshop. [www.cancer.gov/cancerinfo/ere-workshop-report](http://www.cancer.gov/cancerinfo/ere-workshop-report). Accessed March 25, 2003.