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INDUCED ABORTION AND THE RISK OF BREAST CANCER

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ABSTRACT

Background It has been hypothesized that an interrupted pregnancy might increase a woman's risk of breast cancer because breast cells could proliferate without the later protective effect of differentiation.

Methods We established a population-based cohort with information on parity and vital status consisting of all Danish women born from April 1, 1935, through March 31, 1978. Through linkage with the National Registry of Induced Abortions, information on the number and dates of induced abortions among those women was combined with information on the gestational age of each aborted fetus. All new cases of breast cancer were identified through linkage with the Danish Cancer Registry.

Results In the cohort of 1.5 million women (28.5 million person-years), we identified 370,715 induced abortions among 280,965 women (2.7 million person-years) and 10,246 women with breast cancer. After adjustment for known risk factors, induced abortion was not associated with an increased risk of breast cancer (relative risk, 1.00; 95 percent confidence interval, 0.94 to 1.06). No increases in risk were found in subgroups defined according to age at abortion, parity, time since abortion, or age at diagnosis of breast cancer. The relative risk of breast cancer increased with increasing gestational age of the fetus at the time of the most recent induced abortion: <7 weeks, 0.81 (95 percent confidence interval, 0.58 to 1.13); >12 weeks, 1.38 (1.00 to 1.90) (reference category, 9 to 10 weeks).

Conclusions Induced abortions have no overall effect on the risk of breast cancer. (N Engl J Med 1997; 336:81-5.)

A FULL-TERM pregnancy increases a woman's short-term risk of breast cancer, possibly as a result of the growth-enhancing properties of pregnancy-induced estrogen secretion. By contrast, such a pregnancy decreases the long-term risk of breast cancer, perhaps by inducing terminal differentiation of the susceptible mammary cells.[1-5] Studies in animals suggest that the potential for terminal differentiation of breast cells is lower for a pregnancy terminated by abortion than for a full-term pregnancy. On this basis Russo and Russo[3] have proposed that a full-term pregnancy allows complete differentiation of breast cells, thereby protecting against cancer, whereas an abortion forestalls the late protective effect of differentiation, thereby increasing the risk of breast cancer.

Epidemiologic studies of the association between abortion and the subsequent risk of breast cancer have yielded inconsistent results, with estimates of risk ranging from moderately elevated to significantly lowered.[6-24] In a recent case–control study, Daling et al. found evidence of an elevated risk in women who had an induced abortion between 9 and 12 weeks' gestation, but this finding was based on a very limited number of women.[7] In the present study, we took advantage of Denmark's mandatory reporting of all induced abortions, together with the week of gestation, to evaluate the hypothesis of Russo and Russo.[3]

METHODS

Population Registries

Before initiating this study, we obtained permission from Denmark's National Scientific Ethics Committee and Data Protection

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Board. For this investigation we linked data from the Civil Registration System (CRS) with data from the National Registry for Induced Abortions and the Danish Cancer Registry. Since April 1, 1968, the CRS has assigned a unique identification number to all Danish residents, which permits information from different registries to be linked. The CRS also keeps updated files on the dates of live births and documents demographic variables such as emigration and deaths.

The reporting of induced abortions to the National Board of Health has been mandatory since 1939. In 1973, the legal right to an induced abortion through 12 weeks' gestation was established for women with residence in Denmark. Induced abortions after week 12 were permitted under medical or other circumstances, such as rape, that could greatly interfere with the proper care of the newborn child. Since 1973, information on all induced abortions, including the date of the procedure and the week of gestation at the time, has been computerized in the national registry of induced abortions.[25] The induced abortions included in this analysis (those occurring between 1973 and 1992) were performed almost exclusively by surgical removal.

The Danish Cancer Registry contains information on all cases of cancer diagnosed in the country since 1943. It receives reports from clinicians, pathologists, clinics, radiotherapy units, and hospitals.[26]

Subjects

A research data base comprising all Danish women born between April 1, 1935, and March 31, 1978, and including information on any live-born children, was established on the basis of information from the CRS. The individually identifiable CRS numbers were used to form a link with the national registry of induced abortions, which supplied information on the date of any induced abortion and the gestational age of the aborted fetus. Subjects' CRS numbers were subsequently linked with the Danish Cancer Registry to identify the subjects with a diagnosis of invasive breast cancer.

Statistical Analysis

Follow-up for breast cancer for all the women began on April 1, 1968, or on their 12th birthday, whichever came later. The period at risk continued until a diagnosis of breast cancer, death, emigration, loss to follow-up, or December 31, 1992 (at which date the cancer registry was considered complete) — whichever occurred first. The possible effect of the duration of the pregnancies that ultimately ended in induced abortions was investigated in a log-linear Poisson regression model.[27] The numbers of person-years at risk were calculated for groups defined according to the week of gestation for induced abortions that took place at <7, 7 to 8, 9 to 10, 11 to 12, 13 to 14, 15 to 18, and >18 weeks' gestation. Women with more than one induced abortion were, in the period between the first and second abortion, considered at risk according to the week of gestation at the time of the first induced abortion; between the second and third abortions they were considered at risk according to the week of gestation at the time of the second induced abortion; and so on.

Adjustment was made for attained age in one-year intervals and for the calendar period in which the abortion occurred (1968–1972, 1973–1977, 1978–1982, 1983–1987, and 1988–1992), parity (0, 1, 2, 3, 4, 5, 6, and ≥7), and age at delivery of a first child (12 to 19, 20 to 24, 25 to 29, 30 to 34, and >34 years). In an exploratory analysis we also categorized the women according to calendar period and age at first delivery in one-year intervals, but this had no effect on the results — a finding that argues against residual confounding. For simplicity, the attained age of a woman is denoted as her "age at the time of diagnosis of breast cancer." "Calendar period" and "calendar period at time of diagnosis of breast cancer" are used synonymously. Tests for trend were performed with gestational age treated as a continuous variable and the mean gestational age used as the value for each group. Rate ratios for the incidence of breast cancer were estimated with the use of the SAS procedures software package PROC GENMOD.[28] These rate ratios are referred to as relative risks in this article.

RESULTS

Overall, 1,529,512 women were included in the cohort. Of these, 280,965 (18.4 percent) had a total of 370,715 induced abortions, distributed as follows: 215,902 women (76.8 percent) each had one induced abortion; 47,906 women (17.1 percent) each had two; and 17,157 women (6.1 percent) each had three or more. The distribution of the number of induced abortions according to gestational age was as follows: <7 weeks, 3.1 percent; 7 to 8 weeks, 37.1 percent; 9 to 10 weeks, 41.8 percent; 11 to 12 weeks, 15.7 percent; >12 weeks, 2.3 percent. Women without a history of induced abortion accounted for 25,850,000 person-years of follow-up. In this group, there were 8908 cases of breast cancer. In comparison, among women with a history of induced abortion, accounting for 2,697,000 person-years of follow-up, there were 1338 cases of breast cancer.

Overall, the risk of breast cancer in women with a history of induced abortion was not different from that in women without such a history, after potential confounding by age, parity, age at delivery of a first child, and calendar period was taken into account (relative risk, 1.00; 95 percent confidence interval, 0.94 to 1.06).

Table 1 presents the association between variables related to abortion history and the risk of breast cancer. We calculated both the relative risk adjusted for age, parity, calendar period, and age at first delivery and the further adjusted multivariate relative risk (adjusted also for the other variables shown in the table). The adjustment had little or no effect on any of the risk estimates. Age at the time of the induced abortion did not significantly influence the overall risk, but there was a tendency toward a higher risk of breast cancer among women in the lowest age category — between 12 and 19 years of age (relative risk, 1.29; 95 percent confidence interval, 0.80 to 2.08). Neither the number of induced abortions nor whether or not the woman had given birth to a live infant (i.e., whether the induced abortion occurred in a nulliparous woman or either before or after a live birth) significantly influenced the risk of breast cancer. We also examined the time interval between the induced abortion and the diagnosis of breast cancer but found no indication of a differential effect (<1 year, relative risk = 0.97; 1 to 4 years, relative risk = 0.99; ≥5 years, relative risk = 1 [reference category]) (Table 1).

There was no effect of induced abortion on the risk of breast cancer after adjustment for the ages of the women at the time of the diagnosis of breast cancer (12 to 34 years, relative risk = 0.95 [95 percent confidence interval, 0.78 to 1.14]; 35 to 39 years,

TABLE 1. ADJUSTED RELATIVE RISK OF BREAST CANCER IN WOMEN WITH A HISTORY OF INDUCED ABORTION.

ABORTION HISTORY	NO. OF CANCERS	PERSON-YEARS (THOUSANDS)	RELATIVE RISK (95% CI)*	MULTIVARIATE RELATIVE RISK (95% CI)†
Wk of gestation				
<7	36	82	0.81 (0.58–1.13)	0.81 (0.58–1.13)
7–8	526	1012	1.01 (0.89–1.14)	1.01 (0.89–1.14)
9–10‡	534	1118	1	1
11–12	205	422	1.12 (0.95–1.31)	1.12 (0.95–1.31)
13–14	6	14	1.13 (0.50–2.52)	1.13 (0.51–2.53)
15–18	17	35	1.24 (0.76–2.01)	1.23 (0.76–2.00)
>18	14	14	1.92 (1.13–3.26)	1.89 (1.11–3.22)
Age at induced abortion (yr)				
12–19	23	458	1.32 (0.82–2.12)	1.29 (0.80–2.08)
20–24‡	68	617	1	1
25–29	161	552	0.91 (0.68–1.20)	0.93 (0.69–1.25)
30–34	366	529	0.99 (0.76–1.29)	1.03 (0.77–1.38)
≥35	720	541	1.04 (0.81–1.34)	1.07 (0.80–1.43)
No. of induced abortions				
1‡	1105	2220	1	1
2	191	376	1.08 (0.92–1.26)	1.09 (0.94–1.28)
≥3	42	101	0.99 (0.73–1.35)	1.02 (0.75–1.40)
Time since induced abortion (yr)				
<1	63	339	0.97 (0.75–1.25)	0.97 (0.75–1.25)
1–4	315	1048	0.99 (0.87–1.12)	0.99 (0.87–1.13)
≥5‡	960	1310	1	1
Time of induced abortion and live-birth history				
Nulliparous women	95	694	1.04 (0.83–1.29)	1.04 (0.83–1.31)
Parous women				
Induced abortion before 1st live birth	77	350	1.08 (0.85–1.36)	1.08 (0.82–1.44)
Induced abortion after 1st live birth‡	1154	1582	1	1
Other§	12	71	0.76 (0.43–1.34)	0.74 (0.41–1.33)

*The relative risks were calculated separately for each of the five variables, with adjustment for women's age, calendar period, parity, and age at delivery of a first child. CI denotes confidence interval.

†Values were adjusted for women's age, calendar period, parity, age at delivery of a first child, and the other variables shown in the table.

‡The women with this characteristic served as the reference group.

§"Other" denotes induced abortion occurring after delivery of a first child in women who also had induced abortion before delivery of a first child.

relative risk = 0.99 [0.87 to 1.14]; 40 to 44 years, relative risk = 1.01 [0.91 to 1.12]; 45 to 49 years, relative risk = 1 [reference category]; ≥50 years, relative risk = 1.03 [0.88 to 1.21]; P for trend = 0.97). Also, neither the calendar period at the time of diagnosis of breast cancer (P = 0.17) nor the calendar period at the time of induced abortion (P = 0.83) modified the relation between induced abortion and the risk of breast cancer.

With each one-week increase in the gestational age of the fetus, however, there was a 3 percent increase in the risk of breast cancer. The relative risk increased from 0.81 (95 percent confidence interval, 0.58 to 1.13) among women whose most recent induced abortion was at less than 7 weeks of gestation to 1.38 (95 percent confidence interval, 1.00 to 1.90) among women whose most recent abortion was at more than 12 weeks of gestation. We acknowledge the small number of cases in the group with abortions later than 12 weeks, but we evaluated this period further and found the following relative risks: weeks 13 to 14, 1.13 (95 percent confidence interval, 0.51 to 2.53); weeks 15 to 18, 1.23 (0.76 to 2.00); weeks >18, 1.89 (1.11 to 3.22) (P for trend = 0.016, Table 1).

DISCUSSION

Our study of a population-based cohort uncovered no overall increased risk of breast cancer among women with a history of induced abortion. This result is very much in line with the results of previous retrospective cohort studies,[9,10,15,16] two of which actually suggested a decreased risk.[10,15] However, all previously published retrospective cohort studies lack detailed information on the week of gestation at the time of abortion. The results of case–control

studies have been inconsistent,[6-8,11-14,17-24] but several groups have reported an increased risk of breast cancer among women with a history of induced abortion.[7,8,13,21-24]

A recent meta-analysis found an overall increased risk of breast cancer among women with a history of induced abortion of 1.3 (95 percent confidence interval, 1.2 to 1.4).[24] The authors concluded that "such a broad base of statistical agreement rules out any reasonable possibility that the association is the result of bias or any other confounding variable." However, since almost all 23 studies included in the analysis were case–control studies, it is not unreasonable to assume that many of them were inherently biased, making the pooled conclusions biased as well. Furthermore, the authors based their results on a crude analysis of published odds ratios and relative risks with no attempt to incorporate the original raw data into a more sophisticated statistical analysis.

Almost inevitably, case–control studies arouse concern about the potential problem of differential misclassification. Even after its legalization, abortion remains a sensitive issue. It is possible that women with breast cancer might be more willing to report induced abortions than healthy women. A Swedish study that compared registry information with interview data regarding induced abortion attributed an increase in the risk of breast cancer of between 16 and 50 percent to differential misclassification in interview data.[7,29] The problem of misclassification based on reporting led Newcomb et al. to conclude that studies that do not rely on interviews with case and control subjects are necessary to resolve whether there is a link between induced abortion and breast cancer.[8] In our study, all the information on dates and the number of induced abortions, reproductive history, and cancer diagnosis was obtained from national registries, which are compiled through a system of mandatory reporting for the entire population. Follow-up included complete information on death and emigration and was performed through computerized linkage of registry information by means of individually identifiable registration numbers. These measures, we believe, allowed us to avoid some of the major methodologic problems of previous studies.

A limitation of our research data base was that information on induced abortions has been computerized only since 1973. Therefore, we might have obtained an incomplete history of induced abortions for some of the oldest women in the cohort. However, we found that the risk of breast cancer among women with a history of induced abortion was no different from that among women without such a history, nor did we find that the number of induced abortions influenced the risk of breast cancer. Therefore, it is unlikely that missing information about abortions before 1973 affected the results of our analysis.

Induced abortion had no overall effect on the risk of breast cancer, but we found a statistically significant increase in risk among women with a history of second-trimester abortion. The fact that such an increase did not affect the overall result clearly indicates that it is based on small numbers and therefore requires cautious interpretation. The increased risk among women who had had second-trimester abortions finds biologic support in experiments in rats and is in line with the hypothesis of Russo and Russo.[3]

We were concerned that women whose breast cancer was diagnosed during pregnancy might have been advised to have induced abortions, a situation that would not be equally distributed according to the week of gestation at the time of the abortion. Since the time at risk was calculated only up to the diagnosis of breast cancer, only late abortions that were misclassified as occurring before the diagnosis of cancer could represent a problem. However, a stratified analysis of the risk of breast cancer according to the length of time since an induced abortion showed no differential risk and, in particular, no increased risk within the first year after abortion. Abortions induced at gestational ages of more than 12 weeks were performed primarily for medical or social reasons. The women who had such abortions could have had a relatively high risk of breast cancer, but we could not identify any medical condition associated with both a high risk and late induced abortion. Women with drinking problems might delay the interruption of their unwanted pregnancies, but the association between alcohol and breast cancer is weak and inconsistent.[30]

We cannot explain why a very early induced abortion was associated with a slight, although insignificant, decrease in risk. Nulliparous women with a history of induced abortion did not differ from parous women in their risk of breast cancer. Among nulliparous women, the possible effects of lactation and later births are irrelevant. We are therefore confident that neither of these variables had any confounding effect on our overall result.

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