RESEARCH REPORT

Risk of breast cancer after miscarriage or induced abortion: a Scottish record linkage case-control study

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Study objective: To assess the risk of breast cancer in patients with a previous history of miscarriage or induced abortion.
Design: Case-control study relating ''exposure'' to outcome by linkage of national hospital discharge and maternity records, the national cancer registry, and death records.
Setting: Scotland.
Participants: Miscarriage analysis—2828 women with breast cancer and 9781 matched controls; induced abortion analysis—2833 women with breast cancer and 9888 matched controls.
Main results: After stratification for age at diagnosis, parity, and age at first birth, the odds ratio (95% confidence intervals) of breast cancer was 1.02 (0.88 to 1.18) in women with a previous miscarriage, and 0.80 (0.72 to 0.89) in women with a previous induced abortion. Further adjustments for age at bilateral oophorectomy, socioeconomic status (based on small area of residence), and health board area of residence had only minor effects on these odds ratios.
Conclusion: These data do not support the hypothesis that miscarriage or induced abortion represent substantive risk factors for the future development of breast cancer.

Childbearing has been consistently shown to reduce the risk of breast cancer in the long term.[1] Until recently, incomplete pregnancies were thought to have no effect, or perhaps slightly reduce the risk of breast cancer.[2] However, in 1990, Remennick carried out a literature review and suggested that induced abortion might increase the risk of breast cancer.[3] Brind came to similar conclusions in 1996,[4] although others who reviewed the evidence came to different conclusions.[5–7] Although some have quoted animal evidence[8] to support the view that induced abortion might increase the risk of breast cancer, it is difficult to know the relevance of these findings for humans.

To investigate the potential role of miscarriage and induced abortion as risk factors for the future development of breast cancer, the Collaborative Group on Hormonal Factors in Breast Cancer collated and analysed data on individual women from 53 studies undertaken in 16 countries.[9] Among 44 000 women with prospectively recorded information on miscarriage or induced abortion (that is, information that had been recorded before the diagnosis of breast cancer), the group found that there was no evidence of an increased risk of breast cancer. However, this study did not investigate the risk of breast cancer in subgroups of women, stratified by factors such as week of gestation or maternal age at miscarriage or induced abortion.

This paper reports the results of a study designed to assess the risk of breast cancer in patients with a previous history of miscarriage or induced abortion, using computerised NHS records collated routinely in Scotland, which has a limited private healthcare sector, especially relating to obstetrics and oncology. Although these data had not been published previously, they were included in the meta-analysis referred to above. However, for reasons of space, it was only possible to provide limited details of study design, methods, and results in the ensuing publication.[9] In this paper, we provide further details of study design, methods, results of subgroup analyses, and some consideration of the study's strengths and limitations.

METHODS

From the linked database of acute hospital discharge (SMR01) records, cancer registrations, and death records in Scotland,[10] ''cases'' were identified and ''controls'' selected from the period spanning 1981–1998. Cases were defined as women with new incident breast cancers diagnosed before 55 years of age (most older women are unlikely to have been exposed to miscarriage or induced abortion in the time frame of this study). Controls were defined as women without cancer admitted to acute hospitals for any non-obstetric, non-gynaecological conditions and were matched for year of admission for breast cancer (corresponding to the date of the case's breast cancer diagnosis), year of birth, health board of residence, and 1991 census based Carstairs' deprivation quintile, the last two based on postcode sector of residence at the time of hospital admission (corresponding to the case's breast cancer diagnosis). The Carstairs deprivation score is a small area indicator of socioeconomic status based on the prevalence measured at the decennial census of four characteristics: overcrowding, male unemployment, social class, and car ownership.[11] Although based on small area of residence rather than individual characteristics, it can be used to show clearly the lower risk of breast cancer among women from more deprived communities.[12] Cases and controls were excluded if they had any history of cancer (other than non-melanoma skin cancer) or carcinoma in situ of breast before the date of diagnosis of breast cancer/hospital admission. All potentially eligible matched controls were identified and up to four per case were selected randomly.

Using computerised probability matching[10] and with the approval of the Privacy Advisory Committee that advises the NHS Information Services in Scotland, all acute hospital discharge (SMR01), cancer registration, and death records for each case and control were linked to their corresponding records on the linked maternity (SMR02) database (spanning 1980 onwards) to generate an anonymised dataset for analysis. It is estimated that this method of linkage results

Table 1 Number of cases and controls in the miscarriage analysis

Miscarriage	Cases	%	Controls	%
No	2575	91.1	8873	90.7
Yes	253	9.0	908	9.3
Total	2828	100.0	9781	100.0

in mismatched records in less than 2% of cases.[10] The following information was extracted for each case and control: nature and date of each reproductive event; gestational age of any miscarried or aborted fetus; history of bilateral oophorectomy; cancer diagnoses and dates; date and causes of death; and hospital admissions.

Although the variables were available for 1981 onwards, the maternity database included the number of previous reproductive events for each woman, based on a combination of self reporting, general practitioner referral letter, and available medical records, so that it was possible to identify women for whom their whole reproductive history was known. The following women were eligible for inclusion in the study:

- those with all reproductive events occurring from 1981 onwards
- those with some reproductive events occurring before 1981, and number of pregnancies equalled number of births—that is, no miscarriages or induced abortions before 1981 (note that the age at first birth was unknown for this group).

Statistical analysis

Odds ratios (OR) of breast cancer and 95% confidence intervals (95% CI), according to miscarriage/induced abortion history, were calculated using conditional logistic regression stratifying for age at diagnosis rather than preserving the individual matching, to increase efficiency. Separate models were applied to each subgroup analysis. The analyses were repeated using individually matched sets (also conditional logistic regression) and the results did not deviate from those presented here (data not shown). All the statistical analyses were conducted using Stata (version 8.2, StataCorp, 1985–2003).

RESULTS

Miscarriage

This analysis included 2828 cases and 9781 controls whose reproductive history of miscarriage was known. The average year of breast cancer diagnosis was 1994; of these women a similar proportion (9%) had a history of miscarriage (table 1).

After stratifying for age at diagnosis and the potential confounding factors, parity (0, 1–2, 3–4, 5–6, 7+ births) and age at delivery of first child (12–19, 20–24, 25–29, 30+, unknown age, no children), the odds ratio of breast cancer was 1.02 in women with a previous miscarriage compared with women with no history of miscarriage (95% CI: 0.88 to 1.18; p = 0.8).

Age at delivery of first child was unknown (as before 1981) for 61% of cases and 58% of controls. When women with unknown age at delivery of first child were excluded from the analyses, the odds ratio was little changed (OR = 0.96; 95% CI: 0.72 to 1.30; p = 0.8) compared with the overall odds ratio of 1.02.

Table 2 Adjusted* odds ratios of breast cancer for women who have had a pregnancy ending in miscarriage compared with women with no pregnancy ending in miscarriage

Subgroup	Number of women	Odds ratio (95% CI)	p Value
No miscarriage	11448	1.00	
Miscarriage	1161	1.02 (0.88 to 1.18)	0.81
Week of gestation (of earliest miscarriage)			
No miscarriage	11448	1.00	
<9 weeks	192	1.10 (0.78 to 1.55)	0.61
9–10 weeks	178	0.81 (0.55 to 1.19)	0.29
11–12 weeks	162	0.89 (0.60 to 1.32)	0.55
>12 weeks	205	0.90 (0.63 to 1.27)	0.55
Unknown	424	1.20 (0.96 to 1.51)	0.12
Age at miscarriage			
No miscarriage	11448	1.00	
12–19 years	17	1.34 (0.43 to 4.18)	0.61
20–24 years	134	0.65 (0.38 to 1.09)	0.10
25–29 years	278	0.96 (0.71 to 1.29)	0.77
30+ years	732	1.10 (0.92 to 1.32)	0.29
Number of miscarriages			
0	11448	1.00	
1	1031	1.01 (0.86 to 1.18)	0.91
2	110	1.19 (0.76 to 1.87)	0.44
3+	20	0.67 (0.20 to 2.32)	0.53
Time since miscarriage			
No miscarriage	11448	1.00	
<1 year	51	1.16 (0.6 to 2.23)	0.66
1–4 years	253	1.21 (0.9 to 1.62)	0.22
5–9 years	377	1.05 (0.82 to 1.35)	0.70
10+ years	480	0.89 (0.71 to 1.12)	0.33
Temporal sequence†‡			
No miscarriage	11448	1.00	
Miscarriage while nulliparous	207	1.08 (0.78 to 1.49)	0.66
Live birth then miscarriage	537	0.79 (0.64 to 0.99)	0.04
Unknown sequence§	417	1.11 (0.88 to 1.39)	0.37

*Adjusted for age, parity, and age at delivery of first child. †No information on miscarriages/induced abortions before 1981. ‡Adjusted for age only (as includes nulliparous women). §"Unknown" includes women who have had a miscarriage since 1981 (and no live births since 1981) but whose maternal history sequence before 1981 is unknown.

Table 3 Number of cases and controls in the induced abortion analysis

Induced abortion	Cases	%	Controls	%
No	2322	82.0	7651	77.4
Yes	511	18.0	2237	22.6
Total	2833	100.0	9888	100.0

Of the initial cohort of women whose reproductive history of miscarriage was known, 2.55% had a bilateral oophorectomy before the breast cancer diagnosis/control's hospital admission date. Adjustment in turn for potential confounding factors including age at bilateral oophorectomy (never, <40, 40–44, 45–49, 50+), and the initial matching variables, deprivation category and health board of residence, had only a minor effect on the odds ratio (OR = 1.02, OR = 1.01 and OR = 1.05, respectively).

There were no clear or significant effects when investigating breast cancer risk in relation to week of gestation of miscarriage, age at miscarriage, number of miscarriages, or time since miscarriage (table 2). However, the risk of breast cancer seemed to be lower than expected for women who had a live birth followed by a miscarriage (OR = 0.79; 95% CI: 0.64 to 0.99; p = 0.04) compared with women who had no history of miscarriage.

Induced abortion

This analysis included 2833 cases and 9888 controls whose reproductive history of induced abortion was known. The average year of breast cancer diagnosis was 1994; of these women 18% of cases and 23% of controls had a history of induced abortion (table 3).

After stratifying for age at diagnosis, parity, and age at delivery of first child, the odds ratio of breast cancer was 0.80 in women with a previous induced abortion compared with women with no history of induced abortion (95% CI: 0.72 to 0.89; p<0.001).

Age at delivery of first child was unknown (as before 1981) for 61% of cases and 58% of controls. When women with unknown age at delivery of first child were excluded from the analyses, the odds ratio was reduced further (OR = 0.73; CI: 0.57 to 0.93; p = 0.01).

Of the initial cohort of women whose reproductive history of induced abortion was known, 2.5% had a bilateral oophorectomy before the breast cancer diagnosis/control's hospital admission date. Adjustment in turn for age at bilateral oophorectomy, deprivation category, and health board of residence, had only a minor effect on the odds ratio (OR = 0.79, OR = 0.79, and OR = 0.82, respectively).

There were no clear effects when investigating breast cancer risk in relation to week of gestation of induced abortion, age at induced abortion, number of induced abortions, time since induced abortion, or the temporal sequence of live births and induced abortions (table 4).

DISCUSSION

The results of our study do not support the hypothesis that prior miscarriage or induced abortion represent significant risk factors for later development of breast cancer. Historically, much of the epidemiological data relating to the potential association between induced abortion and

Table 4 Adjusted* odds ratio of breast cancer for women who have had a pregnancy ending in induced abortion compared with women with no pregnancy ending in induced abortion

Subgroup	Number of women	Odds ratio (95% CI)	p Value
No abortion	9973	1.00	
Abortion	2748	0.80 (0.72 to 0.89)	<0.001
Week of gestation (of earliest abortion)			
No abortion	9973	1.00	
<9 weeks	203	0.65 (0.44 to 0.97)	0.03
9–10 weeks	194	0.93 (0.65 to 1.33)	0.69
11–12 weeks	63	0.87 (0.46 to 1.65)	0.67
>12 weeks	119	0.35 (0.19 to 0.66)	<0.01
Unknown	2169	0.83 (0.73 to 0.93)	<0.01
Age at abortion			
No abortion	9973	1.00	
12–19 years	98	1.08 (0.64 to 1.83)	0.76
20–24 years	311	0.67 (0.48 to 0.95)	0.02
25–29 years	487	0.84 (0.66 to 1.07)	0.15
30+ years	1852	0.80 (0.70 to 0.91)	<0.01
Number of abortions			
0	9973	1.00	
1	2383	0.82 (0.73 to 0.93)	<0.01
2	302	0.62 (0.45 to 0.86)	<0.01
3+	63	0.74 (0.37 to 1.48)	0.40
Time since abortion			
No abortion	9973	1.00	
<1 year	105	0.64 (0.37 to 1.09)	0.10
1–4 years	608	0.85 (0.69 to 1.05)	0.14
5–9 years	953	0.83 (0.70 to 0.99)	0.04
10+ years	1082	0.75 (0.64 to 0.89)	<0.001
Temporal sequence†‡			
No abortion	9973	1.00	
Abortion while nulliparous	155	0.77 (0.51 to 1.15)	0.20
Live birth then abortion	876	0.72 (0.60 to 0.86)	<0.001
Unknown sequence§	1717	0.75 (0.66 to 0.85)	<0.001

*Adjusted for age, parity, and age at delivery of first child. †No information on miscarriages/induced abortions before 1981. ‡Adjusted for age only (as includes nulliparous women). §"Unknown" includes women who have had an induced abortion since 1981 (and no live births since 1981) but whose maternal history sequence before 1981 is unknown.

Key points

- Although miscarriage is generally not considered to be a risk factor for the subsequent development of breast cancer, there is less consensus about the possible role of induced abortion.
- The risk of breast cancer in patients with a previous history of miscarriage or induced abortion was investigated in a hospital based record linkage case-control study in Scotland.
- The results of this study do not support the hypothesis that miscarriage or induced abortion represent substantive risk factors for the future development of breast cancer.

breast cancer has been generated from case-control interview studies. An important issue is whether such studies are subject to reporting bias as far as a history of induced abortion is concerned.[13–19] Studies based on linkage of independent records are not subject to this potential source of bias and, with one exception,[20] have not found a statistically significant increase in risk of breast cancer after induced abortion.[21–24] This underlines the importance of assigning exposure (to induced abortion) status based on information recorded before the diagnosis of breast cancer. Our results are also consistent with the recently published meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer.[9] Although our data were included in this meta-analysis, it is evident that their exclusion would not change the overall conclusion that miscarriage or induced abortion do not seem to increase the risk of subsequent breast cancer. A more recent prospective study in African-American women also found that induced abortion did not increase the risk of subsequent breast cancer.[25]

The main strengths of our study are the size and national coverage of the study population, the objective recording of prior induced abortion status, the matching of controls for variables such as year of birth, place of residence, and socioeconomic status, and the availability of information on the important potential confounding variables, parity, and age at delivery of first child. However, the study is based on computerised health records collected routinely to serve many purposes, but not specifically for the purpose of this study. While this does not necessarily invalidate the use of the data for this study, it does mean that there are potential weaknesses inherent to the study design that must be acknowledged.

The important weakness of the study relates to missing data on miscarriage and induced abortion status and potential confounding factors for a substantial proportion of the original potential study population. Women with no reproductive history, or all of their reproductive history occurring before 1981, were not eligible for inclusion in the study. However, the percentages of women who had to be excluded from the study on this basis were similar between cases (79%) and controls (80%). As the information available to us was derived from inpatient and day-case hospital records, the study is not strictly population based, and we did not have access to information about recognised or unrecognised miscarriages managed entirely outside hospital (unless this became incorporated in the history fields of maternity records). This may explain the lower than expected percentage of women with a recorded history of miscarriage. In contrast, the data on induced abortion seem likely to be reasonably complete. Based on statutory returns for the year 2001, less than 4% of abortions induced in Scottish residents took place outside NHS hospitals in Scotland (Chalmers J, personal communication). Overall, we think that differential misclassification of miscarriage, induced abortion, and reproductive history is unlikely to be present to any significant extent among the study populations included in each analysis. Indeed, if our finding of no association between miscarriage and subsequent breast cancer is valid, it is difficult to think of a credible, systematic bias that would apply exclusively to our other analysis and conceal a positive association between induced abortion and subsequent breast cancer.

While we did find an apparently reduced risk of breast cancer among women who had a live birth followed by a miscarriage, it is difficult to think of a satisfactory explanation, and it could represent a chance finding in the context of multiple tests of statistical significance. Similarly, although our results actually suggest a possible protective effect of induced abortion, this finding might be explained by incomplete information on confounding factors, and is not supported by our subgroup analyses in which we found no clear trends in risk. Of particular interest, we did not find evidence of an increased risk of breast cancer among women having abortions induced after 12 weeks gestation, in contrast with Melbye *et al* who, in their Danish record linkage cohort study, observed a statistically significant increase in risk among women undergoing induced abortion after 18 weeks gestation, admittedly based on a comparatively small number of cases in this subgroup.[23]

In summary, like almost every epidemiological study, our study does have strengths and weaknesses, and it would be unwise to draw conclusions based on the data from this one alone. However, the data we have analysed and presented do not support the hypothesis that miscarriage or induced abortion represent substantive risk factors for the future development of breast cancer.

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