

In vitro fertilization and breast cancer: is there cause for concern?

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Objective: To examine the incidence rate of breast cancer in a cohort of women undergoing treatment for infertility, comparing the rate in women who had in vitro fertilization (IVF) with those who did not.

Design: Population-based cohort study using linked hospital and registry data.

Setting: Hospital.

Patient(s): All women aged 20–44 years seeking hospital investigation and treatment for infertility in Western Australia during the period 1983–2002 (n = 21,025).

Intervention(s): None.

Main Outcome Measure(s): Hazard ratios (HRs) for breast cancer.

Result(s): There was no overall increase in the rate of breast cancer in women who had IVF (HR 1.10, 95% confidence interval [CI] 0.88–1.36), but there was an increased rate in women who commenced IVF at a young age. Women who commenced hospital infertility treatment at 24 years and required IVF had an unadjusted HR of breast cancer of 1.59 (95% CI 1.05–2.42) compared with women of the same age who had infertility treatment but no IVF. When adjusted for late age at first delivery, which is associated with an increased rate of breast cancer, and delivery of twins and higher-order multiples, which is associated with a decreased rate of breast cancer, the HR remained elevated at 1.56 (95% CI 1.01–2.40). Hazard ratios were not elevated in women who commenced treatment at age 40 and required IVF (adjusted HR 0.87, 95% CI 0.62–1.22).

Conclusion(s): Commencing IVF treatment at a young age is associated with an increased rate of breast cancer. (Fertil Steril® 2012;98:334–40. ©2012 by American Society for Reproductive Medicine.)

Key Words: In vitro fertilization, breast cancer, Cox regression, hazard ratios

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Reproductive hormones, particularly estrogen, have long been implicated in the development of breast cancer (1). Longer lifetime exposure to endogenous estrogen, with early menarche and late menopause, is associated with an increased risk of breast cancer (2), and oophorectomy is

associated with a decreased risk (3). Administration of exogenous estrogens in the form of the oral contraceptive pill and hormone replacement therapy increases risk (4, 5), whereas synthetic antiestrogens, such as tamoxifen, decrease risk (6). Higher circulating estrogen levels in postmenopausal

and possibly premenopausal women are linked to an increased risk of developing breast cancer (7, 8).

In vitro fertilization (IVF) is associated with a transient but significant elevation in circulating estrogen, with estrogen levels in an IVF cycle peaking at ~4,000 pg/mL (9), compared with 300 pg/mL in a normal menstrual cycle (10). Could this short-term elevation in estrogen levels, along with accompanying changes in other reproductive hormones, increase the risk of breast cancer in IVF patients? Only a few studies have specifically addressed this question, and the results and conclusions have been mixed.

Venn et al. (11, 12) compared the risk of breast cancer in women undergoing IVF with that in women seeking infertility treatment but not

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exposed to IVF, as well as with the general female population. They found no difference in breast cancer incidence among the three groups. Limitations of their studies included the relatively short periods of follow-up, with medians of ≤ 10 years and an inability to adjust for important breast cancer risk factors, including parity. Their results were confirmed in two later papers (13, 14), but these were based on only a few breast cancer cases ($n = 11$ and 4) and short periods of follow-up (mean follow-ups 3.6 and 6.5 years). In contrast, two other studies found a possible increase in the risk of breast cancer in those undergoing IVF, with those aged >40 years (15) and >30 years (16) at increased risk. In yet another contrast, three other studies (17–19) found a slight decrease in the risk of breast cancer in women who gave birth after IVF, compared with either the general population of women who gave birth or with women who gave birth but did not have IVF treatment.

In view of these inconsistencies, and because IVF is assuming a role of central importance in the treatment of infertility, we thought this question warranted further investigation. The aim of the present study was to examine the incidence rate of breast cancer in a large cohort of women undergoing investigation and treatment for infertility, comparing the rate in those exposed to IVF with those unexposed.

MATERIALS AND METHODS

Study Cohort

The study cohort comprised women undergoing hospital investigation or treatment for infertility in any hospital in Western Australia (WA) from 1983 to 2002. Women were included in the study cohort if they had a hospital diagnosis of either infertility (ICD-9 628.0–628.9 or ICD-10 N97.0–N97.9) or procreative management (ICD-9 V26.1–V26.9 or ICD-10 Z31.1–Z31.9). The cohort was restricted to women aged 20–44 years at their first infertility admission.

Women who had a diagnosis of breast cancer before their first infertility admission ($n = 13$) were excluded from the cohort, as were women who developed breast cancer within 6 months of their first infertility admission ($n = 5$).

Data Sources

This study made use of the resources of the WA Data Linkage System (20). Six separate data collections were accessed to extract the desired information. Women to be included in the cohort were identified from their hospital records; women undergoing IVF were identified from their hospital records or from the statutory Reproductive Technology Register, which has recorded all cycles for assisted reproductive technology in WA since 1993 as mandated by law. Breast cancer cases were identified from the WA Cancer Registry, births from the Midwives' Register, and deaths from the Deaths Register. The WA Electoral Roll was used to identify women who had moved interstate or overseas after 1988, when the first records became available. These women were excluded from the study population.

Data Analysis

Women were followed from their first hospital infertility admission to the censor date (August 15, 2010), date of

breast cancer diagnosis, or date of death, whichever came first.

Data were analyzed by Cox regression modeling with fixed and time-dependent covariates with the use of SPSS version 19.

Variables considered for inclusion in the regression model were IVF, birth classified according to age at first delivery, delivery of twins or higher-order multiples, age at entry to the cohort, and socioeconomic status. Each variable was first considered singly, in univariate analysis, then in a full model. The interaction between age and IVF was explored. The *P* value for the interaction term was estimated and the effect of IVF treatment at specific ages calculated using methods described by Hosmer, Lemeshow, and May (21). IVF was modeled as a time-dependent binary covariate to partition follow-up time accurately into time before and after IVF treatment.

Age at first delivery was ascertained by extracting each woman's first record from the Midwives' Register. Births that occurred either interstate, overseas, or before 1980 (when records commenced) were not included in the register, although the number of previous births was listed on each record. We found that in 88% of cases, the first birth record in the Midwives' Register was, in fact, the first delivery. For the remainder, we estimated the previous birth to be 2 years before the recorded birth, because in women with complete records, the median time from first to second birth was 33 months and the mode was 22 months. Women were grouped into 5-year age-at-first-birth categories. Women without a birth record on the Midwives' Register may still have delivered previously, either interstate, overseas, or before 1980, and could therefore not be classified as nulliparous in our analysis. This group was labeled as "no birth recorded."

The cohort included women with both primary and secondary infertility; i.e., a woman's first birth could occur either before or after the first infertility admission. Age group at first birth was entered in the model as a time-dependent covariate with time set at zero for women with secondary infertility and the appropriate number of days after the start of follow-up for women who delivered their first child after commencing infertility investigation.

Multiple delivery was entered into the model as a time-dependent binary variable.

Age at start of follow-up was initially included in the model as a continuous covariate. It was found to be linear in the log hazard, so no transformation was necessary. However, it did not satisfy the proportional hazards assumption, so two separate models were created. The first model was stratified by age; the second included the interaction between age and time. Both models produced essentially the same results, except that the age-stratified model was more precise with narrower confidence intervals. This is the model presented in the Results section.

Socioeconomic status at the date of first infertility diagnosis was estimated with the use of two separate indices: the Index of Economic Resources and the Index of Education and Occupation (22). Within the cohort, these indices were divided into quartiles and the upper quartile compared with the lower three quartiles. Each index was entered into separate models as a fixed binary covariate.

Institutional Review Board Approval

This study received Institutional Review Board approval from The University of Western Australia Human Research Ethics Committee and the Department of Health WA Human Research Ethics Committee.

RESULTS

Characteristics of the Study Cohort

The study cohort comprised 21,025 women in total, followed for a mean of 16 years (Table 1). Within the cohort, 7,381 women had IVF and 13,644 did not. The proportion of women undergoing IVF increased gradually over time: among women commencing hospital infertility treatment in 1983, 29% had IVF and 71% did not. Among women commencing infertility treatment in 2002, 32% had IVF and 68% did not. Within each age group, the relative proportions of women undergoing and not undergoing IVF remained reasonably constant, with the exception of women in the 40–44 years age group. In that age group, through 1983–1988 ~40% of the women had IVF, but in 1999–2002 the proportion increased to 51%. Women undergoing IVF were, on average, older at their first infertility diagnosis and delivered their first child at a later age. They were also more likely to be in the upper quartile of socioeconomic status, as measured by the Indices of Economic Resources and Education and Occupation. Not

surprisingly, women undergoing IVF were more likely to deliver twins and higher-order multiples (Table 1).

Some 384 women developed breast cancer after infertility treatment. Of these, 55 were classified as in situ breast carcinomas; 23 in women who had IVF and 32 in women who did not have IVF. The distribution of breast cancer diagnoses over follow-up time, separately for women who did and did not have IVF, is shown in Figure 1.

IVF

IVF was only weakly associated with breast cancer risk in univariate analysis, where the hazard ratio for IVF treatment compared with no IVF treatment was 1.22 (95% confidence interval [CI] 0.99–1.49). In the adjusted model, which was stratified by age group and adjusted for confounding by age at first birth and multiple delivery, the hazard ratio fell to 1.10 (95% CI 0.88–1.36; Table 2). Further examination suggested that the effect of IVF on the rate of breast cancer differed according to the age at which women commenced treatment (see subsequent section, Age-Specific Analysis).

Age at First Delivery

Later age at first delivery was associated with an increased breast cancer rate in univariate analysis and in the adjusted model (Table 2).

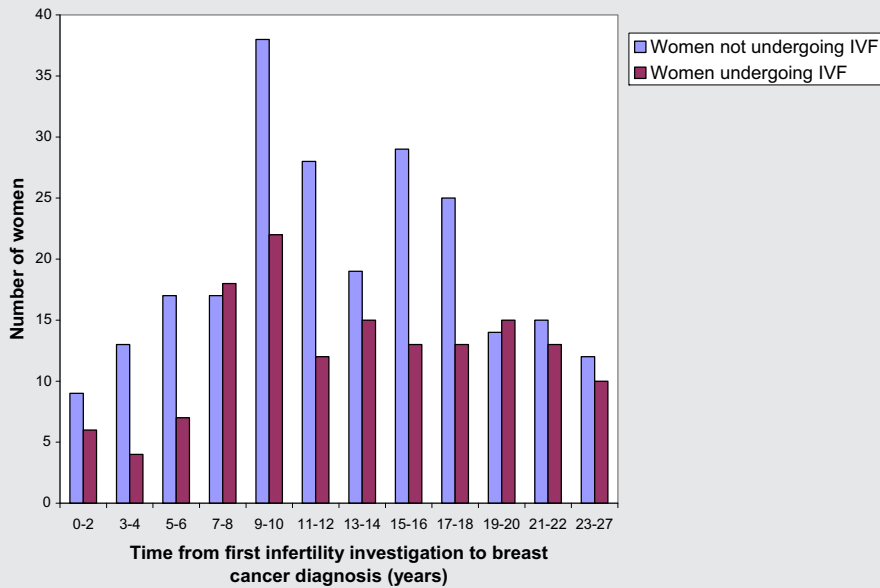
TABLE 1

Characteristics of the study cohort.

Characteristic	Women seeking infertility treatment but not undergoing IVF	Women seeking infertility treatment and undergoing IVF	All women seeking infertility treatment
No. of women	13,644	7,381	21,025
Mean length of follow-up (y)	16.4 ± 5.6	16.1 ± 5.6	16.3 ± 5.6
Mean length of follow-up for each age group (y)			
20–24	17.5 ± 5.7	17.9 ± 5.7	17.6 ± 5.7
25–29	17.2 ± 5.6	17.1 ± 5.5	17.2 ± 5.6
30–34	16.0 ± 5.5	16.2 ± 5.6	16.1 ± 5.5
35–39	15.5 ± 5.5	15.1 ± 5.6	15.3 ± 5.6
40–44	14.8 ± 5.1	14.4 ± 5.5	14.7 ± 5.3
Total person-years of follow-up	223,342	119,039	342,381
Median year of first infertility investigation	1993	1994	1993
No. of women with breast cancer (%)	236 (1.7)	148 (2.0)	384 (1.8)
Time from start of follow-up to breast cancer diagnosis (y, mean ± SD)			
Women aged ≥31 y at start	11.6 ± 5.7	12.1 ± 5.9	11.8 ± 5.8
Women aged <31 y at start	14.7 ± 5.9	16.2 ± 5.7	15.2 ± 5.8
Age quartiles at first infertility investigation (y)			
25 (Q1)	27	29	28
50 (Q2)	31	32	31
75 (Q3)	34	35	35
Mean age at first infertility investigation (y)	30.9 ± 5.3	32.1 ± 4.8	31.3 ± 5.1
Mean age at end of follow-up (y)	47.6 ± 7.0	48.6 ± 6.7	48.0 ± 6.9
Mean age at breast cancer diagnosis (y)	46.4 ± 7.0	47.1 ± 5.9	46.7 ± 6.6
Mean age at first delivery (y)	28.4 ± 5.9	32.2 ± 5.4	29.6 ± 6.0
No. of women with twin or higher-order multiple birth (%)	435 (3.2)	929 (12.6)	1,364 (6.5)
% of women in highest quartile of Index of Economic Resources	22	30	25
% of women in highest quartile of Index of Education and Occupation	21	31	24

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FIGURE 1



Time (years) from first hospital infertility admission to breast cancer diagnosis in women undergoing and not undergoing IVF.

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Multiple Delivery

The delivery of twins or higher-order multiples was suggestive of a reduced rate of breast cancer in univariate analysis and in the final model (Table 2).

Socioeconomic Status

We observed a slight association between socioeconomic status and breast cancer rate in univariate analysis with a hazard ratio of 1.21 (95% CI 0.97–1.52) for the Index of Economic Resources, and 1.22 for the Index of Education and Occupation (95% CI 0.97–1.52), comparing the highest quartile with the

other three. This association disappeared after stratification by age group. In the adjusted model, the hazard ratio for the Index of Economic Resources was 1.04 (95% CI 0.83–1.31); in a separate model, the hazard ratio for the Index of Education and Occupation was 0.97 (95% CI 0.78–1.22). Including or excluding either index in the adjusted model made no difference to the other variables in the model. Socioeconomic status was therefore not included in the final regression model.

Age-specific Analysis

This analysis showed that the effect of IVF on breast cancer rate differed according to the age of the woman at commencement of treatment. IVF treatment was associated with an increased rate of breast cancer in younger, but not older, patients (Table 3). After adjustment for potential confounders, the incidence rate ratio in women commencing infertility treatment at 24 years of age and requiring IVF was 1.56 times greater than in women of the same age not having IVF (95% CI 1.01–2.40; (Table 3). When potential confounders were not included in the regression model, the association appeared to be stronger (Table 3). When only age at first birth was included in the model, the association appeared to be weaker, and the precision fell below that required for statistical significance. For example, the subsequent breast cancer incidence rate in women requiring IVF at age 24 years was 1.47 times greater than in age-matched women not having IVF (95% CI 0.96–2.26) when the analysis was not adjusted for multiple delivery. This effect was not apparent in women who commenced IVF treatment later in life, with an adjusted hazard ratio of 0.87 (95% CI 0.62–1.22) in women commencing

TABLE 2

Hazard ratios for breast cancer in women undergoing infertility treatment.^a

Subgroup	Hazard ratio (95% CI)
IVF (no) (reference group)	1.00
IVF (yes)	1.10 (0.88–1.36)
Age <25 y at first delivery (reference group)	1.00
Age 25–29 y at first delivery	1.35 (0.86–2.13)
Age 30–34 y at first delivery	1.75 (1.13–2.72)
Age ≥ 35 y at first delivery	1.91 (1.20–3.03)
No birth recorded	1.16 (0.75–1.78)
No multiple birth (reference group)	1.00
Multiple birth	0.69 (0.41–1.16)

^a Cox regression model showing the effect of IVF treatment on breast cancer rate. Model is stratified into 5-year age groups and adjusted for confounding by age at first birth and the delivery of twins and higher-order multiples.

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TABLE 3

Age-specific estimates of the effect of IVF on breast cancer rate.^a

Age at start of infertility investigation (y)	Hazard ratio (95% CI) comparing breast cancer rate in women having IVF with women not having IVF		
	Unadjusted	Adjusted for confounding by age at first birth only	Adjusted for confounding by age at first birth and multiple delivery
20	1.86 (1.06–3.25)	1.69 (0.95–2.99)	1.80 (1.01–3.20)
24	1.59 (1.05–2.42)	1.47 (0.96–2.26)	1.56 (1.01–2.40)
28	1.36 (1.02–1.83)	1.29 (0.95–1.73)	1.34 (0.99–1.82)
32	1.17 (0.95–1.45)	1.12 (0.90–1.39)	1.16 (0.93–1.45)
36	1.00 (0.79–1.27)	0.98 (0.77–1.24)	1.00 (0.79–1.27)
40	0.86 (0.61–1.20)	0.85 (0.61–1.20)	0.87 (0.62–1.22)
44	0.74 (0.46–1.18)	0.74 (0.46–1.19)	0.75 (0.47–1.20)

^a Estimates derived from Cox regression models that include the interaction between IVF and age at the specific ages shown. The first column of results shows the unadjusted analysis; the second gives hazard ratios after adjusting for confounding by age at first birth only; and the final model in the third column of results shows hazard ratios after adjusting for age at first birth and multiple birth.

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infertility treatment at age 40 years and having IVF compared with women of the same age not having IVF.

DISCUSSION

Overall, IVF was not associated with an increased risk of breast cancer in this research. However, this overall result obscured the underlying age-related connection between IVF treatment and breast cancer. There was an increased rate of breast cancer in women who commenced IVF at a young age, but no positive association between IVF and breast cancer in those who delayed treatment. Women who commenced infertility treatment at 24 years of age and had IVF had an adjusted estimated relative risk of breast cancer of 1.56 (95% CI 1.01–2.40) compared with women of the same age who had infertility treatment but no IVF, whereas women who commenced IVF at age 40 years had no increased risk (hazard ratio 0.87, 95% CI 0.62–1.22).

Is this a causal relationship, or could these results be explained by confounding and bias? We attempted to minimize confounding in this study, first, in the study design by making comparisons within a cohort of women seeking infertility treatment, rather than comparing IVF patients with the general population, and second, in the analysis by adjusting for important known confounders, including age and age at first birth. Nevertheless, residual confounding was still a possibility. We had no information on other known breast cancer risk factors, including family history, mutations in *BRCA1* and *BRCA2* genes, age at menarche, age at menopause, breastfeeding history, breast density, use of oral contraceptives, and hormone replacement therapy (23). Even so, to explain the observed effect, these confounders would have to have been much more prevalent in young but not older women undergoing IVF.

A limitation of our study was our inability to include types or doses of fertility drugs in the analysis, because this information was unavailable. Some of the women in our study who did not have IVF may still have undergone ovarian stimulation; however, the levels of estrogens developed in such treatment would have been of an order of magnitude less than in women who underwent IVF.

Apart from random error, which would have tended to bias the estimate toward the null, we have no reason to suspect that exposure status (IVF) was misclassified. Misclassification of outcome (breast cancer) could have occurred if there was differential loss to follow-up. Interstate migration from WA is low (24), and we attempted to limit loss to follow-up further by excluding all women with either an out-of-state address on their hospital records or a movement off the Electoral Roll. Nevertheless, some of the women in our cohort may have moved out of the state, and if this happened to a greater extent in young women who did not have IVF, then we would have underestimated their rate of breast cancer and consequently overestimated the relative risk in young women who had IVF. Surveillance bias was a possible explanation if women who had IVF underwent more screening with consequent earlier detection. If this was the case, we would have expected more cases of in situ breast carcinoma in women undergoing IVF than in those not undergoing IVF. However, we did not find this. Of the seven cases of in situ breast carcinoma in women who commenced infertility treatment in their twenties, two were in women who had IVF and five in women who did not, providing some evidence in support of the assertion that the results were not due to surveillance bias.

We made a number of other salient observations in this study. The first was to confirm the well known association between age at first delivery and breast cancer risk (25). We observed an almost twofold increase in the rate of breast cancer in women who delivered their first baby when they were ≥ 35 years, compared with women who delivered before their 25th birthday. The second observation was not as well known. We found, in agreement with some (26–28), but not others (29, 30), that the delivery of twins or higher-order multiples was suggestive of a reduced breast cancer risk. Our third observation was that, contrary to most (but not all) earlier studies (31), we found no association between socioeconomic status and breast cancer risk. However, this may have been due to misclassification. Our measures of socioeconomic status were based, not on the individual, but rather the area in which she lived. Where possible, we used the estimate that was based on the

smallest residential area: ~200 households. However, where this was unavailable (in 54% of the cohort), we used a larger aggregate based on postal area. It is possible that this introduced a level of misclassification that may have diluted any real association (32).

The mean duration of follow-up in the younger members of our cohort (those <31 years old at their first infertility admission) was 17.5 years (95% CI 17.4–17.6), compared with 15.9 years (95% CI 15.8–16.0) in those ≥31 years old at the start ($P<.001$). Longer follow-up of the older members of our cohort could see an increased breast cancer rate in this subgroup with, as a consequence, similar hazard ratios for younger and older women. In contrast, given that the mean age at the end of follow-up was 44.3 years (95% CI 44.2–44.4) for women who commenced infertility treatment at a young age, and 51.1 years (95% CI 50.0–51.2) for those ≥31 years old at their first infertility investigation, extended follow-up could see heightened rates of breast cancer in the younger women who are then at the age at which the risk of breast cancer continues to climb. The mean age at breast cancer diagnosis in this study was 47 years, with most cancers (73% of the total) diagnosed in women aged ≤50 years. With longer follow-up there may also be a different mix of premenopausal and postmenopausal breast cancers and estrogen receptor-positive and -negative breast cancers (33) with consequently different estimates of the effects of risk factors (34).

This study could be extended to investigate the relationship between IVF “dose” and breast cancer rate. Whether the best measure of dose would be the total number of cycles or the number of egg collection cycles (where hormone exposure is greater) would need to be determined. The total number of cycles in our cohort is low, with 50% of women having only one or two cycles (35). A suitable study population would be one in which women undergo a greater range of cycles, thus enabling an accurate estimate of the effect of the number of fresh and frozen embryo replacement cycles on breast cancer rate.

The results of this study will be reassuring to women who commence IVF treatment in their thirties and forties, because for these women, there appears to be no direct association between IVF treatment and breast cancer risk. Nevertheless, women should be aware that delivering their first child late in reproductive life, whether assisted by IVF or not, is associated with an increased risk of breast cancer. For younger women there is some cause for concern, because it appears that they may face an increased risk of breast cancer after IVF treatment. If the veracity of this result stands up to critical review and confirmation, it will be an important part of the process of informed consent for younger women commencing IVF to appreciate the trade-off in lifetime objectives and risks that they may face.

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