ORIGINAL INVESTIGATION

A Prospective Study of Infertility Due to Ovulatory Disorders, Ovulation Induction, and Incidence of Breast Cancer

Kathryn L. Terry, ScD; Walter C. Willett, MD, DrPH; Janet W. Rich-Edwards, ScD, MPH; Karin B. Michels, ScD, PhD

Background: Anovulation has been hypothesized to decrease the risk of breast cancer. Therefore, infertility attributed to ovulatory disorders and ovulation-induction therapy may influence breast cancer risk.

Methods: We analyzed prospectively collected data from the Nurses' Health Study II, a cohort of 116 671 female registered nurses aged 25 to 42 years at baseline. Information on infertility was assessed every 2 years starting in 1989, ovulation induction was assessed every 2 years from 1993 to 1997, and incident cases of breast cancer were included through 2001.

Results: During 1 275 566 person-years of follow-up (1989-2001), 1357 incident cases of invasive breast cancer were diagnosed. Overall, women who reported infertility due to ovulatory disorder had a significantly lower incidence of breast cancer than women who did not report problems conceiving during a 12-month period (covariate-adjusted hazard ratio, 0.75; 95% confidence interval, 0.59-0.96). The incidence of breast cancer was lowest among women with infertility due to ovulatory disorder who received ovulation-induction therapy (covariate-adjusted hazard ratio, 0.60; 95% confidence interval, 0.42-0.85).

Conclusions: Among women who participated in the Nurses' Health Study II, we observed an inverse association between infertility due to ovulatory disorder and breast cancer incidence. We observed the greatest reduction in the incidence of breast cancer for women who reported ovulatory disorder and use of ovulation-induction therapy, but these results should be interpreted with caution because these women may be the most infertile.

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Author Affiliations:
Departments of Epidemiology (Drs Terry, Willett, and Rich-Edwards) and Nutrition (Dr Willett), Harvard School of Public Health, Boston, Mass; Channing Laboratory, Department of Medicine (Drs Terry, Rich-Edwards, and Michels), and Obstetrics and Gynecology Epidemiology Center (Drs Terry and Michels), Brigham and Women's Hospital and Harvard Medical School, Boston; and Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Care and Harvard Medical School (Dr Rich-Edwards).

EPIDEMIOLOGIC STUDIES HAVE consistently found an association between the timing of menarche and menopause and the risk of breast cancer.[1] These events affect the number of lifetime ovulatory cycles and consequently influence exposure to ovarian hormones. Thus, fewer lifetime ovulatory cycles might reduce breast cancer risk.[2,3]

Estrogen levels increase rapidly before ovulation, remaining elevated throughout the luteal phase, whereas progesterone levels are low before ovulation and elevated during the luteal phase.[4] Cycles lacking ovulation skip the luteal phase completely. Women with infertility due to ovulatory disorder have fewer ovulatory cycles than do fertile women and therefore a lower lifetime exposure to luteal-phase hormones.

In 1977, two groups found significantly greater breast cell proliferation during the luteal phase than during the follicular phase.[5,6] Subsequent epidemiologic evidence indicated that exogenous estrogen plus progestin increases breast cancer risk beyond that of estrogen alone.[7,8] However, these studies were restricted to postmenopausal women; whether these combinations have a similar influence on premenopausal breast cancer risk is not known. Because women with anovulatory cycles have a lower lifetime exposure to luteal-phase hormones, women with infertility due to ovulatory disorders may have a lower breast cancer risk.

Earlier studies suggest an inverse association between infertility due to ovulatory disorders and breast cancer risk,[9-16] but results are inconsistent across studies and often limited by small samples. Ovulation-induction therapy, particularly long-term use, has been implicated in ovarian cancer risk.[17,18] However, these findings were based on a few cases and have not been substantiated in more recent cohorts.[16,19,20] Regardless, the safety of ovulation induction remains a concern, particularly in light of trends in de-

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layed childbearing and increased use of infertility treatments.[21-23]

We hypothesized that ovulatory disorders may decrease and ovulation induction may increase breast cancer risk, given their association with lifetime number of ovulatory cycles. Our group previously reported reduced breast cancer risk among premenopausal women with infertility due to ovulatory disorder in this cohort based on limited follow-up.[13] Herein we provide an updated analysis, with almost 5 times the number of cases of breast cancer (both premenopausal and postmenopausal), and an evaluation of infertility treatments.

METHODS

POPULATION

In 1989, 116 671 female registered nurses aged 25 to 42 years living in 14 US states responded to a baseline questionnaire about their medical histories and lifestyles. Those reporting cancer at enrollment (not including nonmelanoma skin cancer) were excluded. Follow-up questionnaires have been sent biennially to update information on risk factors and medical events. Follow-up exceeds 90%. This study was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard School of Public Health.

ASSESSMENT OF INFERTILITY AND OVULATION-INDUCTION THERAPY

Infertility status was assessed at baseline and on every subsequent questionnaire. Participants were asked whether they had tried to get pregnant for 1 year without success. If they answered yes, they were asked for the cause(s) (tubal blockage, ovulatory disorder, endometriosis, cervical mucus factors, factors related to their spouse, no investigation done, cause not found, or other). Because ovulatory disorder is often discovered when a couple is trying to conceive, we considered a woman reporting infertility due to ovulatory disorder to be infertile due to ovulatory disorder throughout follow-up unless she reported a pregnancy or infertility due to another cause before reporting ovulatory infertility. Women who reported ovulatory infertility but later became pregnant were still classified as infertile due to ovulatory disorder.

All participants were asked in the 1993, 1995, and 1997 questionnaires whether they had ever taken drugs to induce ovulation. If any participant failed to respond to this question, we assumed she had not taken ovulation-induction drugs. If she answered yes, we considered her as having used ovulation induction at least once during follow-up. Women who reported ovulation-induction therapy were asked what drug they had used (clomiphene citrate [Clomid] or menotropins [Pergonal/Metrodin]) and the duration (0, 1, 2-3, 4-5, 6-11, or ≥12 months).

Self-reported infertility was validated with 100 randomly selected women who reported primary infertility.[24] Ninety women responded to the supplementary questionnaire on infertility diagnosis and treatment; of these, 84 (93%) reported a confirmatory diagnostic test (abnormal basal body temperature chart, progesterone assay, endometrial biopsy, or other confirmatory test) or treatment (clomiphene, menotropins, human chorionic gonadotropin, or other confirmatory treatment). Of 40 medical records obtained for these women, 38 (95%) confirmed the infertility diagnosis by a diagnostic test or treatment.

Exposure to potential confounding variables was measured at baseline and during follow-up. Participants were asked their date of birth, age at menarche, family history of breast cancer (in mother, sister, or grandmother), weight at age 18 years, and height at baseline. Weight, history of benign breast disease, parity, age at first birth, alcohol intake, oral contraceptive use, and physical activity were assessed on baseline and subsequent questionnaires. Data were updated using subsequent questionnaires for each individual in each period.

DOCUMENTATION OF BREAST CANCER

New cases of breast cancer were identified through biennial questionnaires mailed between 1991 and 2001. Deaths were reported by family members or the US Postal Service in response to the follow-up questionnaires, and the National Death Index was searched to investigate deaths of nonresponders. Following a report of breast cancer, we asked the participant (or next of kin for those who had died) for confirmation of the diagnosis and permission to obtain relevant medical records. These were obtained for 90% of cases. Pathology reports confirmed breast cancer in 99% of women whose reports were reviewed. Cases of carcinoma in situ were censored at diagnosis.

STATISTICAL ANALYSIS

Analyses of infertility included follow-up from baseline (1989) through 2001. Women were excluded at baseline if they were ineligible (n=1), had been diagnosed as having breast cancer (n=16), had a history of another type of cancer (n=1047), or did not report their height (n=239) or weight (n=100). Analyses, including information on ovulation induction, included follow-up starting in 1993, when we first asked about ovulation induction, through 2001. Analyses on ovulation induction excluded women who had died by 1993 (n=123), had been diagnosed as having breast cancer by 1993 (n=342), had been diagnosed as having another type of cancer (n=1848), or did not report their height (n=232) or weight (n=45). We also excluded women who did not meet our criterion for infertility but reported ovulation-induction therapy because their fertility status was unclear (n=1095).

Women were censored during follow-up when they reported having developed cancer (breast or other), failed to report their weight in 3 or more questionnaires, or had an unclear fertility status. Women who did not respond to the full questionnaire in a particular cycle had an opportunity to answer an abridged questionnaire, which did not include questions regarding ovulation induction. Therefore, women who had never answered a full questionnaire did not contribute person-time to the analyses evaluating ovulation induction but were entered into the analysis in future cycles if they subsequently answered the full questionnaire.

Each participant contributed follow-up time, measured in months, from return of the 1989 questionnaire until breast cancer diagnosis, death, return of the 2001 questionnaire, or the last returned questionnaire. Analyses including ovulation induction were restricted to follow-up between 1993, when first assessed, and 2001.

We used Cox proportional hazards regression models to estimate the hazard ratio (HR) of breast cancer while controlling for potential confounding variables (SAS, version 8.2; SAS Institute Inc, Cary, NC). Covariate-adjusted models included age in months, family history of breast cancer (yes or no), history of benign breast disease (yes or no), height (continuous), current body mass index (calculated as weight in kilograms divided by the square of height in meters, continuous), body mass index at age 18 years (continuous), age at menarche (≤10, 11,

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Table 1. Association Between Infertility Due to Ovulatory Disorder and Breast Cancer Incidence, Nurses' Health Study II, 1989-2001

Infertility	No. of Cases	Follow-up, Person-years*	HR (95% CI) Age-Adjusted	HR (95% CI) Covariate-Adjusted†
All breast cancers				
No reported infertility	1167	1 054 220	1.00	1.00
Infertile due to ovulatory disorder	69	87 458	0.76 (0.60-0.98)	0.75 (0.59-0.96)
Infertile due to other reason	40	41 509	1.13 (0.82-1.56)	1.05 (0.76-1.45)
Estrogen receptor–positive analysis				
No reported infertility	678	1 053 655	1.00	1.00
Infertile due to ovulatory disorder	40	87 424	0.78 (0.56-1.07)	0.77 (0.56-1.06)
Infertile due to other reason	25	41 492	1.26 (0.84-1.89)	1.18 (0.78-1.77)
Estrogen receptor–negative analysis				
No reported infertility	278	1 053 190	1.00	1.00
Infertile due to ovulatory disorder	11	87 395	0.49 (0.27-0.90)	0.47 (0.26-0.87)
Infertile due to other reason	9	41 471	1.01 (0.52-1.97)	0.99 (0.50-1.95)

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Cases with other or unknown receptor status were excluded from estrogen receptor–positive and estrogen receptor–negative analyses.
†Adjusted for age, height, current body mass index, body mass index at age 18 years, family history of breast cancer, history of benign breast disease, age at menarche, parity, age at first birth, oral contraceptive use, alcohol use, and physical activity.

12, 13, 14, or ≥15 years), parity (0, 1, 2, 3, or ≥4 live births), age at first birth (≤24, 25-30, or >30 years), oral contraceptive use (ever used or never used), alcohol intake (0, <7.5, or ≥7.5 g/d), and physical activity (<3, 3-8, 9-17, 18-26, 27-41, or ≥42 metabolic equivalents per week). Trend tests used the midpoint of the intervals. We examined whether the association between infertility and breast cancer varied by menopausal status and parity and tested for significant interactions using Wald tests.

We used polychotomous logistic regression with 3 outcome categories (estrogen receptor [ER]–positive, ER-negative, and no breast cancer) to evaluate whether associations differed by tumor ER status. We used likelihood ratio tests to compare a model with different slopes for each outcome to one with a common slope and χ^2 tests to obtain 2-sided *P* values for the likelihood ratio statistics.[25]

RESULTS

During 1 275 566 person-years of follow-up between 1989 and 2001, 1357 incident cases of invasive breast cancer developed (1125 in premenopausal women, 126 in postmenopausal women, and 106 in women of unknown menopausal status). At baseline, 5798 prevalent cases of infertility due to ovulatory disorder were reported and, throughout the follow-up, 2392 incident cases of infertility due to ovulatory disorder were reported.

Breast cancer incidence was significantly lower in women who reported infertility due to ovulatory disorder than in women who did not report infertility, but infertility for other reasons was not related to breast cancer incidence. A separate evaluation by ER status resulted in a stronger inverse association between infertility due to ovulatory disorder and breast cancer among ER-negative cases (**Table 1**), but the fit was not significantly better for the model evaluating ER-positive and ER-negative breast cancer separately than for the model with a single outcome (*P*=.10 for heterogeneity).

More than half of the women reporting infertility due to ovulatory disorder also reported ovulation-induction therapy. Breast cancer incidence was 40% lower for women with infertility due to ovulatory disorder who used ovulation-induction therapy than for women with no reported infertility, whereas women with infertility due to ovulatory disorder who did not have ovulation induction had a nonsignificant increase in risk (**Table 2**); these estimates differed significantly (*P*=.002 for heterogeneity).

We observed no overall association between clomiphene use and breast cancer risk (covariate-adjusted HR, 0.87; 95% confidence interval [CI], 0.70-1.10). An analysis restricted to women with infertility due to ovulatory disorder noted a significant reduction in breast cancer incidence with clomiphene use (covariate-adjusted HR, 0.42; 95% CI, 0.25-0.73), with the strongest risk reduction among women who took clomiphene for more than 10 months (**Table 3**). We observed no association between clomiphene use and breast cancer risk among women with other types of infertility (data not shown).

In additional analyses stratifying our population by parity, we observed no differences in the association between infertility due to ovulatory disorder and breast cancer among parous (covariate-adjusted HR, 0.77; 95% CI, 0.58-1.02) and nulliparous (covariate-adjusted HR, 0.76; 95% CI, 0.46-1.25) women and no difference in the association when we restricted the analysis to premenopausal women (data not shown).

COMMENT

These prospective data from the Nurses' Health Study II suggest an inverse association between breast cancer and infertility due to ovulatory disorder but not other forms of infertility. This association may be restricted to ER-negative tumors. These results suggest that ovulation induction with clomiphene does not increase breast cancer incidence.

Earlier studies[9-11,15,16,26-31] have generally demonstrated no significant association between infertility and

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Table 2. Association Between Infertility Due to Ovulatory Disorder With and Without Ovulation-Induction Therapy and Breast Cancer Incidence, Nurses' Health Study II, 1993-2001*

Infertility	No. of Cases	Follow-up, Person-years	HR (95% CI)	
			Age-Adjusted	Covariate-Adjusted†
No reported infertility	932	661 080	1.00	1.00
Ovulatory infertility, no ovulation induction	29	14 159	1.41 (0.97-2.04)	1.37 (0.94-1.99)
Ovulatory infertility with ovulation induction	32	41 559	0.62 (0.43-0.88)	0.60 (0.42-0.85)
Other type of infertility	10	15 413	0.71 (0.38-1.33)	0.67 (0.35-1.25)

Abbreviations: CI, confidence interval; HR, hazard ratio.
*These analyses begin in 1993 because participants in the Nurses' Health Study II were first asked about ovulation induction on the 1993 questionnaire.
†Adjusted for age, height, current body mass index, body mass index at age 18 years, family history of breast cancer, history of benign breast disease, age at menarche, parity, age at first birth, oral contraceptive use, alcohol use, and physical activity.

breast cancer risk. However, a recent cohort study[32] that included more than 12 000 infertile women reported a significant increase in breast cancer incidence associated with infertility, and other studies[13,14,16] have observed associations with specific categories of infertility. Discrepancies in these study results may be explained in part by differences in study designs, study populations, or type of infertility considered.

Some previous cohort studies lacked the statistical power to detect a significant association because they had a limited number of cases and were unable to adjust for important breast cancer risk factors such as parity and age at first birth. Studies unable to control for these factors may capture the overall association between infertility and breast cancer but are unable to assess the association between infertility and breast cancer risk independent of these risk factors. Studies not adjusting for parity and age at first birth observed either no association[9,16,30,31] or a slight increase[10,11,27-29,32] in breast cancer risk associated with infertility. Because infertile women probably have fewer children and are older at first birth than fertile women, confounding by these factors is likely.

We hypothesized that a reduction in ovulations may reduce breast cancer risk; therefore, we separated women who reported infertility due to ovulatory disorder from other infertile women. Most studies evaluating women with this type of infertility, described as anovulation, hormonal infertility, or ovarian defects, reported no association with breast cancer risk.[10-12,16,31,32] Moseson et al[14] reported a significant increase in breast cancer risk with recurrent amenorrhea; however, recruitment of participants from a breast cancer screening clinic may limit the applicability of their results to other populations. Two other groups[13,15] observed an inverse association between infertility due to ovulatory disorder and breast cancer risk; however, their reference group included women with other forms of infertility, making it difficult to determine whether the association was attributable to a reduced risk with ovulatory disorders or an increased risk with other types of infertility.

Most infertile women pursue infertility treatment; thus, determining whether an observed association is attributable to infertility or treatment is difficult. Many cohorts assembled to evaluate infertility are identified through infertility clinics; therefore, most, if not all, participants were seeking infertility treatment.[9,11,15,27,30-32] Our study has the advantage of following up a large group of women identified for other purposes. However, separating the independent effects of infertility and infertility treatment remains challenging because duration of fertility treatment may be linked to severity of infertility. Women who do not become pregnant after a single cycle of fertility drugs are likely to receive additional cycles; therefore, women with the longest exposure to fertility drugs may have the most severe infertility.

Table 3. Association Between Lifetime Clomiphene Exposure and Breast Cancer Incidence Among Women With Ovulatory Infertility, Nurses' Health Study II, 1993-2001

Clomiphene Citrate Use, mo	No. of Cases	Follow-up, Person-years	Covariate-Adjusted HR (95% CI)*
Never†	29	17 693	1.00
<2.5	12	12 116	0.47 (0.23-0.97)
2.5-5	6	7425	0.46 (0.18-1.15)
6-10	10	10 239	0.49 (0.22-1.06)
>10	4	9405	0.25 (0.09-0.75)
P for trend			.02

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Adjusted for age, height, current body mass index, body mass index at age 18 years, family history of breast cancer, history of benign breast disease, age at menarche, parity, age at first birth, oral contraceptive use, alcohol use, and physical activity.
†Never users are those who used clomiphene less than 1 month or never.

Use of ovulation induction drugs, the most common infertility treatment,[33] has increased dramatically in recent years,[22] as has concern about possible risks associated with these treatments.[34] Previous studies of infertility treatment and breast cancer risk are difficult to compare because of differences in reference populations. Some used the general population as a reference group[11,16,28,29,31,35,36] while others used untreated infertile women for comparison.[13,15,27,31,32] In all but one[31] of the earlier cohort studies, no significant association between ovulation induction and breast cancer risk was reported,* perhaps owing in part to a lack of statistical power.

Lerner-Geva and colleagues[31] observed a higher breast cancer incidence among infertile women who received

**References 11, 15, 16, 27, 29, 30, 32, 35-37.*

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clomiphene than among infertile women who did not receive ovulation induction. However, this association was restricted to infertile women who did not appear to have ovulatory disorders and may represent a unique group (ie, a group resistant to other infertility treatments). Consequently, the increased risk in this group may be attributable to the severity of its members' infertility rather than to clomiphene treatment. The authors observed no association between clomiphene use and breast cancer incidence among women with ovulatory disorders.

Brinton and colleagues[32] reported an increased risk of invasive breast cancer among infertile women who received clomiphene more than 20 years previously (relative risk, 1.6; 95% CI, 1.0-2.5), suggesting that breast cancer risk increases with time since clomiphene use. In the Nurses' Health Study II population, we could not assess the influence of time since clomiphene use because our initial question about ovulation induction was "have you ever used" ovulation-induction therapy without requesting the specific time.

Clomiphene, a selective estrogen receptor modulator, increases or decreases estrogenic effects mediated through the estrogen receptor, depending on the tissue. In the hypothalamus, clomiphene blocks the estrogen receptor, increasing gonadotropin secretion from the pituitary gland and ultimately increasing ovulation.[38] Clomiphene elevates both estradiol and progesterone levels, which may increase breast cell proliferation; therefore, an inverse association between clomiphene and breast cancer may seem counterintuitive.[26] However, clomiphene inhibits cellular proliferation in the mammary glands of rats[39] and growth in breast cancer cell lines,[40,41] suggesting that clomiphene may have a role in treating breast cancer. A small clinical trial performed more than 30 years ago showed remission in 20 of 51 patients with advanced breast cancer treated with clomiphene,[42] and a closely related antiestrogen (tamoxifen citrate) is an established adjuvant therapy for breast cancer.[43,44]

Limitations of our study include the potential for misclassification of infertility. However, a validation study showed a high concordance between self-reported infertility and infertility confirmed by diagnostic testing or treatment.[24] Some exposure information is recalled, but these data were collected before breast cancer diagnosis. Consequently, differential reporting based on disease status is unlikely.

Limited follow-up is another study limitation, particularly for those analyses including assessment of ovulation-induction therapy. To preserve our study's prospective nature, we were only able to evaluate the association between ovulation-induction therapy and breast cancer using cases occurring in the questionnaire cycles that followed the initial collection of the data on ovulation induction in 1993. Therefore, only cases occurring between 1995 and 2001 were included in these analyses.

Strengths of our study include its large size, prospective design, updated follow-up information, and detailed data on many relevant covariates, which allowed us to adjust for important reproductive risk factors. We also were able to compare, in the same population, breast cancer rates between infertile women and women without a history of infertility. In our study, differential access to health care, which influences whether a woman is diagnosed and treated for infertility, was not a problem because all participants were nurses and presumably had access to health care through their profession.

In conclusion, our data suggest an inverse association between infertility due to ovulatory disorder and breast cancer incidence and no increase in breast cancer incidence with ovulation induction. Further research is needed to delineate the separate associations between infertility and ovulation induction with breast cancer risk.

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Correspondence: Kathryn L. Terry, ScD, Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, 221 Longwood Ave, Boston, MA 02115 (kterry@hsph.harvard.edu).
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