

# Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study

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**Objective:** To determine the association between infertility drug use and invasive breast cancer in a population-based case-control study.

**Design:** Multicenter case-control study.

**Setting:** Women aged 35 to 64 years in metropolitan Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle.

**Patient(s):** The 4,575 case patients had histologically confirmed primary invasive breast cancer. The 4,682 control subjects were women without breast cancer identified in the same geographic locations using randomized-digit dialing.

**Intervention(s):** A standardized questionnaire focusing on reproductive health and family history as well as use of oral contraceptives and other hormones and infertility drugs was administered to all subjects. Data on the type of breast cancer were also obtained.

**Main Outcome Measure(s):** Odds ratios examining the association between use of various infertility drugs and invasive breast cancer.

**Result(s):** Overall, a history of infertility drug use was not associated with the risk of developing breast cancer. Compared with women who never used any fertility medication, however, women using human menopausal gonadotropin (hMG) for ≥6 months or for at least six cycles had a relative risk of breast cancer ranging between 2.7 to 3.8.

**Conclusion(s):** Long-term use of certain infertility drugs could adversely affect risk of breast cancer. Additional confirmatory studies are needed. (*Fertil Steril*® 2003;79:844-51. ©2003 by American Society for Reproductive Medicine.)

**Key Words:** Breast cancer, infertility, infertility drugs, human menopausal gonadotropins (hMG)

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Because of the concern that most women have regarding breast cancer, investigators are continuing their efforts to identify risk factors for the disease, especially those that are potentially modifiable. Toward this end, the relationship between exogenous reproductive hormones and breast cancer has been widely studied (1-3). Other factors, such as menstrual cycle characteristics and infertility, including various treatment approaches, have also been examined with varying results (4-14). Some studies indicate that increased numbers of ovulatory menstrual cycles may increase the risk of breast cancer (15). This is supported by find-

Received July 2, 2002; revised and accepted September 24, 2002. Supported by contracts from the Contraception and Reproductive Health Branch, Center for Population Research, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland (contracts N01 HD 3-3168, N01 HD 2-3166, N01 HD 3-3174, N01 HD 3-3176, and N01 HD 3-3175), an intraagency agreement with the Centers for Disease Control and Prevention (contract Y01 HD-7022), and through additional support by the Surveillance, Epidemiology, and End Results Programs (SEER; contracts N01 CN-0532, N01 CN-65064, N01 PC-57010, and N01 PC-67006). Use of brand names is for identification only and does not imply endorsement by the National Institutes of Health, Centers for Disease Control and Prevention, or the United States Department of Health and Human Services.

No reprints will be available.

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0015-0282/03/\$30.00  
 doi:10.1016/S0015-0282(02)04950-6

ings that elevated risk of breast cancer is associated with early menarche and late menopause, occurrences that probably increase the lifetime number of ovulatory menstrual cycles (5). In addition, studies indicate that peak mitotic activity occurs in breast cells during the luteal phase of the menstrual cycle (16). Thus, increasing the number of ovulatory cycles would extend periods of increased mitotic activity in the breast.

Women with infertility due at least in part to ovulatory dysfunction may undergo various drug treatments that stimulate ovulation and alter levels of endogenous reproductive hormones. Although some prior studies failed to demonstrate an association between pharmacologic therapy for infertility and breast cancer risk (10, 12, 17), others have shown an association (6, 8, 18). As part of a multicenter, population-based, case-control study, the National Institute of Child Health and Human Development (NICHD) Women's Contraceptive and Reproductive Experiences (CARE) Study, we elected to analyze the relationship between use of various drug therapies for infertility treatment and the risk of breast cancer.

## MATERIALS AND METHODS

The design and conduct of this study have been presented in detail elsewhere (19). The study was conducted in five geographic regions: Atlanta, Detroit, Philadelphia, and Seattle, as well as Los Angeles County. The protocol was approved by institutional review boards at the field centers and by a Data Coordinating Center at the Centers for Disease Control and Prevention, Atlanta, Georgia. Case patients were women newly diagnosed with breast cancer between July 1994 and April 1998. Except for Philadelphia, where case patients were identified by field staff, case patients were ascertained by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry program using rapid-reporting systems. Younger case subjects and black women who were cases or controls were oversampled to achieve a more uniform distribution across six age groups and the two race groups.

Eligibility criteria for cases included the following: age 35 to 64 years; presence of histologically confirmed, primary invasive breast cancer with no prior invasive or in situ breast cancer history; US birth with residence at date of diagnosis in a study region; white or black race (including Hispanic ethnicity); a working telephone at the individual's residence at date of diagnosis; ability to be interviewed in English; and physical and mental capability to undergo the interview process. Other than the case-defining event (invasive breast cancer), eligibility criteria for cases and controls were identical. Controls were identified from the same counties as were the cases, through random-digit dialing using unclustered sampling, with automated elimination of nonworking numbers. Control subject selection rates were designed to

match case interview frequencies within the strata of study center, race, and age group. Interviews were completed on 4,575 of 5,982 eligible cases (76.5%) and 4,682 of 5,956 controls (78.6%).

All study subjects were interviewed in person using a detailed questionnaire. Sections dealing with hormone use were modeled after instruments used in prior studies to obtain detailed histories on use of oral contraceptives, hormone replacement therapy, and other hormones. The questionnaire also obtained detailed information on demographics; pregnancy and reproductive history; exercise, health, and family history of cancer; smoking and alcohol use; and other factors. In addition, we collected information on history of infertility and infertility drug use.

Women were asked if they had ever visited a doctor, clinic, or hospital because of a problem becoming pregnant, or to seek help in becoming pregnant. For women who reported that they had sought medical help for becoming pregnant, information was collected on whether they or their partner had tests performed for possible infertility, on the causes of the infertility, on whether they had been prescribed infertility drugs, and on the types and duration of use of such drugs if prescribed. Information on use of IVF or GIFT techniques was also obtained. The interviews were conducted in a standardized manner using extensively trained interviewers. Data on tumor characteristics including International Classification of Disease for Oncology (ICD-O) codes, histologic type, extent of disease, laterality, and estrogen and progesterone receptor status were collected on cases.

## Data Analysis

A multiple logistic regression model was used to determine odds ratios (ORs) and confidence intervals (CI) as estimates of relative risks for breast cancer associated with infertility drug use (20). Analyses involved adjustment for age (in 5-year age groups), race (white, black), and study site (5 study sites). The reference date for analyses was the date of breast cancer diagnosis for cases and the date of telephone screening for controls. Evaluation by a health professional was required for a subject to be defined as being infertile. Women were considered to have been diagnosed with infertility if they reported having had testing because of a problem becoming pregnant and if these tests detected a probable cause. The causes included the following: problems with cervical mucus; other abnormalities of the cervix, uterus, fallopian tubes, or ovaries; endometriosis; and endocrinological dysfunction. Variables including first-degree family history of breast cancer, body mass index, age at first full-term pregnancy (>26 weeks of gestation), age at menarche, smoking status, alcohol consumption, screening mammogram in the past 2 years, income, education, and use of oral contraceptives and hormone replacement therapy did not change the OR by  $\geq 10\%$  and therefore were not included in the regression models.

TABLE 1

Characteristics of cases and controls.

Characteristic	Case (n = 4,575)		Controls (n = 4,682)	
	No.	% <sup>a</sup>	No.	% <sup>a</sup>
Age (y)				
35–39	689	15.1	666	14.2
40–44	758	16.6	832	17.8
45–49	782	17.1	857	18.3
50–54	844	18.5	825	17.6
55–59	770	16.8	801	17.1
60–64	732	16.0	701	15.0
Race				
White	2,953	64.5	3,021	64.5
Black	1,622	35.5	1,661	35.5
Study site				
Atlanta	881	19.3	895	19.1
Detroit	679	14.8	779	16.6
Los Angeles County	1,242	27.2	1,255	26.8
Philadelphia	707	15.5	736	15.7
Seattle	1,066	23.3	1,017	21.7
Education				
Less than high school	399	8.7	444	9.5
High school	1,335	29.2	1,350	28.8
Some college	1,483	32.4	1,495	31.9
College graduated	1,357	29.7	1,393	29.8
Income (\$)				
<10,000	424	9.6	397	8.7
10,000–<20,000	437	9.9	472	10.4
20,000–<35,000	891	20.1	925	20.3
35,000–<50,000	807	18.3	789	17.3
≥50,000	1,864	42.1	1,978	43.4
Smoking status				
Never	2,095	45.8	2,104	45.0
Former	1,498	32.8	1,469	31.4
Current	980	21.4	1,107	23.7
Alcohol use (number of drinks per week at reference age minus 2 y)				
None	2,529	55.4	2,682	57.4
1–6	1,498	32.8	1,522	32.6
≥7	536	11.8	472	10.1
Body mass index at reference date minus 5 y (kg/m <sup>2</sup> )				
9–19	314	6.9	364	7.8
20	352	7.7	305	6.5
21–22	895	19.7	864	18.5
23–24	829	18.2	800	17.2
25–26	594	13.1	578	12.4
27–29	715	15.7	779	16.7
30–33	452	9.9	514	11.0
34–60	398	8.8	457	9.8
Age at menarche (y)				
<12	1,197	26.2	1,262	27.0
12–13	2,528	55.4	2,464	52.7
>13	840	18.4	950	20.3
Number of full-term pregnancies				
0	890	19.5	805	17.2
1	770	16.8	717	15.3
2	1,371	30.0	1,355	29.0
≥3	1,541	33.7	1,796	38.4
Age at first full-term pregnancy (y)				

**TABLE 1. Continued.**

Characteristic	Case (n = 4,575)		Controls (n = 4,682)	
	No.	% <sup>a</sup>	No.	% <sup>a</sup>
Never had full-term pregnancy	890	19.5	805	17.2
<20	1,046	22.9	1,191	25.5
20–24	1,368	29.9	1,461	31.3
25–29	777	17.0	718	15.4
≥30	492	10.8	497	10.6
Menopausal status				
Premenopausal	2,116	52.4	2,061	50.4
Postmenopausal	1,924	47.6	2,029	49.6
Use of oral contraceptives				
Never	1,042	22.8	990	21.2
<6 mo	512	11.2	508	10.9
6 mo–<5 y	1,488	32.6	1,612	34.5
≥5 y	1,525	33.4	1,566	33.5
Use of hormone replacement therapy				
Never	2,387	62.1	2,749	58.7
<6 mo	318	7.0	388	8.3
6 mo–<5 y	610	13.3	716	15.3
≥5 y	807	17.7	827	17.7
Screening mammogram in 24 mo preceding reference date				
No	1,751	38.3	2,043	43.6
Yes	2,824	61.7	2,639	56.4
First-degree family history of breast cancer <sup>b</sup>				
No	3,616	82.3	4,050	89.9
Yes	778	17.7	453	10.1
Sought care for fertility problem				
Never sought care	3,993	87.4	4,064	86.8
Medical care sought, no testing <sup>c</sup>	160	3.5	185	4.0
Medical care sought, testing done <sup>c</sup>	416	9.1	432	9.2
Identified causes of female infertility <sup>d</sup>				
No cause identified	179	43.0	158	36.6
Diagnosed with female infertility	229	55.0	269	62.3
Cervical mucous	16	3.8	17	3.9
Tubal problem	96	23.1	106	24.5
Ovulatory problem	49	11.8	67	15.5
Endocrine problem	31	7.5	43	10.0
Uterus problem	43	10.3	51	11.8
Endometriosis	39	9.4	61	14.1
Other	6	1.4	10	2.3

<sup>a</sup> Percentages calculated with nonmissing values.

<sup>b</sup> First-degree family history in mother, full sister, or daughter.

<sup>c</sup> Indicates whether women received test for fertility problem.

<sup>d</sup> Among women who were tested for infertility problem; some women were diagnosed with more than one infertility problem. For cases, n = 416; for controls, n = 467.

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We examined whether there was an association between infertility drug use and risk of breast cancer. We also examined whether any association of infertility history or infertility drug use and breast cancer varied by the total duration or actual cycles (usually treatment within a 1-month interval) of each infertility drug use. In addition, we evaluated the possible modification of any association between breast cancer and infertility medication by histologic type (ductal vs.

lobular), menopausal status, parity, and family history of breast cancer.

## RESULTS

When compared with controls, women with breast cancer were more likely to have had fewer full-term pregnancies, their first full-term pregnancy at a later age, an earlier men-

arche, and a family history of breast cancer (Table 1). Among 1,193 women who ever sought medical care for help becoming pregnant (576 cases and 617 controls), 71% (416 cases and 432 controls) had been tested for infertility, and 42% (229 cases and 269 controls) reported that a cause for their infertility had been identified. Three hundred thirty-seven women (179 cases and 158 controls) had had infertility testing, but no specific etiology had been identified. A total of 184 cases (4.0%) and 200 controls (4.3%) reported ever using infertility drugs (Table 2). This included 79 cases and 82 controls who, based on our definition of infertility, were never diagnosed with infertility but were prescribed infertility drugs.

Overall, as shown in Table 2, women who had ever used infertility drugs had the same risk of breast cancer as did women who had never used such medication (OR, 0.9; 95% CI, 0.8–1.2). Among women who had been diagnosed with infertility, use of infertility drugs was not associated with an overall increase in risk of breast cancer (OR, 1.2; 95% CI, 0.8–1.7). The OR did not vary substantially according to age at first fertility drug use.

Within subgroups of women who used specific types of fertility drugs, an association was observed among women who had used hMG (Pergonal; Serono Laboratories, Inc., Norwell, MA) for  $\geq 6$  months or for at least six treatment cycles (for all women:  $\geq 6$  months of use, OR, 2.1; 95% CI, 1.0–4.4;  $\geq 6$  cycles of use, OR, 2.7; 95% CI, 1.0–6.9; for women with an infertility diagnosis:  $\geq 6$  months of use, OR, 2.8; 95% CI, 1.1–6.8;  $\geq 6$  cycles of use, OR, 3.8; 95% CI, 1.2–11.8). There was a suggestion of increased risk of breast cancer for women with a prior diagnosis of infertility who had used clomiphene citrate (Clomid; Aventis Pharmaceutical Company, Bridgewater, NJ) for  $< 6$  months or for fewer than six treatment cycles (OR, 1.7; 95% CI, 0.9–3.2 and OR, 1.7; 95% CI, 0.9–3.0, respectively).

Overall, a history of taking infertility drugs was not associated with an increased risk of either invasive ductal or invasive lobular breast cancer. However, compared with the case of women who had never taken any infertility medication, a greater risk of ductal carcinoma appeared to be associated with use of hMG (OR, 1.6; 95% CI, 1.0–2.7; Table 3). Further, results were similar in strata of menopausal status, parity, and family history of breast cancer (data not shown).

## DISCUSSION

Overall, a history of infertility drug use was not associated with an increased risk of breast cancer. However, our study, based on a small number of women, did suggest that women who used hMG for  $\geq 6$  months or who used hMG for at least six treatment cycles had a risk of breast cancer that was two to three times greater than that of other women.

These results should be interpreted with caution. The particular strengths of the Women's CARE study include the

population-based case and control ascertainment through the SEER registries, and detailed data on a large number of potential variables and effect modifiers. However, there are weaknesses that pertain to the current analysis. The number of women reporting a history of infertility treatment including use of infertility drugs was small. The Women's CARE study was not primarily designed to extensively evaluate the association between infertility or use of fertility drugs and breast cancer. The study, except for the breast cancer case ascertainment, did not survey or verify information from medical records. Finally, as is true in many case-control studies, recall bias potentially could influence the risk estimates.

Another potential problem in our analysis is the difficulty of distinguishing the effect of infertility from that of treatment for infertility. Among women who never used infertility medications, we found no association between a history of infertility and risk of breast cancer (OR, 0.9; 95% CI, 0.7–1.1; adjusted for age, race, and study site). To eliminate the potential role of infertility, the analysis was confined to women who had been diagnosed with a specific infertility problem. The latter analysis was limited by the small number of women remaining after exclusion of 337 women with no specific infertility diagnosis. The results, however, were similar if the analyses included these 337 women in the infertility group. Among 384 women who used infertility drugs, 108 women (59 cases and 49 controls) had used two or more types of infertility medications. For these women, the main effect of each type of infertility drug may be difficult to differentiate. When we restricted our analyses to women using only one infertility drug, the results were not statistically significant because of small numbers of women.

Other investigators have evaluated the relationship between use of fertility drugs and breast cancer with mixed results. Brzezinski et al. (18) identified 16 women in their center in Israel between 1982 and 1991 who were treated with either clomiphene citrate alone (2 cases) or in combination with hMG (14 cases) and who subsequently were diagnosed with breast cancer. Of interest to the current study is that 12 of the 14 women undergoing treatment with hMG had been treated for at least six cycles, with a mean number of treatment cycles of 12.7. On the basis of an age-adjusted estimate of expected cases of breast cancer using data from the Israel Cancer Registry, they noted that the observed rate of breast cancer in these women was about double that of the general population. However, this study is limited by the small number of cases and the use of a historical cohort design.

Braga and co-workers (4) conducted a case-control study of breast cancer and potential risk factors in Italian women, and detected an OR of 1.43 (95% CI, 0.9–2.3) for breast cancer in women who received drug therapy for infertility compared with women who had never received such treatment. However, this study was hampered by the small num-

TABLE 2

## Risk of breast cancer and use of fertility medications.

Characteristics	All women			Women diagnosed with infertility		
	Cases (n = 4,566), N (%)	Controls (n = 4,676), N (%)	OR <sup>a</sup> (95% CI)	Cases (n = 227), N (%)	Controls (n = 266), N (%)	OR <sup>a</sup> (95% CI)
Fertility drug use						
Never	4,382 (96.0)	4,476 (95.7)	1.0	121 (53.3)	145 (54.5)	1.0
Ever	184 (4.0)	200 (4.3)	0.9 (0.8–1.2)	106 (46.7)	121 (45.5)	1.2 (0.8–1.7)
Duration of use						
<6 mo	74 (1.6)	77 (1.7)	1.0 (0.7–1.4)	31 (13.7)	34 (12.8)	1.2 (0.7–2.2)
≥6 mo	110 (2.4)	121 (2.6)	0.9 (0.7–1.2)	75 (33.0)	86 (32.5)	1.2 (0.8–1.8)
Cycles of use (n)						
<6	79 (1.7)	88 (1.9)	0.9 (0.7–1.3)	34 (15.5)	44 (17.2)	1.1 (0.6–1.9)
≥6	96 (2.1)	100 (2.1)	1.0 (0.7–1.3)	65 (30.0)	67 (26.2)	1.4 (0.9–2.2)
Age at first use (y)						
<30	89 (2.0)	105 (2.3)	0.9 (0.7–1.2)	51 (22.5)	58 (21.9)	1.2 (0.8–2.0)
≥30	94 (2.1)	93 (2.0)	1.0 (0.8–1.4)	55 (24.2)	62 (23.4)	1.2 (0.7–1.9)
Type of fertility drug <sup>b</sup>						
hCG	23 (0.5)	21 (0.5)	1.2 (0.6–2.1)	15 (6.6)	16 (6.0)	1.5 (0.7–3.4)
Duration of use (mo)						
<6	11 (0.3)	11 (0.2)	1.1 (0.5–2.5)	7 (3.1)	9 (3.4)	1.8 (0.6–5.4)
≥6	11 (0.3)	9 (0.2)	1.3 (0.5–3.0)	8 (3.6)	6 (2.3)	2.2 (0.7–7.0)
Cycles of use (n)						
<6	13 (0.3)	15 (0.3)	0.9 (0.4–1.9)	9 (4.0)	11 (4.1)	1.8 (0.7–4.8)
≥6	9 (0.2)	6 (0.1)	1.5 (0.5–4.3)	6 (2.6)	5 (1.9)	2.0 (0.5–7.3)
Clomiphene citrate	141 (3.1)	145 (3.1)	1.0 (0.8–1.3)	85 (37.4)	91 (34.2)	1.4 (0.9–2.1)
Duration of use (mo)						
<6	58 (1.3)	56 (1.2)	1.1 (0.7–1.5)	29 (12.8)	27 (10.2)	1.7 (0.9–3.2)
≥6	83 (1.8)	87 (1.9)	1.0 (0.7–1.3)	56 (24.7)	63 (23.7)	1.3 (0.8–2.2)
Cycles of use (n)						
<6	69 (1.5)	67 (1.4)	1.1 (0.8–1.5)	37 (16.3)	36 (13.5)	1.7 (0.9–3.0)
≥6	69 (1.5)	75 (1.6)	1.0 (0.7–1.3)	45 (19.8)	53 (19.9)	1.2 (0.7–2.0)
hMG	38 (0.8)	28 (0.6)	1.5 (0.9–2.4)	25 (11.0)	24 (9.0)	1.7 (0.9–3.3)
Duration of use (mo)						
<6	16 (0.4)	17 (0.4)	1.0 (0.5–2.0)	8 (3.5)	14 (5.3)	1.2 (0.5–3.3)
≥6	22 (0.5)	11 (0.2)	2.1 (1.0–4.4) <sup>b</sup>	17 (7.5)	10 (3.8)	2.8 (1.1–6.8) <sup>b</sup>
Cycles of use (n)						
<6	22 (0.5)	19 (0.4)	1.2 (0.7–2.3)	13 (5.7)	15 (5.6)	1.7 (0.7–4.1)
≥6	15 (0.3)	6 (0.1)	2.7 (1.0–6.9) <sup>b</sup>	11 (4.8)	6 (2.3)	3.8 (1.2–11.8) <sup>b</sup>
Other fertility drug <sup>c</sup>	18 (0.4)	25 (0.5)	0.8 (0.4–1.4)	16 (7.1)	17 (6.4)	1.5 (0.7–3.3)
Duration of use (mo)						
<6	7 (0.2)	15 (0.3)	0.5 (0.2–1.2)	6 (2.6)	9 (3.4)	1.5 (0.5–4.7)
≥6	11 (0.2)	9 (0.2)	1.3 (0.5–3.1)	10 (4.4)	7 (2.6)	2.4 (0.8–7.0)
Cycles of use (n)						
<6	10 (0.2)	18 (0.4)	0.6 (0.3–1.3)	9 (0.4)	12 (4.5)	1.5 (0.6–4.1)
≥6	7 (0.2)	7 (0.2)	1.1 (0.4–3.0)	6 (2.6)	5 (1.9)	2.0 (0.5–7.2)
Other hormones <sup>d</sup>	34 (0.7)	36 (0.8)	1.0 (0.6–1.5)	22 (9.7)	22 (8.3)	1.2 (0.6–2.4)
Duration of use (mo)						
<6	13 (0.3)	18 (0.4)	0.7 (0.4–1.5)	8 (3.5)	8 (3.0)	0.9 (0.3–2.7)
≥6	21 (0.5)	18 (0.4)	1.2 (0.6–2.3)	14 (6.2)	14 (1.5)	1.4 (0.6–3.3)
Cycles of use (n)						
<6	13 (0.3)	19 (0.4)	0.7 (0.3–1.4)	9 (4.0)	9 (3.4)	1.1 (0.4–3.0)
≥6	18 (0.4)	14 (0.3)	1.3 (0.7–2.7)	12 (5.2)	10 (3.8)	1.9 (0.7–4.9)

Note: Excludes women with unknown history of fertility drug use. Data missing for women who cannot recall the duration/actual cycles of use.

<sup>a</sup> Odds ratio was relative to never taking any fertility medication; adjusted for age, race, and study site.

<sup>b</sup> The confidence interval does not include 1.0.

<sup>c</sup> Includes Danazol, Lupron Depot, Metrodin, and so on.

<sup>d</sup> Includes hormonal contraceptives and other hormones for infertility treatment.

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TABLE 3

Risk of invasive breast cancer in relation to fertility medication use, according to histologic type.

Characteristics	Controls (n = 4,676)		Ductal (n = 3,456)			Lobular (n = 274)			Other (n = 836)		
	N	%	N	%	OR (95% CI) <sup>a</sup>	N	%	OR (95% CI) <sup>b</sup>	N	%	OR (95% CI) <sup>a</sup>
Fertility drug treatment											
Never	4,472	95.6	3,311	95.8	1.0	263	96.0	1.0	807	96.5	1.0
Ever	204	4.4	145	4.2	1.0 (0.8–1.2)	11	4.0	1.0 (0.5–1.9)	29	3.5	0.8 (0.5–1.2)
Type of fertility drug											
HCG	21	0.5	21	0.6	1.4 (0.7–2.5)	1	0.4	1.1 (0.1–8.0)	1	0.1	0.3 (0.1–2.0)
Clomiphene citrate	145	3.1	113	3.3	1.0 (0.8–1.3)	6	2.2	1.0 (0.4–2.5)	22	2.6	0.9 (0.6–1.4)
hMG	28	0.6	32	0.9	1.6 (1.0–2.7) <sup>b</sup>	1	0.4	0.8 (0.1–6.1)	5	0.6	1.0 (0.4–2.6)
Other fertility drug <sup>c</sup>	25	0.5	18	0.5	1.0 (0.5–1.8)	0	0.0	—	0	0.0	—
Other hormone <sup>d</sup>	36	0.8	27	0.8	1.0 (0.6–1.7)	4	1.5	1.6 (0.6–4.7)	3	0.4	0.5 (0.1–1.5)

Note: Excludes women with unknown history of fertility drug use. The tumors were grouped into their histologic types: [1] ductal, ICD-O code 8500; [2] lobular, ICD-O code 8520, or mixed lobular, ICD-O code 8522; and [3] other specific histologies including papillary, ICD-O code 8050, 8260, or 5603; tubular, ICD-O 8211; mucinous, ICD-O 8480 or 8481; and medullary, ICD-O 8510 or 8512.

<sup>a</sup> In each histologic group, odds ratio was relative to never taking any fertility drug; adjusted for age, race, and study site.

<sup>b</sup> The confidence interval does not include 1.0.

<sup>c</sup> Includes Danazol, Lupron Depot, Metrodin, and so on.

<sup>d</sup> Includes hormonal contraceptives and other hormones used for infertility treatment.

Burkman. Infertility drugs and breast cancer risk. *Fertil Steril* 2003.

ber of subjects with a history of infertility. Potashnik et al. (8) also evaluated the role of fertility drugs using a historical cohort design among 1,197 women receiving infertility treatment in Israel between 1960 and 1984. When compared with the expected rate of breast cancer in the Israel Cancer Registry, the standardized incidence ratio for breast cancer was increased only in patients undergoing one or two clomiphene citrate cycles (relative risk, 2.6; 95% CI, 1.2–5.0) and a total dose of the drug of  $\leq 1,000$  mg (relative risk, 2.5; 95% CI, 1.2–4.6). Of the 780 women receiving fertility drug therapy, only 177 received hMG in some form. Further, because only 16 cases of breast cancer occurred in the 780 women undergoing fertility drug therapy, one must be cautious about attributing too much significance to the results of this study.

Other studies have failed to show an association between fertility drug treatment and breast cancer. Ron and co-workers (10) evaluated the incidence of breast and female reproductive cancers through 1981 in a cohort of 2,632 Israeli women treated for infertility between 1964 and 1974. Although they observed an excess of breast cancer cases in their cohort compared with that expected using data from the Israel Cancer Registry, the increase did not achieve statistical significance. Further, use of hMG or clomiphene citrate alone or in combination did not affect this risk. However, these authors reported no data regarding the number of treatment cycles or duration of treatment.

Modan et al. (7) continued follow-up of this same cohort through 1991. Again, no association was reported between use of clomiphene citrate or hMG and breast cancer, and

whether duration effects were examined is unclear. Finally, in a case-control study of breast cancer in the greater Milan, Italy area that was conducted between 1983 and 1991, no association between fertility drug therapy and breast cancer was found (9). However, the total number of cases and controls in the analysis relating to fertility drug use was small.

When Rossing and colleagues (11) compared the number of breast cancer cases in 3,837 women treated for infertility in Seattle, Washington to that expected from population-based data, they did not detect an elevated risk for breast cancer. In fact, the investigators found that the risk of breast cancer was reduced (adjusted relative risk, 0.5; 95% CI 0.2–1.2) among users of clomiphene citrate, compared with women who had not used the drug, although this result was not statistically significant. Because only 4.4% of women in this study had been exposed to hMG and the overall number of women receiving infertility drug treatment was low, the role of hMG in modifying the risk of breast cancer could not be adequately evaluated.

The potential mechanisms for the associations observed in the current study are unclear. Fertility drugs have varying effects on hormonal output. The drug hMG consists of a mixture of follicle-stimulating hormone and luteinizing hormone. Through stimulation of the ovary, the medication produces plasma estradiol levels of 1,000 to 1,500 pg/mL daily and midluteal phase plasma progesterone levels of around 29 ng/mL (21, 22). In comparison, during natural menstrual cycles, peak estradiol levels infrequently exceed

600 pg/mL, whereas luteal phase progesterone levels usually do not rise above 20 ng/mL (23). Thus, hMG may mediate risk of breast cancer through its effects on either of these two hormones. Although estrogen is reasonably accepted as a promoter of breast cell proliferation and the development and growth of some forms of breast cancer, the role of progesterone is still being debated (24). Clomiphene citrate structurally resembles selective estrogen receptor modulators such as tamoxifen and thus, its use potentially could reduce breast cancer risk. However, the potential increased risk of breast cancer among women with a prior history of infertility using clomiphene citrate for a short duration in the current study appears in conflict with this possible mechanism. Because these effects were observed in women with a prior history of infertility, the possibility of some predisposition to breast cancer when such women are exposed to certain types of fertility medications must also be considered. Regardless of the potential mechanism or interactions, additional larger studies evaluating the association between breast cancer and infertile women using various types of fertility medications are needed to either confirm or refute the findings in this study.

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