Original Study

Breast Cancer and Ovulation Induction Treatments

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Abstract

In this case control study of 928 women with breast cancer and 928 controls, we found no statistically significant relationship between infertility and ovulation induction drugs with the risk of breast cancer development, except for significant increases in the risk of breast cancer among patients who had used human menopausal gonadotropin for >6 months.

Background: This study was performed to determine whether the use of ovulation induction drugs in treatment of infertility have a significant effect on the risk of breast cancer. **Patients and Methods:** This case control study (928 cases, 928 controls), was performed in the gynecology and oncology clinics of Shahid Beheshti University of Medical Sciences between 2011 and 2013. Data were collected via in-person interviews using a questionnaire, which included demographic and gynecologic information. Statistical analysis was performed using SPSS statistics software version 20 (IBM Corp). **Results:** The use of ovulation induction drugs was not significantly associated with an increased risk of breast cancer (odds ratio [OR], 1.13; 95% confidence interval [CI], 0.7-1.855) among women with infertility (OR, 1.28; 95% CI, 0.8-1.95). **Conclusion:** We observed no statistically significant relationship between infertility and ovulation induction drugs with the risk of breast cancer, except for significant increases in the risk of breast cancer among patients who had used fertility drugs for >6 months.

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Introduction

Currently cancer prevention is an important subject and many studies have been performed in this regard.[1-4] Breast cancer is the most common and lethal malignancy among women and the fifth leading cause of women's death in Iran. In the fact sheet N°334 published by the World Health Organization regarding women's health (updated in September 2013), breast cancer is 1 of 7 important key facts.[5]

Hormones play a significant role in the etiology of breast cancer. Documented risk factors of breast cancer, such as late age at first birth, early menarche, late menopause, and long-term hormone therapy, are related to the duration of exposure to progesterone and estrogen and have been widely studied.[6-10] Experimentally, it has been shown that ovarian hormones play a role in the development of breast cancer.[11,12] In contrast, much less is known about the influence of hormonal fertility drugs on the risk of breast cancer. Existing information about the relationship between infertility treatment and the risk of breast cancer is inconsistent. Several studies have investigated the possibility of an association between infertility, fertility treatments, and the risk of breast cancer,[13-15] and some have reported a small increase in the risk of breast cancer associated with the use of ovulation induction drugs.[16,17] However, some other studies have found no association between any fertility treatment and breast cancer risk,[7-10,18-24] and even in 1 study infertility treatment was associated with a significant decrease in the risk of breast cancer.[13]

The use of fertility drugs has held an important place in infertility treatment during the past 35 years, with a large and constantly growing number of women seeking advice for infertility treatment.[25] Approximately 7.4 million American women have used infertility treatments between 2004 and 2010.[26] Considering the increased incidence of breast cancer around the world, determining whether the use of fertility drugs increases the risk of breast cancer is a matter of great public health concern. In this study, we performed a case control comparison to evaluate the effect of ovulation induction drugs on the risk of breast cancer.

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Patients and Methods

The present study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences and all participants gave informed consent before entering the study. The data used in the present study were collected between 2011 and 2013 in Tehran province, Iran. Study subjects included patients who were referred to the clinic of radio-oncotherapy with the diagnosis of breast cancer in teaching and general hospitals of the Shahid Beheshti University of Medical Sciences. Trained interviewers identified and questioned these women. Eligible cases were women with histopathologically confirmed breast cancer diagnosed within 1 year preceding the interview. A total of 928 women (range, 25-81 years) were admitted during this period. The controls included 928 women (range, 19-86 years), residing in the same area, who had been admitted in the same hospitals where cases were identified because of diseases other than malignant conditions and had no history of malignancy or chronic disease. A structured questionnaire was used to obtain data regarding personal characteristics and menstrual habits, reproductive factors, infertility history, and related use of fertility drugs. All logistic statistical analysis was performed using SPSS statistics software version 20 (IBM Corp). Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were computed and P values $< .05$ were considered statistically significant.

Results

Because of the sampling strategy, there were no significant differences in demographic variables between the case and control groups. The demographic information related to the case and control groups is shown in Table 1. We compared other influent factors on breast cancer (such as: body mass index, number of full-term pregnancies, age at first full-term pregnancy, hormone replacement therapy and oral contraceptive pills consumption) and did not find significant statistical differences between cases and controls. Only the age at menarche was significantly different between the case and control groups (OR, 0.51; 95% CI, 0.38-0.70; $P < .001$). The average age of menarche was 12.93 ± 0.66 years in the control group and 12.57 ± 0.63 years in the case group. Also, positive history of breast cancer showed a significant difference between cases and controls (OR, 1.5; 95% CI, 1.1-1.9; $P < .003$; Table 1).

We examined the association between infertility and the use of any fertility drugs and subsequent risk of breast cancer and compared 928 cases with a mean age of 50.7 ± 9.6 years and 928 controls with a mean age 48.35 ± 9.15 years. There was no statistically significant increase in the risk of breast cancer due to ovulation induction drugs. The OR for ever using fertility drugs was 1.1 (95% CI, 0.7-1.8).

A total of 52 cases (5.6%) and 41 controls (4.4%) reported a history of infertility. Compared with women with no history of infertility, the OR of breast cancer was 1.28 (95% CI, 0.8-1.95). Thirty-five cases (3.8%) and 31 controls (3.3%) reported a history of the use of fertility drugs. The corresponding OR was 1.13 (95% CI, 0.7-1.85).

The use of fertility drugs, and association between the risk of breast cancer and induction drugs usage is shown in Table 2. In total there were 93 infertile women in the case and control groups and 32.7% of infertile cases and 31.7% of infertile controls did not use any fertility drugs and treatment.

We did not find any significant difference regarding the risk of breast cancer between cases and controls, when the period of infertility treatment with ovulation induction drugs was < 6 months, but there was a statistically significant increased risk of breast cancer among women who received ovulation induction treatment for > 6 months. Also, a history of human menopausal gonadotropin (hMG) treatment in the case group showed a statistically significant relation with increased risk of breast cancer compared with controls (OR, 2.25; 95% CI, 1-5; $P < .05$).

The most frequently used fertility drugs among infertile cases were hMG (40%) and clomiphene citrate (25%). In contrast, the most frequently used fertility drugs in infertile controls were clomiphene citrate (67%) and hMG (18%). Twenty-nine infertile cases (83%) and only 14 infertile controls (45%) used more than 6 months of ovulation induction drugs. The association between the risk of breast cancer and months of usage of any form of ovulation induction drugs is shown in Table 2. The prevalence of different types of breast cancer among all studied patients and infertile women are presented in Table 3.

Discussion

In general, on the basis of the results of the present study, the average age of menarche was significantly lower among the patients in the case group (12.93 years for controls and 12.57 years for cases, $P < .001$), which is in agreement with the previously known risk and protective factors for breast cancer. The other risk factor that was significantly different between the groups was the positive family history of breast cancer. We did not find any other significant difference regarding other known risk factors for breast cancer in our studied population. Some of it, such as body mass index might be justified by the retrospective method of the study (this factor might have changed during the time). Also similar to other retrospective studies, the recall bias might significantly affect our data regarding the risk factors for breast cancer in this study. However, our results indicated that treatment with ovulation induction drugs is not related to breast cancer risk, a result that is in line with the main findings from most previous studies.[13,16,18,20] As an exception, more than 6 months of fertility treatment especially with hMG was associated with a higher risk of breast cancer.

The mechanism for an association between ovulation induction drugs and breast cancer is not completely clear. Gonadotropins do not have direct influence on breast, but might increase the estrogen levels during the follicular phase of ovulation induction cycles. Combined with a high progesterone level resulting from the simultaneous ovulation of multiple follicles, this might expose infertile women to an environment that favors the development of breast cancer.[15] We found a higher risk of breast cancer in association with the use of hMG for > 6 months. The total cumulative dose of hMG prescribed to studied women during their course of infertility treatment is unknown. Sufficient information about possible in vitro fertilization (IVF) treatment protocols for the infertile cases is also unavailable. Our findings were in line with results from a study on 9257 women by Burkman et al,[27] who reported an increased risk of breast cancer after the use of hMG for

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Table 1 Demographic Findings of Patients in the Case and Control Groups

Characteristics	Case (n = 928)		Control (n = 928)		P[a]
	No	%[b]	No	%[b]	
Education					>.05
Less than high school	530	57.1	634	68.3	
High school	338	36.4	262	28.2	
College graduated	60	6.5	32	3.4	
Body Mass Index					>.05
<20	11	1.2	17	1.8	
20-24	219	23.6	196	21.1	
25-29	397	42.8	417	44.9	
≤30	338	36.4	298	32.1	
Age at Menarche, Years					<.001
<12	153	19.74	86	9.27	
≥12	775	83.51	842	90.73	
Number of Full-Term Pregnancies					>.05
0	98	10.6	109	11.7	
1	94	10.1	129	13.9	
2	252	27.2	281	30.3	
≥3	484	52.2	409	44.1	
Age at First Full-Term Pregnancy, Years					>.05
Never	98	10.6	109	11.7	
<20	365	39.4	354	38.2	
20-24	276	29.7	287	30.9	
25-29	131	14.1	125	13.5	
30-34	44	4.7	42	4.5	
≥35	14	1.5	11	1.2	
Menopausal Status					>.05
Premenopausal	316	34.1	443	47.7	
Postmenopausal	612	65.9	485	52.3	
OCPs Consumption					>.05
Never	377	40.6	422	45.5	
1-6 months	217	23.4	235	25.3	
6 months to 5 years	214	23.1	151	16.3	
>5 years	120	12.9	120	12.9	
HRT Consumption					>.05
Never	888	95.7	889	95.8	
1-6 months	17	1.8	16	1.7	
6 months to 5 years	21	2.3	21	2.3	
>5 years	2	0.2	2	0.2	
Screening Mammogram in 24 Months Preceding Reference Date					>.05
No	160	17.2	413	44.5	
Yes	768	82.7	515	55.5	
First-Degree Family History of Breast Cancer[c]					<.003
No	770	83	815	87.8	
Yes	158	17	113	12.2	

Abbreviations: HRT = hormone replacement therapy; OCP = oral contraceptive pills.
[a] *P* value < .05 is significant.
[b] Percentages calculated with nonmissing values.
[c] First-degree family history in mother, full sister, or daughter.

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Table 2 Risk of Breast Cancer and the Use of Fertility Medications

Characteristic	Cases (n = 928)		Controls (n = 928)		OR[a] (95% CI)	P[b]
	n	%	n	%		
History of Infertility	52	5.6	41	4.4	1.28 (0.8-1.95)	>.05
Fertility Drug Use	35	3.8	31	3.3	1.13 (0.7-1.85)	>.05
Duration of Use						
<6 Months	6	0.6	14	1.5	0.4 (0.16-1.1)	>.05
>6 Months	29	3.1	17	1.8	1.7 (0.9-3.1)	.02
Type of Fertility Drug						
hCG and clomiphene citrate	3	0.3	3	0.3	1 (0.2-4.96)	>.05
Clomiphene citrate	19	2	23	2.5	0.8 (0.45-1.5)	>.05
Human menopausal gonadotropin	20	2.2	9	1	2.25 (1-5)	.03
Letrozole	6	0.6	7	0.8	0.86 (0.3-2.5)	>.05

[a]Odds ratio was relative to never taking any fertility medication; adjusted for age, race, and study site.
[b]*P* value < .05 is significant.

> 6 months (OR, 2.1; 95% CI, 1-4.4), and no effect for a history of infertility on the risk of breast cancer. However, this finding might indicate that hMG causes a greater breast cancer risk among infertile women compared with fertile women. Whether the seemingly greater risk of breast cancer observed in infertile women is due to a shared genetic susceptibility to breast cancer as well as infertility, or a special biological susceptibility when exposed to fertility drugs is not yet understood, and this subgroup finding will require assessment in future investigations. The relatively low number of the case group who used hMG for > 6 months in our study did not allow us to perform a subgroup statistical analysis. However, it should be noted it is possible that women who required long-term hMG treatment could have been older, more obese, nulligravid, and have other chronic illnesses, which are all possible multiple confounding factors for breast cancer, which were not investigated in this study.

As a weakness of our study, we did not evaluate the estrogen/progesterone receptor status in our breast cancer cases. The records were not available for all patients. Future studies should focus on hormone responsiveness of breast cancer patients with a history of hMG consumption for infertility treatment. Evaluating BReast CAncer gene (BRCA1) and BRCA2 mutations in breast cancer patients with a history of infertility treatment would also be of great clinical value. Kotsopoulos and colleagues published the results of their well performed matched case-control study of 1380 pairs of women with BRCA1 or BRCA2 mutations to determine if a history of infertility, fertility medications, or IVF were associated with, and increased the risk of breast cancer, which revealed no difference, even in higher-risk women.[28]

Clomiphene citrate is structurally similar to tamoxifen, which have been used in the treatment of breast cancer, and could therefore potentially reduce the risk of breast cancer.

However our findings, in line with most previous studies, showed no support for the supposed preventive effect of clomiphene because breast cancer risk was not associated with the use of clomiphene.[18,19] In contrast, a recent cohort study by Lerner-Geva et al, which included 5788 infertile women,[16] showed an increased risk of breast cancer after treatment with clomiphene (OR, 2.7; 95% CI, 1.3-5.7). The authors suggested that this finding might be caused by the fact that the direct antiestrogenic effects of the drug on breasts are overridden by the elevated estradiol levels induced by clomiphene among women in reproductive age.

Our study had several strengths: it was the first large case control study on this topic in Asia and had a high precision of the risk estimates because it included 928 women with breast cancer, which is by far the largest number of cases ever included in a case-control study examining the association between the risk of breast cancer and the use of fertility drugs in Iran. Most previous studies have been limited by the small number of cases (< 300 cases) or were epidemiologic studies.[14,17-20,29] Also in our study, we adjusted for potentially important risk factors such as the cause of infertility and the use of oral contraceptives, when comparing the case and control groups. We also performed analyses on the

Table 3 Prevalence of Different Types of Breast Cancer

Kind of Breast Cancer	All Women With Breast Cancer (n = 928)		Infertile Women With Breast Cancer (n = 52)	
	n	%	n	%
Ductal Carcinoma	745	80.3	42	80.8
Lobular Carcinoma	119	12.8	6	12.3
Infiltrative Carcinoma	29	3.1	0	0
Other Breast Cancer	35	3.8	4	7.7

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subsets of women, who had information about causes of infertility or oral contraceptive use, but these adjustments did not change the overall estimates, indicating that these risk factors are not confounders in the association between the use of fertility drugs and the risk of breast cancer.

In summary, the results from our study were generally assuring that treatment with fertility drugs does not cause breast cancer, except for the use of hMG for > 6 months, which increased the risk of breast cancer. It should be noted that breast cancer is a multifactorial malignancy and we could not investigate the effect of other factors such as lifestyle or environmental pollutions. Additional long-term follow-up studies with larger sample sizes should be performed to confirm or refute the findings of the present study.

Conclusion

We observed no statistically significant relationship between infertility and ovulation induction drugs with the risk of breast cancer, except for significant increases in the risk of breast cancer among patients who had used fertility drugs for > 6 months.

Clinical Practice Points

- On the basis of the findings of this study, ovulation induction for infertility treatment appears to be relatively safe regarding the risk of breast cancer.
- However, until sufficient data are available, gonadotropins for the duration of >6 months should be prescribed with caution.

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Disclosure

The authors have stated that they have no conflicts of interest.

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