

# In Vitro Fertilization and Breast Cancer Risk: A Review

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**ABSTRACT: Introduction**—Breast cancer is a classic model of a hormone-dependent malignancy. Since the drugs used for ovulation induction as part of in vitro fertilization (IVF) treatment increase the levels of endogenous gonadal hormones, concerns have arisen regarding a possible association between IVF and the risk of developing breast cancer. The aim of this paper was to review the literature and examine the potential effects of IVF treatment on breast cancer risk. **Methods**—Medline search was conducted using the key words below in English-language articles. Further papers were obtained using the bibliographies of relevant articles. Furthermore, a combined analysis of retrieved data was performed. **Results**—Fifteen studies were identified; of these, 11 were cohort studies and 4 were case-control studies. None of the individual studies showed an overall significant association between IVF and breast cancer and, in fact, one study showed that treatment with hCG significantly reduced the risk of breast cancer in women whose maximum nonpregnant body mass index was less than 27.5. A combined analysis of the cohort studies including a total of 60,050 women treated with ovulation induction/IVF showed no significant association between these treatments and increased risk of breast cancer (observed vs. expected: 601 vs. 568, pooled relative risk [RR] = 1.06,  $P = 0.337$ ). The case-control studies included a total of 11,303 women in the breast cancer groups and 10,930 controls. Women in the breast cancer groups were slightly less likely to have received IVF (2.2% vs. 2.5%, pooled RR = 0.88,  $P = 0.231$ ). However, one study showed that infertility treatment was associated with an increased risk of breast cancer of borderline significance among women with a family history of the disease. Another study showed that the incidence of breast cancer within the first year of exposure to fertility drugs was higher than expected, possibly due to the promotion of preexisting cancer lesions caused by superovulation or due to the early diagnosis made in the course of IVF treatment. Conflicting results were reported regarding the type of fertility treatment and breast cancer risk. **Conclusion**—Overall, there is no clear evidence that ovulation induction or IVF increases the risk of breast cancer. However, there may be a transient increase in the incidence of breast cancer in the first year due to earlier diagnosis. Furthermore, the risk may be increased in women with a positive family history. Future research should focus on the type of fertility treatment used and breast cancer risk. Aromatase inhibitors should be evaluated further as an alternative to standard ovulation-inducing drugs. *Int J Fertil* 50(5):00–00, 2005

**KEY WORDS:** breast cancer, IVF, ovulation induction, fertility drugs, epidemiology

## INTRODUCTION

**B**REAST CANCER REMAINS THE MOST common malignancy in the Western world. The lifetime risk of developing breast cancer in the United States is 12.5% [1].

Breast cancer is a classic model of a hormone-dependent malignancy, whereby overwhelming evidence points to an association between breast cancer and prolonged exposure to female sex hormones [2]. Early menarche and late menopause, both of which imply a longer exposure to menstrual

TABLE I  
**Summary of cohort studies.**

<i>Study</i>	<i>Size of cohort</i>	<i>Number of treated women</i>	<i>Follow-up (years)</i>	<i>Number of breast cancer cases</i>	<i>Number of breast cancers observed in treated group</i>
Gauthier et al 2004 [11]	92,555	6602	9.7	2571	183
Brinton et al 2004 [12]	12,193	8431	11–34	292	CC use: 108 Gonadotrophine use: 31
Lerner-Geva et al 2003 [13]	NA	1082	6.5	NA	5
Doyle et al 2002 [14]	5556	4188	0.5–15	55	43
Dor et al 2002 [15]	NA	5026	3.6	NA	11
Venn et al 1999 [16]	29,700	20,656	8.5	143	87
Potashnik et al 1999 [17]	1197	780	17.9	20	16
Modan et al 1998 [18]	2496	1309	21.4	93	59
Rossing et al 1996 [19]	NA	3837	6.9	NA	27
Venn et al 1995 [20]	10,358	5564	5.2	34	16
Ron et al 1987 [21]	NA	2575	12.3	NA	15

RR = relative risk; SIR = standardized incidence ratio; CI = confidence interval; NA = not applicable; NS = not specified; CC = clomiphene citrate; HCG = human chorionic gonadotropin; HMG = human menopausal gonadotropin; GnRH = gonadotropin-releasing hormone

<i>Number of breast cancers expected in treated group</i>	<i>Drugs used</i>	<i>Results</i>	<i>Conclusion</i>
192	All CC hMG hCG	RR = 0.95 (95% CI 0.82–1.11) RR 0.96 (95% CI 0.75–1.23) RR 0.97 (95% CI 0.74–1.27) RR 0.99 (95% CI 0.65–1.49)	No overall association Borderline increase of risk in women with family history of breast cancer
83.46 22.11	CC Gonadotropin	SIR 1.29 (95% CI 1.1–1.6) SIR 1.4 (95% CI 0.9–2.0)	No overall increase in risk Significant increased risk for invasive breast cancer RR 1.60, (95% CI 1.0–2.5) Nonsignificant increased risk after CC use ≥20 years RR 1.39 (95% CI 0.9–2.1)
4.88	NS	SIR 1.02 (95% CI 0.33–2.39)	No association
37.2	CC hMG hCG GnRH agonists	SIR 1.16(95% CI 0.84–1.56)	No association
15.86	CC hMG	SIR 0.69 (95% CI,0.46–1.66)	No increased risk
95.4	All  CC CC + hMG hMG hMG + GnRH Agonist Not Known	SIR 0.91 (95% CI 0.74–1.13) Within first 12 months of treatment SIR 1.96 (95%1.22–3.15) SIR 0.85 (95% CI 0.32–2.26) SIR 1.17 ( 95% CI 0.85–1.62) SIR 0.99 ( 95% CI 0.55–1.79) SIR 0.94 (95% CI 0.63–1.40) SIR 0.83 ( 95% CI 0.43–1.60)	No overall association, there is a transit increase in risk within the first year of treatment
9.6	CC hMG	SIR 1.7 (95% CI 0.94–2.69)	No association
46.6	All CC CC + hMG	SIR 1.3 (95% CI 0.96–1.6) SIR 1.2 (95% CI 0.7–1.9) SIR 1.6 (95% CI 0.7–3.4)	No association
28.8	CC hCG	SIR 0.9 (95% CI 0.6–1.4)	No overall association; CC nonsignificantly reduce breast cancer RR 0.5 (95%CI 0.2–1.2)
17.9	CC CC + hMG + hCG GnRH agonists GnRH + hMG + hCG	SIR 0.89 (95% CI 0.6–1.5)	No association
14.1	NS	SIR 1.1 (95% CI not significant)	No association

**TABLE II**  
**Summary of case-control studies.**

<i>Study</i>	<i>Number of cases of breast cancer</i>	<i>Number of controls</i>	<i>Number treated for infertility in case group</i>	<i>Number treated for infertility in control group</i>
Bernstein et al 1995 [22]	744	744	45	65
Burkman et al 2003 [23]	4575	4682	106	121
Braga et al 1996 [24]	2569	2588	86	76
Recci et al 1999 [25]	3415	2916	16	11

OR = odds ratio; hMG = human menopausal gonadotropin; hCG = human chorionic gonadotropin; RR = relative risk; CC = clomiphene citrate; NS = not specified

cycles, are recognized risk factors for developing the disease [3].

In the United States, the proportion of women aged 15 to 44 years reporting some form of fertility problems increased from 8% in 1982 to 10% in 1995 [4]. Furthermore, the number of women (per year) treated with fertility drugs nearly doubled between 1973 and 1991 [5]. Such agents are used routinely in in vitro fertilization (IVF) treatment to induce a state of superovulation in order to increase the chances of pregnancy in a given treatment cycle and allow the freezing of excess embryos for subsequent treatments.

Because the drugs used for ovulation induction in IVF increase the levels of endogenous gonadal hormones, which are known to play a role in the etiology of breast cancer, concerns have arisen regarding a possible association between IVF and the risk of developing breast cancer. Given the increasing number of women undergoing IVF treatment and the rising incidence of breast cancer among young women, this issue is of public health importance.

Clomiphene citrate (CC) is the most commonly used drug in IVF. It is a selective estrogen receptor modulator (SERM), which acts as a direct antiestrogen on the hypothalamus. CC suppresses the naturally circulating estrogens and stimulates the pituitary gland to produce higher levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which, in turn, stimulate the ovaries to mature a follicle. The use of CC is associated with a two- to

threefold increase in estradiol levels as well as an increase in progesterone levels [6–8]. Human menopausal gonadotropin (hMG), which contains FSH and LH, also is used commonly in IVF and increases the serum levels of estradiol and progesterone as well as the number of ovulations to about 6 to 9 times that of untreated women [9]. Other drugs used in IVF include human chorionic gonadotropin (hCG), which is given to support the luteal phase of the menstrual cycle by stimulating ovulation and progesterone secretion.

The aim of this paper is to review the literature, beginning with a case report from 1977 [10], and examine the potential effects of IVF treatment on breast cancer risk.

## METHODS

We conducted a Medline search using the listed key words in English-language articles. Additional papers were obtained using the bibliographies of relevant articles. These studies are summarized in Table I and Table II. We also performed a pooled analysis of both types of study.

## RESULTS

Fifteen studies were identified. Of these, 11 were cohort studies [11–21], and 4 were case-control studies [22–25]. None of these studies showed an overall

<i>Results</i>	<i>Drugs used</i>	<i>Conclusions</i>
OR 0.77 (95% CI 0.50–1.19)	hCG	Treatment with HCG reduces risk
OR 1.2 (95% CI 0.8–1.7) For treatment with HMG: ≥6 months	CC	No overall association
OR 2.8 (CI 1.1–6.8) For treatment with HMG: ≥6 cycles	hMG	There is increased risk if hMG is given ≥6 months or for ≥6 cycles RR 2.7–3.8
OR 3.8 (CI 1.2–11.8)		
OR 1.08 (95% CI 0.8–1.5)	NS	No association
OR 1.2 (95% CI 0.5–2.6)	NS	No association

association between IVF treatment and breast cancer risk.

In the cohort studies, a total of 60,050 patients were treated with ovulation induction agents and IVF. After a follow-up period ranging from 0.5 to 34 years, 601 patients were observed to develop breast cancer, compared with 567.91 expected. The pooled relative risk (RR) was 1.06 ( $P = 0.337$ ).

The four case control studies compared a total of 11,303 patients with established breast cancer with 10,930 patients in the control groups. The pooled analysis showed that 253 patients were exposed to ovulation-inducing drugs in the case groups, compared with 273 patients in the control groups. The pooled RR was 0.88 ( $P = 0.224$ ).

Overall, 14 studies demonstrated no overall significant association between ovulation induction and IVF treatment and increased risk of breast cancer [11–21,23–25] and one study showed a decreased risk [22]. However, in a large case series of 27,900 women who had been referred for IVF treatment, Venn et al found no increased risk of breast cancer after a long follow-up period. Nevertheless, they observed that the incidence of breast cancer within the first year of exposure to fertility drugs was higher than expected, possibly due to the promotion of preexisting cancer lesions caused by superovulation or due to the early diagnosis made in the course of IVF treatment [16]. They observed 17 cases of breast cancer, compared with 8.7 expected (standardized incidence ratio [SIR] = 1.96; 95% CI: 1.22–3.15).

In a prospective cohort study, Gauthier et al reported that infertility treatment was associated with an increased risk of breast cancer of borderline significance among women with a family history of the disease [11].

Four studies raised concerns about a possible link between specific drugs and the development of breast malignancy [12,19,22,23]. In one case–control study, CC was found to cause a nonsignificant reduction in the risk of breast cancer in infertile women, compared with infertile women who had not used this drug [19]. This finding was attributed to the fact that CC is a SERM similar to tamoxifen. Such a reduction in risk did not increase with duration of use.

On the contrary, although Brinton et al observed no overall association between breast cancer and the use of ovulation-inducing drugs, they reported a significant association between the risk of developing invasive breast cancer and the use of CC [12]. There also was a slight and nonsignificant elevation in risk seen for CC and gonadotropin after 20 years of follow-up [12].

Similar to the majority of the studies, no association was observed in a long-term historic prospective case–control study by Potashnik et al [17]. However, the SIR for breast cancer was increased significantly only in patients with one or two CC treatments and a dose of  $\leq 1000$  mg [17]. Additionally, Burkman et al showed that the long-term use of certain infertility drugs such as hMG for

≥6 months or for at least 6 cycles was associated with a relative risk of breast cancer ranging between 2.7 and 3.8 [23].

Finally, only one case-control study conducted by Bernstein et al showed that treatment with hCG significantly reduced the risk of breast cancer in women whose maximum nonpregnant body mass index was less than 27.5; no such reduction in risk was observed in more obese women [22]. Although the odds ratios were reduced for both nulliparous and parous women with a maximum nonpregnant weight mass index of 27.5, only the results for the nulliparous women were statistically significant.

## DISCUSSION

Attention was first drawn to a possible association between breast cancer risk and ovulation-inducing drugs in a case report published in the *Lancet* in 1977 [10]. Since then, several additional case reports have been published [26–28]. However, case reports have limited value, in view of the fact that breast cancer is a common neoplasm. In general, the association between female gonadal hormones and the development of breast cancer is still not fully understood, and several possible explanations have been proposed [29–32].

In this review, we found no significant overall association between IVF treatment and breast cancer risk. All individual studies identified by our research had limitations; therefore, a definite conclusion could not be drawn from a single study. These limitations include the small numbers of breast cancer cases or incomplete ability to control for other correlates of risk, including a variety of well-recognized familial and other risk factors. Hence, we performed a combined analysis of all studies identified and found no significant link between IVF and breast cancer risk.

Some studies supported the notion that fertility medication and IVF treatment may affect the breast cancer risk. In those studies that suggested that fertility drugs may increase [12,23] or reduce the risk [19,22], the findings were conflicting and were based on a small number of events. For instance, CC was observed to increase the risk as well as reduce the risk of breast cancer in two different studies [12,19]. Brinton et al showed that CC increased breast cancer risk [12]. On the other hand, CC was found by Rossing et al to be a chemopreventive agent for breast cancer in infertile women undergoing ovula-

tion induction and IVF treatment [19]; this was due to its similarity to tamoxifen, which is a recognized preventive agent [33].

One study found that treatment with hCG was associated with a reduced risk of developing breast cancer [22]. This reduction in breast cancer risk after hCG treatment was comparable to that of full-term pregnancy and was supported by animal studies [35]. Despite the fact that neither constituent of hMG such as FSH nor LH (both constituents of hMG) is thought to influence breast tissue, Burkman et al reported a relative increase in breast cancer risk with hMG treatment for at least 6 months [23].

In a large epidemiological Australian study, Venn and colleagues reviewed and followed up a cohort of 29,700 patients who underwent IVF treatment [16]. Although they found no overall association between the different ovulation-inducing drugs and breast cancer risk, they observed a twofold increase in breast cancer risk within the first year after treatment. This prompted the suggestion that ovulation-stimulating drugs might promote the rapid development of preexisting tumors, similar to the short-term transient increase in breast cancer risk following a recent pregnancy [35]. The other possible explanation is that early diagnosis was made in the course of management of infertility or other related health problems due to extensive screening in these women. Other studies have not reported such findings [12]. Therefore, this hypothesis requires further evaluation in prospective studies with larger numbers of patients and longer follow-up. Despite the conflicting results, breast cancer screening in women undergoing IVF treatment should be considered. Women with a family history of breast cancer are particularly at risk [11]; therefore, this group of women should be considered for breast cancer screening that includes MRI [36]. Furthermore, tamoxifen stimulation appears to result in a higher number of embryos and may provide a safe method of IVF and fertility preservation in breast cancer patients. Therefore, it should be considered in high-risk women, such as those with a strong family history, BRCA-1 or BRCA-2 mutations, or a recent history of breast cancer diagnosis [37].

Further research is required to examine the relationship between the different fertility drug types and breast cancer risk, so that the safest drugs can be used. Moreover, the issue of whether breast cancer in patients who had IVF treatment is associated with poor prognostic features also requires further evaluation [38].

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