Outlook

Long-term effects of ovulation-stimulating drugs on cancer risk

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Abstract

Although nulliparity has been extensively related to the risk of ovarian, breast and endometrial cancers, with many studies showing the relationship largely attributable to infertility, treatment effects on cancer risk are poorly understood. Two early studies raised substantial concern when ovulation-stimulating drugs were linked with large increases in ovarian cancer, supporting the notion of an important aetiological role of incessant ovulation. Subsequent studies have been mainly reassuring, although some have suggested possible risk increases among nulligravid women, those with extensive follow-up, and those developing borderline tumours. Results regarding effects of fertility drugs on breast cancer risk are conflicting, with some showing no associations and others demonstrating possible risk increases, although for varying subgroups. In contrast, endometrial cancer results are more consistent, with two recent studies showing increased risks related to clomiphene usage. This is of interest given that clomiphene is structurally similar to tamoxifen, a drug extensively linked with this cancer. Given the recent marketing of fertility drugs and the fact that exposed women are only beginning to reach the cancer age range, further follow-up is necessary. This will also be important to fully resolve effects of exposures such as gonadotrophins, used more recently in conjunction with IVF.

Keywords: *cancer, epidemiology, fertility drugs, infertility, ovulation stimulation, risk*

Introduction

It is well established that nulliparity is a risk factor for ovarian, breast and endometrial cancers, with many studies suggesting that the association is largely attributable to infertility. Despite the extensive literature on the topic, causes of infertility and treatment effects on cancer risk are poorly understood.

Increasingly, women are delaying their first childbirth, resulting in many more women seeking advice for infertility. In fact, it is estimated that, by the year 2025, between 5.4–7.7 million women aged 15–44 will be diagnosed in the USA with some form of infertility (Stephen and Chandra, 1998). Consequentially, ovulation-stimulating drugs are among the fastest growing groups of drugs, with prescriptions in the USA nearly doubling between 1973 and 1991 (Wysowski, 1993).

The two most commonly used medications, clomiphene citrate and gonadotrophins, are effective at stimulating ovulation, a factor implicated in the aetiology of both breast and ovarian cancers (Fathalla, 1971; Henderson *et al.*, 1985). These drugs also raise both oestradiol and progesterone concentrations (Sovino *et al.*, 2002), hormones which are recognized as affecting the development and growth of breast and gynaecological cancers. Finally, as elaborated below, some clinical and epidemiological studies have linked usage of these drugs with an increased incidence of various cancers.

Ovarian cancer

Numerous clinical reports have raised concern about a potential link between use of ovulation-stimulating drugs and ovarian cancer risk (Fishel and Jackson, 1989; Dietl, 1991; Goldberg and Runowicz, 1992; Nijman *et al.*, 1992; Balasch *et al.*, 1993; Lopes and Mensier, 1993; Willemsen *et al.*, 1993; Adewole *et al.*,

1997; Unkila-Kallio *et al*., 1997). The association has biological credibility, given that 'incessant ovulation' and associated alterations in endogenous hormones during reproductive years are plausible explanations for several factors that alter ovarian cancer risk, including nulliparity and oral contraceptive use (Fathalla, 1971; Cramer and Welch, 1983; Whittemore *et al*., 1992a). Results from two epidemiological studies that found marked elevations in ovarian cancer risk associated with exposure to ovulation-stimulating drugs (Whittemore *et al*., 1992b; Rossing *et al*., 1994) provide additional support for this hypothesis.

The earliest evidence of such a link derived from a meta-analysis of 12 case–control studies of ovarian cancer conducted by Whittemore and coworkers (Whittemore *et al*., 1992b). Only three of these studies, with 526 cases and 966 controls, provided information regarding the use of fertility drugs and there was scant information about the type of drug or the extent of its use. Self-reported prior usage of fertility medications was associated with an odds ratio (OR) of 2.8 (95% CI 1.3–6.1) as compared with women who had no history of infertility. The increased risk was limited to nulligravid women, who experienced a 27-fold increase in risk associated with drug usage (95% CI 2.3–315.6). However, this risk was based on only 12 exposed cases and one exposed control.

Results from a retrospective cohort study involving 3837 women evaluated for infertility in a single Seattle practice between 1974 and 1985 also raised concern (Rossing *et al*., 1994). More details on this and other completed cohort studies are shown in **Table 1**. Information on drug exposures and indications for usage was collected from medical records, and outcome information was obtained via linkage against a regional cancer registry. Effects of other risk factors were evaluated by abstracting information from medical records for all ovarian cancer cases and a subcohort sample of 135 women. Using appropriate case–cohort analytic techniques, they estimated that clomiphene use was associated with an adjusted 2.3-fold increased risk (95% CI 0.5–11.4), based on nine ovarian cancers.

Use of clomiphene for less than 1 year was not associated with an increased risk, but five of the nine women with cancer had taken the drug for 12 or more monthly cycles, resulting in a relative risk of 11.1 (95% CI 1.5–82.3). An enhanced risk associated with long-term treatment was observed in both those with and without ovulatory abnormalities. A large proportion of the observed tumours were borderline (five of the 11 in the cohort).

Although the results of these two initial studies were alarming, subsequent results from a number of case–control studies were largely reassuring (Franceschi *et al*., 1994; Mosgaard *et al*., 1997; Parazzini *et al*., 1997). A meta-analysis of eight studies involving data on 1060 cases and 1337 controls (Ness *et al*., 2002) also showed no risk associations with fertility drug use. In this study, after adjustment for types of infertility, the risk associated with drug usage was somewhat higher among nulligravid women (1.8) and among those who had more than 4 months of exposure (relative risk (RR) 1.5–1.7), but none of these risks was statistically significant.

The results of case control studies are limited by the fact that information on prior drug use is based on patient histories. Most have been further limited by small numbers of ovarian cancer cases reporting prior drug usage. For example, in the largest case–control study (Parazzini *et al*., 2001), based on 1031 cases and 2411 hospital controls, only 1.1–1.5% of the subjects reported prior usage of fertility drugs, resulting in only 15 cases and 26 controls with relevant exposures for analysis.

Although results have also been published from additional cohort studies (Ron *et al*., 1987; Shushan *et al*., 1996; Modan

Table 1. Major cohorts reporting associations between fertility drugs and cancer risk.

Location	*Reference*	*No. of subjects*	*Years evaluated*	*Average years of follow-up*	*Type of cancer*		
					Ovarian	*Breast*	*Endometrial*
Israel	Ron *et al*., 1987	2575	1964–1974	12.3	4	15	5
USA	Rossing *et al*., 1994, 1996	3837	1974–1985	12.3	11	–	–
Australia	Venn *et al*., 1995	10,358	1978–1992	6.5	6	34	5
Israel (Tel Hashomer)	Modan *et al*., 1998	2496	1964–1974	21.4	12	59	21
Israel (Beer-Sheba)	Potashnik *et al*., 1999	1197	1960–1984	17.9	2	20	2
Australia	Venn *et al*., 1999	29,666	Pre-1994	8.5	13	143	12
USA	Croughan-Minihane *et al*., 2001	51,371	1965–1998	5.6	50	–	–
The Netherlands	Klip *et al*., 2002	25,152	1980–1995	5.6	17	116	14
UK	Doyle *et al*., 2002	5556	1975–1989	7.9	6	55	4
Israel (Tel Aviv)	Dor *et al*., 2002	5026	1981–1992	3.6	1	11	2
Israel (Tel Aviv)	Lerner-Geva *et al*., 2003	1082	1984–1992	6.5	3	5	
USA	Althuis *et al*., 2005	12,193	1965–1988	18.8	45	292	39
	Brinton *et al*., 2004a,c						

et al., 1998; Potashnik *et al*., 1999; Dor *et al*., 2002; Doyle *et al*., 2002; Klip *et al*., 2002), most have involved small numbers of ovarian cancers, with the number of exposed cases ranging from two in the smallest study (Potashnik *et al*., 1999) to 12 in the largest study (Modan *et al*., 1998). These studies were also limited by lack of information on causes of infertility or on other factors that could independently influence ovarian cancer risk (including parity, oral contraceptive usage and socioeconomic status).

One of the most recently published studies was designed to overcome many of the limitations of previous studies (Brinton *et al*., 2004a). This retrospective cohort study followed 12,193 infertile women for a median of 18.8 years, and had detailed information on drug exposures and causes of infertility from medical records as well as questionnaire data on potential cancer risk factors for a substantial proportion of the patients. This study was unique in being able to identify subjects who underwent a bilateral oophorectomy and were thus no longer at risk for developing ovarian cancer. The number of ovarian cancers, 45, was larger than in other cohort studies, but this number was still too limited for analyses of small subgroups of women. The results were largely reassuring, showing no increase in risk associated with ever using either clomiphene or gonadotrophins. There were non-significant increases in risk (RR 1.5–2.5) associated with use of either clomiphene or gonadotrophins among the subjects followed for the longest periods of time (15 years or more).

While this study focused on women exposed to ovulation-stimulating agents prescribed during earlier times, a number of other studies have concentrated on exposures received during IVF. One other US study, published to date only in abstract form, found no evidence for an effect of ovulation-stimulating drugs on ovarian cancer risk. After 5.6 years of follow-up of 51,371 patients seen for conception or ovum donation in 15 California clinics, 50 ovarian cancers were diagnosed (Croughan-Minihane *et al*., 2001). The only significant associations with ovarian tumour risk observed in the study were with length of time in infertility treatment and nulligravidity. However, no associations of risk were found for ovulation-stimulating drugs and risk, even when dose, formulation and number of treatment cycles were considered.

Among 29,666 women referred to 10 Australian IVF clinics, 13 ovarian cancers were observed during a follow-up period averaging 7.8 years (Venn *et al*., 1999). The investigators had detailed information on indications for drug usage, but only limited information on patient characteristics. Comparing risks to the general population, the standardized incidence ratio (SIR) was 0.99, with no higher risk for the women who received at least one IVF treatment cycle (0.88) as compared with those who received no drug treatment (1.16). Women with unexplained infertility were at a significantly increased risk compared with the general population, but within this subgroup there was no difference in risk between treated and untreated women.

In a cohort of 25,152 women treated for subfertility in the Netherlands, 17 ovarian cancers developed during 5.6 years of follow-up (Klip *et al*., 2002). Strengths of this study included detailed information on causes of infertility and drug exposures from medical records, as well as on cancer risk predictors obtained through completed questionnaires from many of the study subjects. Thus, the study was able to assess risks associated with different parameters of drug exposures, while adjusting for other risk factors. Results showed no difference in risk between treated and untreated subjects, even when the number of cycles or ampoules received were considered.

While the results of the most recent studies are consistently reassuring when compared with the results of earlier studies, several observations indicate a need for further monitoring. These include the findings in the two most recent studies (Ness *et al*., 2002; Brinton *et al*., 2004a) of modest increases in risk estimates with either extended follow-up or increased exposure to ovulation-stimulating drugs. Given that these ovulation-stimulating drugs first became available beginning in the early 1960s, women who were exposed to them are just beginning to enter the ovarian cancer age range. Furthermore, less information is available on gonadotrophins than clomiphene, given that the latter was the drug of choice in earlier time periods. Thus, additional follow-up data are needed to fully evaluate effects of both exposures.

In addition, two recent investigations (Ness *et al*., 2002; Brinton *et al*., 2004a) and Whittemore's early meta-analysis (Whittemore *et al*., 1992b) found drug effects to be greatest among nulligravid women, suggesting the possibility of an enhanced effect of the medications among women with certain indications for usage.

That ovulation-stimulating drugs might preferentially affect the risk of borderline ovarian tumours is also suggested by several studies. Both cohort (Rossing *et al*., 1994; Shushan *et al*., 1996) and case–control (Parazzini *et al*., 1998; Ness *et al*., 2002) investigations have shown risk ratios in the range of 3–4 associated with fertility drug usage. In one study, the relationship was restricted to nulligravid women (Ness *et al*., 2002) and in another specifically to gonadotrophins (Shushan *et al*., 1996). These findings, in conjunction with case reports of ovarian neoplasms developing in women during or shortly after treatment with ovulation-stimulating agents (Dietl, 1991; Goldberg and Runowicz, 1992; Nijman *et al*., 1992; Willemsen *et al*., 1993; Hull *et al*., 1996; Adewole *et al*., 1997; Bayar *et al*., 2006), have led to speculations that ovarian stimulation may induce growth in existing highly differentiated indolent tumours. Alternatively, the findings simply could reflect more intensive medical surveillance among infertile women.

Breast cancer

The epidemiology of breast cancer has been extensively studied, with many investigations supporting the notion of an important aetiological role for endogenous as well as exogenous hormones (Bernstein, 2002). Specific concerns regarding the effects of fertility drugs have been raised by the recognized effects on breast cancer risk of ovulation and hormonal patterns (Henderson *et al*., 1985; Parazzini *et al*., 1993). Furthermore, there are a number of clinical reports of breast cancer occurring among users of such drugs (Arbour *et al*., 1994; Brzezinski *et al*., 1994; Jourdain *et al*., 1996; Unkila-Kallio *et al*., 1997).

Many cohort (Ron *et al*., 1987; Venn *et al*., 1995; Modan *et al*., 1998; Venn *et al*., 1999; Doyle *et al*., 2002; Klip *et al*.,

2002; Lerner-Geva *et al*., 2003) and case–control (Braga *et al*., 1996; Weiss *et al*., 1998; Ricci *et al*., 1999) studies have failed to find any remarkable associations between fertility drug use and breast cancer risk. Most, however, were limited by small numbers of cancers, imprecise information on patterns of, or indications for, drug usage, and incomplete ability to control for other related risk factors, including well-recognized reproductive risk factors.

Several studies have suggested links between fertility drugs and breast cancer risk, but the results are conflicting, with some suggesting potential increases in risk and others decreases. A recent case–control study involving over 4500 breast cancer cases was able to carefully control for potential confounding variables but had to rely on self-reports of infertility and had few women exposed to fertility drugs (Burkman *et al*., 2003). Although this study found no association of risk related to use of clomiphene, there was some indication of a risk elevation among women with long-term use of menopausal gonadotrophins. Use for at least 6 or more months or at least six cycles was associated with RR ranging from 2.7–3.8. The finding was somewhat unexpected given that neither of the constituents of human menopausal gonadotrophin – FSH and LH – are thought to have direct effects on breast tissue (Healy and Venn, 2003). Since gonadotrophin therapy increases both serum oestrogen and progesterone concentrations, the investigators suggested this as a possible explanation for their findings. Whether the increases in hormones that would be associated with six or more cycles of exposure would be sufficient to substantially affect the subsequent risk of breast cancer is questionable (Healy and Venn, 2003).

The opposite relationship, namely a non-significantly reduced risk of invasive and in-situ breast cancer associated with clomiphene (adjusted RR 0.5, 95% CI 0.2–1.2) was found in Rossing's retrospective cohort study (Rossing *et al*., 1996). This estimate was based on only 12 exposed cases and there was no indication of any further risk reduction with extended duration of use. A chemopreventive effect of clomiphene would be of interest given that it is a selective oestrogen receptor modulator (SERM), and thus could have properties similar to another SERM, tamoxifen (Fisher *et al*., 1998). Additional epidemiological support of a reduced risk of breast cancer associated with clomiphene use was provided from The Nurses Health Study II (Terry *et al*., 2006), which showed a RR of 0.40 (95% CI 0.2–0.7) associated with use of clomiphene among women treated for ovulatory infertility. Risk decreased significantly with duration of use of clomiphene, with users of 10 or more months having a RR of 0.25 (95% CI 0.09–0.75) compared with non-exposed women. The findings were based on self-reports of both drug usage as well as causes of infertility.

On the other hand, the recent multi-centre US cohort study, involving 292 breast cancer cases, failed to find any substantial alterations in risk related to ever using either clomiphene or gonadotrophins (Brinton *et al*., 2004b). However, there were small non-significant increases in risk after extended follow-up periods (>15 years), with the RR in the range of 1.4–2.5, similar to the long-term risks observed for ovarian cancer in this same cohort study. When analyses were restricted to invasive breast cancers, the RR after 20 years of follow-up became statistically significant (RR 1.6, 95% CI 1.0–2.5).

More recent results are now beginning to emerge regarding the effects on breast cancer risk among IVF exposed cohorts. In a study of 5788 women attending an Israeli clinic in whom 131 breast cancers developed, a significantly elevated risk was found related to clomiphene exposure (SIR 1.4, 95% CI 1.0–1.8) (Lerner-Geva *et al*., 2006). Even stronger results were found when internal analyses were conducted through a nested case–control study within the cohort (OR 2.7, 95% CI 1.3–5.7).

However, in a large cohort study in France, involving 92,555 women and 2571 invasive breast cancers, there was no evidence of any increases in risk, regardless of the exposure considered (Gauthier *et al*., 2004). This included overall treatment for infertility, IVF treatment, exposure to specific drugs (e.g., clomiphene), and specifics of exposures (duration of treatment, age at first use). The exposure information, however, was self-reported and no information was available on indications for drug usage, including causes of infertility. The only evidence of any increased risk associated with fertility treatment was among women with a family history of breast cancer (RR 2.32–2.77), with estimates based on fairly small numbers of affected women.

Two other epidemiological investigations of IVF-exposed women, one conducted in Australia (Venn *et al*., 1999) and the other in the Netherlands (Klip *et al*., 2002), did not find differences in risk between exposed and unexposed subjects. However, in the Australian study, an approximately two-fold increased risk of breast cancer was observed within 1 year of last treatment. This prompted the suggestion that ovulation-stimulating drugs might promote the rapid growth of pre-existing tumours, similar to the short-term transient increase in breast cancer following a recent pregnancy (Lambe *et al*., 1994). However, several other studies, which assessed detailed timing effects of last drug usage, found no support for a promotional effect by either clomiphene or gonadotrophins (Klip *et al*., 2002; Brinton *et al*., 2004b).

In the Australian study, Venn and coworkers also assessed causes of death among their cohort of infertile women, observing non-significant decreases in mortality for most causes as compared with the general population (Venn *et al*., 2001). Deaths due to breast cancer showed no appreciable differences between those who did and did not receive IVF. The data therefore provided little support for another report that demonstrated poor prognostic features among breast cancer patients with recent histories of exposure to fertility drugs (Siegelmann-Danieli *et al*., 2003).

Endometrial cancer

Endometrial cancers are well recognized as hormonally sensitive (Akhmedkhanov *et al*., 2001). There is a clinical report of three cases of adenomatous hyperplasia of the endometrium, a precursor condition, occurring among women exposed to ovulation-stimulating agents (Miannay *et al*., 1994). Few analytical studies, however, have assessed the relationship between endometrial cancer and use of fertility drugs.

One small case–control study that assessed the relationship found no association, but, with only seven exposed cases, the investigation had limited power to detect an effect (Benshushan

et al., 2001). Most cohort studies have not observed an association, but the majority had follow-up times of less than 10 years and few associated cases of endometrial cancer (between two and 14) (Venn *et al*., 1995, 1999; Potashnik *et al*., 1999; Klip *et al*., 2002).

The two largest cohort studies both raise some concern regarding effects of ovulation-stimulating agents on the endometrium. In an Israeli cohort, in which 21 uterine cancers were diagnosed during an average of more than 20 years of follow-up, a significant two-fold increase in risk was associated with fertility drug usage (Modan *et al*., 1998). Similarly, the multi-centre US cohort study, which detected 39 cases of endometrial cancer among cohort members, found clomiphene usage associated with a non-significant increase in risk (RR 1.8, 95% CI 0.9–3.3) (Althuis *et al*., 2005). Further, increases in risk were found among subjects with higher dosages of exposure or longer follow-up periods, with trends in risk for the latter variable being statistically significant. Drug effects were also more apparent among nulligravid and obese women (RR of 3.5 and 6.0, respectively).

Because tamoxifen, a SERM which bears structural similarities to clomiphene (Sovino *et al*., 2002), has been repeatedly linked with increases in endometrial cancer risk (Varras *et al*., 2003), these two studies raise concern despite the fact that they were based on fairly small numbers of cancers.

Future research needs

Given that clomiphene was first approved for clinical use in 1967 and gonadotrophins in 1969, the women who first used these drugs during their late twenties and early thirties have only recently reached the age when hormonally-related cancers are common. Most studies to date are reassuring in not showing a strong association between use of these medications and risks of most cancers. On the other hand, several studies have found increasing risks with greater exposures or extended follow-up, indicating that complacency is not warranted and that long-term effects should be further monitored, especially in view of changes in reproductive technology.

There has been little attention focused on the long-term effects of assisted reproductive technologies, which often involve much higher exposures to gonadotrophins than were received by women in previous eras. In addition, most IVF protocols include luteal phase support for several weeks with supplemental progestogens, which raises concern since these agents have been linked in several studies to increases in breast cancer risk (Key and Pike, 1988; Beral, 2003). Since in-vitro techniques have become common only in the last couple of decades, it may be some time before epidemiological studies can amass the follow-up times required to fully address long-term effects.

There is some consistency across studies of a modest enhancement of ovarian cancer risk associated with use of fertility drugs among women who remain nulligravid (Whittemore *et al*., 1992b; Ness *et al*., 2002; Brinton *et al*., 2004c). This may indicate an interactive effect of the drugs with the underlying causes of infertility, including those reflecting unique hormonal perturbations. On the other hand, it may be that women who continue to remain infertile may have received larger doses and longer durations of fertility or other medications than other women.

There are other issues of interest that have not been widely pursued. First is the question of whether women at particularly high risk of cancer, including those with a genetic predisposition, experience unusual risks from the use of fertility medications. Secondly, it is of interest whether fertility drugs have unusual effects among women who have used other hormones. This includes oral contraceptives, which have been shown to be associated with reduced risks of endometrial and ovarian cancers (Deligeoroglou *et al*., 2003) and somewhat increased risks of breast cancers (CGHFBC, 1996), and menopausal hormone replacement therapy, which has been linked with increases in the risk of all three cancer sites (Akhmedkhanov *et al*., 2001; Lacey *et al*., 2002; Beral, 2003).

Some (Rossing *et al*., 1994; Shushan *et al*., 1996; Parazzini *et al*., 1998; Ness *et al*., 2002, Brinton *et al*., 2004a), although not all (Brinton *et al*., 2004a), studies suggest an unusual occurrence of borderline ovarian cancers among women exposed to fertility medications. Whether this reflects a biological effect or is merely the result of more intensive surveillance of women treated with these drugs by ultrasound and clinical examination warrants further scrutiny. Biologically, it is of interest that oestrogen receptor expression is a common feature of borderline ovarian tumours. Thus, further study of the relationship of fertility medications to ovarian, as well as breast cancers, according to hormone receptor status would appear warranted. In addition, investigations of cancer associations by tumour histologies should also be undertaken, given clinical reports of several unusual types of ovarian cancer (e.g., clear cell, germ cell, granulosa cell tumours) occurring among fertility drug users (Willemsen *et al*., 1993; Tewari *et al*., 1998; Makrydimas *et al*., 2003).

Although most attention has focused on effects of fertility drugs on ovarian cancer risk, more recent investigations support the need for further attention on breast and endometrial cancers. This need is supported by the recognition that ovulation-stimulating drugs are effective at increasing both oestrogen and progestin concentrations, alterations that have been linked with both of these cancers. Further, a relationship with breast cancer would parallel findings of an increased risk of this tumour among mothers exposed to diethylstilbestrol during pregnancy (Titus-Ernstoff *et al*., 2001). The preliminary findings regarding an increased risk of endometrial cancer following exposure to clomiphene, a drug closely related to tamoxifen, especially warrants further follow-up in well-designed epidemiological investigations.

References

Adewole IF, Babarinsa IA, Thomas JO *et al*. 1997 Ovarian cancer associated with ovulation induction: a case report. *African Journal of Medicine and Medical Sciences* **26**, 203–204.

Akhmedkhanov A, Zeleniuch-Jacquotte A, Toniolo P 2001 Role of exogenous and endogenous hormones in endometrial cancer: review of the evidence and research perspectives. *Annals of the New York Academy of Sciences* **943**, 296–315.

Althuis MD, Moghissi KS, Westhoff CL *et al*. 2005 Uterine cancer after use of clomiphene citrate to induce ovulation. *American Journal of Epidemiology* **161**, 607–615.

Arbour L, Narod S, Glendon G *et al*. 1994 In-vitro fertilisation and family history of breast cancer. *Lancet* **344**, 610–611.

Balasch J, Pahisa J, Marquez M *et al*. 1993 Metastatic ovarian strumosis in an in-vitro fertilization patient. *Human Reproduction* **8**, 2075–2077.

Bayar U, Demirtas E, Usubütün A *et al*. 2006 Case report: ovarian adenomyoma following gonadotropin treatment for infertility. *Reproductive BioMedicine Online* **13**, 676–679.

Benshushan A, Paltiel O, Brzezinski A *et al*. 2001 Ovulation induction and risk of endometrial cancer: a pilot study. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **98**, 53–57.

Beral V 2003 Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* **362**, 419–427.

Bernstein L 2002 Epidemiology of endocrine-related risk factors for breast cancer. *Journal of Mammary Gland Biology and Neoplasia* **7**, 3–15.

Braga C, Negri E, La Vecchia C *et al*. 1996 Fertility treatment and risk of breast cancer. *Human Reproduction* **11**, 300–303.

Brinton LA, Lamb EJ, Moghissi KS *et al*. 2004a Ovarian cancer risk after the use of ovulation-stimulating drugs. *Obstetrics and Gynecology* **103**, 1194–1203.

Brinton LA, Scoccia B, Moghissi KS *et al*. 2004b Breast cancer risk associated with ovulation-stimulating drugs. *Human Reproduction* **19**, 2005–2013.

Brinton LA, Lamb EJ, Moghissi KS *et al*. 2004c Ovarian cancer risk associated with varying causes of infertility. *Fertility and Sterility* **82**, 405–414.

Brzezinski A, Peretz T, Mor-Yosef S *et al*. 1994 Ovarian stimulation and breast cancer: is there a link? *Gynecologic Oncology* **52**, 292–295.

Burkman RT, Tang MT, Malone KE *et al*. 2003 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. *Fertility and Sterility* **79**, 844–851.

CGHFBC 1996 Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC). *Lancet* **347**, 1713–1727.

Cramer DW, Welch WR 1983 Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. *Journal of the National Cancer Institute* **71**, 717–721.

Croughan-Minihane M, Camarano L, Feigenbaum S *et al*. 2001 The risk of ovarian cancer associated with infertility and infertility treatments. *Fertility and Sterility* **76** (Suppl. 1), S68

Deligeoroglou E, Michailidis E, Creatsas G 2003 Oral contraceptives and reproductive system cancer. *Annals of the New York Academy of Sciences* **997**, 199–208.

Dietl J 1991 Ovulation and ovarian cancer. *Lancet* **338**, 445

Dor J, Lerner-Geva L, Rabinovici J *et al*. 2002 Cancer incidence in a cohort of infertile women who underwent in-vitro fertilization. *Fertility and Sterility* **77**, 324–327.

Doyle P, Maconochie N, Beral V *et al*. 2002 Cancer incidence following treatment for infertility at a clinic in the UK. *Human Reproduction* **17**, 2209–2213.

Fathalla MF 1971 Incessant ovulation – a factor in ovarian neoplasia? *Lancet* **2**, 163.

Fishel S, Jackson P 1989 Follicular stimulation for high tech pregnancies: are we playing it safe? *British Medical Journal* **299**, 309–311.

Fisher B, Costantino JP, Wickerham DL *et al*. 1998 Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *Journal of the National Cancer Institute* **90**, 1371–1388.

Franceschi S, La Vecchia C, Negri E *et al*. 1994 Fertility drugs and risk of epithelial ovarian cancer in Italy. *Human Reproduction* **9**, 1673–1675.

Gauthier E, Paoletti X, Clavel-Chapelon F 2004 Breast cancer risk associated with being treated for infertility: results from the French E3N cohort study. *Human Reproduction* **19**, 2216–2221.

Goldberg GL, Runowicz CD 1992 Ovarian carcinoma of low malignant potential, infertility, and induction of ovulation – is there a link? *American Journal of Obstetrics and Gynecology* **166**, 853–854.

Healy DL, Venn A 2003 Infertility medications and the risk of breast cancer. *Fertility and Sterility* **79**, 852–854.

Henderson BE, Ross RK, Judd HL *et al*. 1985 Do regular ovulatory cycles increase breast cancer risk? *Cancer* **56**, 1206–1208.

Hull ME, Kriner M, Schneider E *et al*. 1996 Ovarian cancer after successful ovulation induction: a case report. *Journal of Reproductive Medicine* **41**, 52–54.

Jourdain O, Avril A, Mauriac L *et al*. 1996 Breast cancer and in-vitro fertilization. About 32 cases. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **67**, 47–52.

Key TJ, Pike MC 1988 The role of oestrogens and progestagens in the epidemiology and prevention of breast cancer. *European Journal of Cancer and Clinical Oncology* **24**, 29–43.

Klip H, Burger C, van Leeuwen F *et al*. 2002 *Risk of hormone-related cancers after ovarian stimulation for in-vitro fertilisation in a cohort of 25,152 women*, PrintPartners Ipskamp BV, Enschede, the Netherlands. pp. 27

Lacey JV, Jr., Mink PJ, Lubin JH *et al*. 2002 Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* **288**, 334–341.

Lambe M, Hsieh C, Trichopoulos D *et al*. 1994 Transient increase in the risk of breast cancer after giving birth. *New England Journal of Medicine* **331**, 5–9.

Lerner-Geva L, Keinan-Boker L, Blumstein T *et al*. 2006 Infertility, Ovulation Induction Treatments and the Incidence of Breast Cancer-a Historical Prospective Cohort of Israeli Women. *Breast Cancer Research and Treatment* **100**, 201–212.

Lerner-Geva L, Geva E, Lessing JB *et al*. 2003 The possible association between in-vitro fertilization treatments and cancer development. *International Journal of Gynecological Cancer* **13**, 23–27.

Lopes P, Mensier A 1993 Ovarian cancer and assisted reproductive technology. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **51**, 171–173.

Makrydimas G, Sotiriadis A, Paraskevaidis E *et al*. 2003 Clear cell ovarian carcinoma in a pregnant woman with a history of infertility, endometriosis and unsuccessful IVF treatment. *European Journal of Gynaecological Oncology* **24**, 438–441.

Miannay E, Boutemy JJ, Leroy-Billiard M *et al*. 1994 [The possible endometrial risk of ovarian stimulation. Apropos of 3 cases]. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction* **23**, 35–38.

Modan B, Ron E, Lerner-Geva L *et al*. 1998 Cancer incidence in a cohort of infertile women. *American Journal of Epidemiology* **147**, 1038–1042.

Mosgaard BJ, Lidegaard O, Kjaer SK *et al*. 1997 Infertility, fertility drugs, and invasive ovarian cancer: a case–control study. *Fertility and Sterility* **67**, 1005–1012.

Ness RB, Cramer DW, Goodman MT *et al*. 2002 Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case–control studies. *American Journal of Epidemiology* **155**, 217–224.

Nijman HW, Burger CW, Baak JP *et al*. 1992 Borderline malignancy of the ovary and controlled hyperstimulation, a report of 2 cases. *European Journal of Cancer* **28A**, 1971–1973.

Parazzini F, Pelucchi C, Negri E *et al*. 2001 Use of fertility drugs and risk of ovarian cancer. *Human Reproduction* **16**, 1372–1375.

Parazzini F, Negri E, La Vecchia C *et al*. 1998 Treatment for fertility and risk of ovarian tumors of borderline malignancy. *Gynecologic Oncology* **68**, 226–228.

Parazzini F, Negri E, La Vecchia C *et al*. 1997 Treatment for infertility and risk of invasive epithelial ovarian cancer. *Human Reproduction* **12**, 2159–2161.

Parazzini F, La Vecchia C, Negri E *et al*. 1993 Lifelong menstrual pattern and risk of breast cancer. *Oncology* **50**, 222–225.

Potashnik G, Lerner-Geva L, Genkin L *et al*. 1999 Fertility drugs and the risk of breast and ovarian cancers: results of a long-term follow-up study. *Fertility and Sterility* **71**, 853–859.

Ricci E, Parazzini F, Negri E *et al*. 1999 Fertility drugs and the risk of breast cancer. *Human Reproduction* **14**, 1653–1655.
Ron E, Lunenfeld B, Menczer J *et al*. 1987 Cancer incidence in a cohort of infertile women. *American Journal of Epidemiology* **125**, 780–790.
Rossing MA, Daling JR, Weiss NS *et al*. 1996 Risk of breast cancer in a cohort in infertile women. *Gynecologic Oncology* **60**, 3–7.
Rossing MA, Daling JR, Weiss NS *et al*. 1994 Ovarian tumors in a cohort of infertile women. *New England Journal of Medicine* **331**, 771–776.
Shushan A, Paltiel O, Iscovich J *et al*. 1996 Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertility and Sterility* **65**, 13–18.
Siegelmann-Danieli N, Tamir A, Zohar H *et al*. 2003 Breast cancer in women with recent exposure to fertility medications is associated with poor prognostic features. *Annals of Surgical Oncology* **10**, 1031–1038.
Sovino H, Sir-Petermann T, Devoto L 2002 Clomiphene citrate and ovulation induction. *Reproductive BioMedicine Online* **4**, 303–310.
Stephen EH, Chandra A 1998 Updated projections of infertility in the United States: 1995–2025. *Fertility and Sterility* **70**, 30–34.
Terry KL, Willett WC, Rich-Edwards JW *et al*. 2006 A prospective study of infertility due to ovulatory disorders, ovulation induction, and incidence of breast cancer. *Archives of Internal Medicine* **166**, 2484–2489.
Tewari K, Rose GS, Balderston KD *et al*. 1998 Fertility drugs and malignant germ-cell tumour of ovary in pregnancy. *Lancet* **351**, 957–958.
Titus-Ernstoff L 2000 An overview of the epidemiology of cutaneous melanoma. *Clinics in Plastic Surgery* **27**, 305–16, vii.
Unkila-Kallio L, Leminen A, Tiitnen A *et al*. 1997 Malignant tumors of the ovary or the breast in association with infertility: a report of thirteen cases. *Acta Obstetricia et Gynecologica Scandinavica* **76**, 177–181.
Varras M, Polyzos D, Akrivis C 2003 Effects of tamoxifen on the human female genital tract: review of the literature. *European Journal of Gynaecological Oncology* **24**, 258–268.
Venn A, Hemminki E, Watson L *et al*. 2001 Mortality in a cohort of IVF patients. *Human Reproduction* **16**, 2691–2696.
Venn A, Watson L, Bruinsma F *et al*. 1999 Risk of cancer after use of fertility drugs with in-vitro fertilisation. *Lancet* **354**, 1586–1590.
Venn A, Watson L, Lumley J *et al*. 1995 Breast and ovarian cancer incidence after infertility and in-vitro fertilisation. *Lancet* **346**, 995–1000.
Weiss HA, Troisi R, Rossing MA *et al*. 1998 Fertility problems and breast cancer risk in young women: a case–control study in the United States. *Cancer Causes and Control* **9**, 331–339.
Whittemore AS, Harris R, Itnyre J 1992a Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case–control studies. IV. The pathogenesis of epithelial ovarian cancer. Collaborative Ovarian Cancer Group. *American Journal of Epidemiology* **136**, 1212–1220.
Whittemore AS, Harris R, Itnyre J 1992b Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case–control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *American Journal of Epidemiology* **136**, 1184–1203.
Willemsen W, Kruitwagen R, Bastiaans B *et al*. 1993 Ovarian stimulation and granulosa-cell tumour. *Lancet* **341**, 986–988.
Wysowski DK 1993 Use of fertility drugs in the United States, 1973 through 1991. *Fertility and Sterility* **60**, 1096–1098.

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