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In Vitro Fertilization and Risk of Breast and Gynecologic Cancers: A Retrospective Cohort Study within the Israeli Maccabi Healthcare Services

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Abstract

Objective—To assess long-term cancer risks associated with *in vitro* fertilization (IVF).

Design—Record-linkage study

Setting—Health maintenance organization in Israel

Patients—87,403 women evaluated and/or treated for infertility on or after September 25, 1994 who were followed for cancer development through June 22, 2011: 522 breast, 41 endometrial, 45 ovarian, 311 *in situ* cervical and 32 invasive cervical cancers were identified.

Intervention(s)—None

Main Outcome Measures—Hazard ratios (HRs) for specific cancers

Results—We found no significant relationships of IVF exposures to the risks of breast, endometrial or ovarian cancers. Compared to women with no fertility treatment, the HR for ovarian cancer associated with IVF was 1.58 (95% CI 0.75–3.29), with higher risk among those receiving 4+ cycles (1.78, 95% CI 0.76–4.13). There was also a non-significantly elevated risk for endometrial cancer among women who received 1–3 IVF cycles (1.94, 0.73–5.12), but additional cycles were associated with lesser risk. In contrast, the risk of *in situ* cervical cancer was significantly reduced and invasive cervical cancer non-significantly reduced among women receiving IVF as well as other fertility treatments.

Conclusions—Our results regarding long-term effects were largely reassuring, but women receiving IVF should continue to be monitored given that the procedures involves potent ovulation stimulators and repeated ovarian punctures.

Keywords

In vitro fertilization (IVF); cancer; risk

Introduction

The relationship of infertility and associated medications to cancer risk has been of widespread interest. Although early studies suggested large increases in ovarian cancer risk related to fertility medications (1;2), this relationship has not been confirmed by subsequent studies (3). Whether there could be residual smaller risks, particularly among subgroups of users, such as nulligravidous or nulliparous women (2;4–7), is still an open question. Some of the difficulty in resolving effects of fertility medications may reflect their high correlation with many other parameters that impact cancer risk, including causes of infertility and the ability to conceive and bear children.

Given that the first in vitro fertilization (IVF) baby was born in 1979, there has been limited ability to assess cancer risk in a cohort of women old enough to be at risk of developing cancer. Thus, the number of epidemiologic studies that have assessed effects of fertility drugs used in conjunction with IVF has been relatively limited, with the vast majority having focused on pre-IVF era drugs. These earlier studies mainly assessed effects related to clomiphene citrate, whereas more recent advances have involved exposure to gonadotrophins, gonadotrophin releasing hormone (GnRH) analogues (agonists or antagonists) and progesterone supplements.

In addition to imprecise information on correlates of drug usage that could independently affect cancer risk, many of the previous studies have had to rely on patient reports of medication exposures. To obtain detailed information on drug exposures, we undertook an investigation in a large health maintenance organization (HMO) in Israel that had documented information on fertility treatments. Israel provides a unique setting for studying the effects of IVF given that universal law entitles women to almost free treatment in order to conceive and give birth to their first two children. In the HMO from which we identified study subjects, a large proportion (87%) had purchased complementary insurance to cover treatments to conceive a third and fourth child. Thus, we were able to evaluate cancer risk among some women who had been heavily exposed to IVF, while simultaneously controlling for other important cancer risk predictors.

Methods

Study Cohort

The present retrospective cohort study was carried out at Maccabi Healthcare Services (MHS), a 2-million enrollee HMO that provides health services to 25% of the total population in Israel. According to the National Health Act in Israel (NHAI), MHS may not bar applicants on any grounds, including age or state of health. Thus, all Israeli sub-populations are represented in MHS; further, the patients seen have a similar age distribution as the general population. The core of MHS activity is its 2,700 independent physicians and

salaried physicians, 250 diagnostic institutes, and 600 pharmacies. In addition, MHS has several contracted hospitals.

The MHS central data registry retains complete historical records of patient demographic data, physician data, laboratory results, and filled prescription information, using the patient's unique national identification number. This registry includes all MHS adult female members that were diagnosed as having problems conceiving, having undergone fertility treatments in either the hospital or community clinics, or having purchased medications for fertility problems.

Cancer Ascertainment

After appropriate institutional review board clearances, we linked our study population with the Israel Cancer Register (ICR), which was established in 1960 and has continuously collected information on cancers diagnosed at all medical institutions in the country. Since 1981, it is mandated by law that information on all incident cancer cases be reported to the ICR. The coverage of solid tumors in the registry is above 90% nationwide (8). All cancer cases are classified according to the International Classification of Diseases (ICD-9) and include histologic findings. In addition the ICR data, we also examined MHS medical records of each study participant to assure completeness of information on malignant tumor diagnoses.

Exposure Information

From the women's electronic medical records (EMR), we attempted to obtain information on demographic factors (date of birth, district of residence, enumeration area), potential cancer risk factors (parity status at cohort entry, parity status at cohort exit, number of children at exit, weight, height, ever smoked cigarettes and infertility indication), and fertility treatments. Socioeconomic status was categorized according to the poverty index of the member's enumeration area as defined by 1995 national census (9) based on several parameters, including household income, educational qualifications, crowding, material conditions and car ownership. Information on weight and height was used to derive a body mass index (BMI), defined as weight (kg)/height (m)² and categorized into underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), and obese (≥30).

Infertility indication was classified into six non-mutually exclusive categories: 1) male infertility, 2) anovulation, 3) mechanical causes, 4) polycystic ovary syndrome (PCOS), 5) endometriosis, and 6) pituitary-hypothalamic problems. Male infertility was defined by diagnoses in the woman's EMR, or one of the following diagnoses in the spouse's EMR: azoospermia, infertility due to germinal cell aplasia, complete spermatogenic arrest, oligozoospermia infertility due to germinal cell desquamation, hypo-spermatogenesis, incomplete spermatogenic arrest infertility due to extra-testicular causes, infertility due to drug therapy, infection, obstruction of efferent ducts, radiation, systemic disease, male infertility unspecified, and oligo-asteno-teratozoospermia. Mechanical infertility included such mechanical problems as occluded tubes or a related diagnosis (e.g., adhesions, fibroids, polyps, or uterine abnormality). In the absence of information allowing consideration of

other criteria, PCOS was defined by a diagnosis or indication of a LH/FSH ratio of 2.5 or higher and maximal tested estradiol of less than 250 pg/ml.

Information on whether the patient had been exposed to any fertility treatment was classified according to whether the patients ever had IVF treatment (even if this included only hormonal exposure and did not result in oocyte retrieval), number of IVF cycles, and whether they had ever been exposed to clomiphene citrate, gonadotrophins or progestational agents.

Analytic Population

From the MHS data repository, we assembled a cohort of 87,418 women who received treatment or were registered with fertility problems on or after September 25, 1994. We considered ineligible for study 6 women who exited prior to or on the same day as entry (1 due to death) and 9 who were diagnosed with cancer before entry into the cohort, leaving 87,403 eligible study subjects. Through June 22, 2011, we identified 1,509 total primary incident cancers.

Statistical Analysis

We started follow-up at the date of first treatment or, for untreated women, first evaluation for infertility and then followed them forward until death, the date they left MHS, date of diagnosis of primary cancer or June 23, 2011, whichever occurred first. We used Cox proportional hazards regression (10), with years of follow-up as the time scale and ties handled by complete enumeration, to estimate hazard ratios (HR) and 95% confidence intervals (CI) of developing cancer among women exposed to a certain factor (e.g., IVF) as compared to those unexposed. To assess whether there could be residual smaller cancer risks among subgroups of IVF users, such as nulliparous women, analyses were stratified by parity at study exit. P-values for all comparisons were two sided and an alpha less than 0.05 indicated statistical significance. SAS statistical software, version 9.1.3 (SAS Institute Inc., Cary, NC) was used for all analyses.

Results

The eligible study subjects contributed 704,241 person-years of follow-up (mean years of follow-up 8.1, SD=3.8). At cohort entry, the mean age of the patients was 31.1 (SD 6.4), whereas at cancer diagnosis it was 38.9 (SD 7.0).

A total of 77.4% of the patients had experienced some type of fertility treatment (Table 1). Treated patients were more likely than untreated patients to be nulliparous at cohort entry whereas at cohort exit they were more likely to be parous. Treated patients were also somewhat more likely to have multiple children. Although there was a fair amount of missing BMI information, treated patients appeared to be somewhat heavier than untreated patients. There were, however, no substantial differences between treated and untreated patients with respect to district of residence, socioeconomic status, or cigarette smoking. Although information on infertility indications was not available for the vast majority of patients, for those for whom it was available the most common indications were male factors and anovulatory problems, as previously documented (11).

The following numbers of breast and gynecologic cancers were recorded: 522 breast, 41 endometrial, 45 ovarian, 311 *in situ* cervical, and 32 invasive cervical cancers. Identified risk factors for breast and gynecologic cancers generally mirrored those found in other epidemiologic studies. For example, we found higher BMIs to be predictive of endometrial cancer (HR=2.52, 95% CI 1.14–5.60 for obese vs. normal), parity to be inversely associated with ovarian and endometrial cancers risks (respective HRs and 95% CIs = 0.39, 0.19–0.80 and 0.29, 0.14–0.59), and cigarette smoking to be directly associated with invasive cervical cancer (HR=2.06, 95% CI 0.90–4.72). As a result of these relationships, we adjusted subsequent analyses for the effects of age at entry (continuous), BMI, parity at cohort exit, cigarette smoking and socioeconomic status (categorization of these variables as shown in Table 1).

Initial analyses focused on relationships of risk with different types of fertility treatments, including any treatment, IVF (and number of IVF cycles), and exposure to GnRH analogues, clomiphene and progestogens. Although there was a strong correlation between IVF and GnRH analogues (Pearson correlation= 0.82), the correlation with other medications was relatively weak (0.29 for clomiphene and 0.40 for progestogens).

There was no alteration in breast cancer risk among women who had received fertility treatment compared to those who received no treatment (HR=0.87, 95% CI 0.71–1.06). In addition, most specific exposures were unrelated to risk, including IVF (0.90, 0.71–1.15), GnRH analogues (0.82, 0.64–1.05) or clomiphene (0.87, 0.71–1.08) (Table 2). However, a significantly decreased risk was seen for progestogen exposures (0.80, 0.65–0.99).

Any infertility treatment was not associated with endometrial cancer risk (HR=1.25, 95% CI 0.55–2.84). A non-significantly elevated risk was seen for those with 1–3 IVF cycles (1.94, 0.73–5.12), but additional cycles were associated with lesser risk, although based on small numbers of subjects. There were no substantial relationships of endometrial cancer risk with GnRH analogue (1.39, 0.54–3.55), clomiphene (1.01, 0.42–2.42), or progestogen (1.24, 0.53–2.87) exposures.

Ever exposure to any fertility treatment was unrelated to ovarian cancer risk (HR=0.90, 95% CI 0.45–1.79), as were most individual treatments, including GnRH analogues (0.93, 0.40–2.16), clomiphene (0.75, 0.36–1.58) and progestogens (0.77, 0.37–1.60). Compared to women with no fertility treatments, the HR associated with IVF was 1.58 (95% CI 0.75–3.29); risk was higher for women with 4 or more IVF cycles (1.78, 0.76–4.13) than those with 1–3 IVF cycles (1.40, 0.59–3.32), although the p for trend was not significant (p=0.18).

In contrast to the other cancers, *in situ* cervical carcinoma risk was significantly decreased among women exposed to any infertility treatment (HR=0.48, 95% CI 0.38–0.61) or IVF (0.41, 0.29–0.56), although no further decreases in risk were observed with increasing numbers of IVF cycles. Similarly, exposures to clomiphene or progestogens were associated with significant risk reductions. A non-significant reduction in risk associated with fertility treatment was also observed for invasive cervical cancers (0.57, 0.27–1.19). Most individual exposures also showed reduced risks, although there was no reduction in risk among patients who received 4 or more IVF cycles (HR=1.09, 95% CI 0.40–2.96).

We further examined risks according to whether patients were nulliparous or parous at cohort exit (Table 3). Although based on relatively small numbers, the risks associated with IVF for both endometrial and ovarian cancers were higher among parous than nulliparous women; the former also had higher rates of exposure to multiple IVF cycles (e.g., among ovarian cancer patients, 33.3% of parous women had 4 or more cycles, as compared with 18.5% of nulliparous women). For breast cancer, risks associated with fertility treatments were slightly higher for parous than nulliparous women, who demonstrated significantly reduced risks related to any fertility treatment (HR=0.69, 95% CI 0.49–0.95) or individual treatments (e.g., clomiphene exposure HR=0.66, 95% CI 0.46–0.95).

Analyses were also pursued to assess the influence of causes of infertility on treatment associations. Results were not affected by additional adjustment for these causes, nor were they modified when examined within subgroups of causes (data not shown). These analyses, however, were limited by the absence of information on causes for many subjects.

We conducted sensitivity analyses to determine the impact of excluding cases according to varying intervals of when the cancer developed in relation to initiation of fertility treatment. This resulted in the elimination of the following numbers of cases: breast (3 cases within 1 year, 31 within 2 years), endometrial (0,0), ovarian (0,3), *in situ* cervix (3, 17), invasive cervix (2, 5). These eliminations did not substantially change the interpretation of risks associated with different fertility treatments. In fact, the ovarian cancer risk associated with IVF was slightly strengthened by eliminating cases diagnosed within 2 years of fertility treatment, but remained non-significant (HR=2.13, 95% CI 0.93–4.87).

Discussion

This investigation provides additional insights regarding the long-term relationships of fertility drugs to cancer risk. Most previous investigations have focused on the effects of ovulation stimulating drugs given outside of the context of IVF, with discrepant findings. Although early cohort findings raised concern regarding effects on ovarian cancer (1;2), more recent findings have been largely reassuring (4;12–14). Results regarding breast cancer are hard to interpret given that in the largest studies the risks have ranged from inverse relationships (15) to increased risks (12;16) to no associations (17–22). The one site for which there is some consistency is that of endometrial cancer, with a number of studies suggesting possible risk increases (12;18;19;23;24).

Although many women who receive IVF have also received ovulation stimulating drugs (usually clomiphene) as a first line approach, the treatment protocols for IVF are more complex—usually involving gonadotrophins to stimulate ovulation, GnRH analogues to shut down the pituitary to prevent spontaneous ovulation, and progesterone supplementation to counteract GnRH down-regulation of the pituitary and interference with luteal phase corpus luteum. Thus, the impact of these treatments needs to be separately considered, although many previous investigations have assessed fertility drugs as a combined exposure.

We considered the number of IVF cycles as well as individual drugs that might have been given prior to this treatment (e.g., clomiphene as a first line approach or to augment the

effects of gonadotrophins) or that varied across subjects receiving IVF (progestational agents). Our findings were largely reassuring in terms of breast and gynecologic cancers, although there were a few observations of non-significant increases for ovarian and endometrial cancers.

Only a limited number of previous studies have assessed the relationship of IVF to ovarian cancer risk. Most studies, like ours, had relatively few events, owing to the relative rarity of this tumor. This has included cohort studies from Australia (two studies, involving 13 and 16 cases, respectively) (14;25), Israel (18 cases) (18), Finland (12 cases) (26), and Sweden (26 cases) (22). In the largest study, involving 77 cases that developed in a Dutch cohort, significantly elevated risks (excluding events in the first year of follow-up) were seen for both invasive (HR 2.14, based on 28 cases) and borderline (4.23, 27 cases) ovarian cancers (27).

Although several studies of pre-IVF drugs have noted increased risks of borderline cancers associated with drug use (1;7;28–30), postulated by some to reflect the influence of surveillance bias (31), this did not appear to explain the increased risks observed in the Dutch investigation (27). We were unable to assess the risk of borderline cancers given that these are not routinely reported to the Israeli cancer registry. Our findings related to IVF exposures for invasive ovarian cancers were not statistically significantly elevated; however, given the significantly elevated risks found in the larger Dutch investigation (which persisted even among patients followed for 15 years) our findings of a trend of increasing risk related to number of IVF cycles, albeit non-significant, may be noteworthy. The need for further follow-up is also supported by increased, although non-significant, risks of ovarian cancer associated with IVF in a recent Finnish study (26) and significant findings related to use of gonadotrophins in a Swedish investigation (32). These positive findings are seemingly at odds with some of the largest studies of pre-IVF drugs and ovarian cancer (4;12;13;18), but these divergent results could reflect varying treatment protocols. Thus, IVF, which involves use of gonadotrophins, can increase the number of ovulations approximately six to nine times that of untreated women (33), as compared to only a doubling for clomiphene (34;35). In addition, IVF often involves repeated ovarian punctures and resultant trauma to the ovarian surface epithelial cells (33;36).

A number of studies have noted that ovarian cancer risks associated with fertility drug use are highest among women with resistant infertility (i.e., those who remain nulligravid or nulliparous) (2;4–7;14), but we found exactly the opposite relationship—higher (although non-significant) risks associated with IVF among parous compared to nulliparous women. Thus, our findings provide stronger support for drug or procedure (follicle punctures) effects rather than indications for usage, although incomplete information on the latter prevented us from specifically being able to disentangle relationships.

In contrast to ovarian cancer, we saw no evidence of any increases in risk of breast cancer, in line with the majority of recent cohort studies of both pre-IVF (12;17–19;21;37) and IVF (22;25;38–41) exposures. In fact, we observed a significantly decreased risk associated with progesterone exposures. This was somewhat surprising, given findings in a Danish infertility cohort of an increased risk associated with progesterone exposure (21). Further, the addition

of progestins to estrogen therapy for relief of menopausal symptoms has been consistently linked to higher risks of breast cancer than use of estrogens alone (42). However, in IVF, the progestogen that is used is natural progesterone and not synthetic progestogens as used for menopausal therapy, which might explain the discrepant effects.

Based on several studies addressing pre-IVF exposures on endometrial cancer risk (12;18;19;23;24), we had hypothesized that we might observe risk increases, but the associations we observed were quite modest and not statistically significant. The highest risks were among women receiving 1–3 IVF cycles; women with 4 or more cycles showed no increased risks, although small numbers were involved. Previous studies that have observed elevated endometrial cancer risks in relation to fertility drugs have mainly focused on clomiphene, a selective estrogen receptor modulator, with chemical properties similar to tamoxifen (43)--a drug linked with endometrial cancer risk increases (44). In our investigation, however, the majority of drug exposure was to gonadotrophins routinely used for IVF.

In contrast to the other cancers, fertility treatments (including IVF) were consistently associated with significant decreases in the risk of *in situ* cervical cancers; most treatments also led to non-significant decreases in invasive cervical cancers. Although only a limited number of studies have assessed fertility drugs in relation to cervical cancer, our observed risk reductions are consistent with previous observations (19;26;45–47). This could reflect that women seeking treatment for infertility have risk factors that would place them at low risk for cervical cancers (e.g., high social class, limited number of sexual partners). Alternatively, the reduced risks could be due to more extensive Pap smear screening among women routinely seen by gynecologists for infertility evaluations (48). In contrast with our observations of most fertility treatments being associated with reduced cervical cancer risks, such a pattern was not observed for invasive cancers among women who received 4 or more IVF cycles. Although this risk was based on small numbers and was not elevated relative to women receiving no fertility treatments, hormonal factors are increasingly being recognized as important in the progression and persistence of human papillomavirus infection (49), the causal agent for cervical cancer.

Our study had a number of strengths, but also some limitations. This included the relatively short follow-up, resulting in a restricted number of cases among a generally young population of women. In addition, given that we had to rely on information available in medical records, we did not have complete information on all potential confounders. Notable was that we had cause of infertility information for only about half of the study population. For ovarian cancer, it has been well documented that endometriosis can have an independent effect on risk (50–52), although we saw no evidence of differential IVF risks according to the cause of infertility. We also had incomplete information on some risk factors (e.g., BMI) and did not have any information on other recognized risk factors (e.g., family history of cancer, oral contraceptive use), which could have affected our risks. However, the most important factor to control for is likely parity (3), for which we had documented (rather than self-reported) information from registry linkages.

In summary, in this study within a large Israeli HMO, our findings regarding the relationships of fertility drugs and cancer risk were largely reassuring. Notably, we found no convincing relationships of fertility treatments to breast or endometrial cancers. For ovarian cancer, like several previous studies, we noted some evidence of increasing risk with number of IVF cycles, but our relationship was not statistically significant, possibly reflecting small numbers. Given the relatively short follow-up in most studies, including ours, further assessment of long-term effects of IVF should be pursued. This is especially important for ovarian cancer given that the induction period associated with most risk factors may exceed 25 years (53).

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Table 1
 Characteristics of the Study Cohort by Demographic and Other Potential Cancer Risk Factors

	Entire Cohort		Any infertility treatment					
			Yes		No			
	(N=87,403)		(N=67,608)		(N=19,795)			
	mean	sd	mean	sd	mean	sd	n	%
Age on Jan 1, 1998	31	6.4	31	6.4	32	6.3		
Age at cancer diagnosis	39	7.0	39	7.0	39	7.1		
Age at Cohort Entry	n	%	n	%	n	%		
< 25	15,081	17.3	12,842	19.0	2,239	11.3		
25–29	26,366	30.2	20,974	31.0	5,392	27.2		
30–34	22,367	25.6	16,521	24.4	5,846	29.5		
35–39	14,907	17.1	10,812	16.0	4,095	20.7		
40–44	7,082	8.1	5,468	8.1	1,614	8.2		
45 +	1,600	1.8	991	1.5	609	3.1		
Parity Status at Cohort Entry								
Nulliparous	70,365	80.5	55,921	82.7	14,444	73.0		
Parous	17,038	19.5	11,687	17.3	5,351	27.0		
Parity Status at Cohort Exit								
Nulliparous	23,291	26.7	17,532	25.9	5,759	29.1		
Parous	64,112	73.4	50,076	74.1	14,036	70.9		
Number of Children at Exit								
0	23,291	26.7	17,532	25.9	5,759	29.1		
1	22,935	26.2	17,725	26.2	5,210	26.3		
2–3	36,562	41.8	28,567	42.3	7,995	40.4		
4+	4,615	5.3	3,784	5.6	831	4.2		
Body Mass Index (BMI)								
<18.5	2,155	2.5	1,642	2.4	513	2.6		
18.5–24.9	25,793	29.5	19,830	29.3	5,963	30.1		
25–29.9	15,665	17.9	12,319	18.2	3,346	16.9		

	Entire Cohort		Any infertility treatment			
	(N=87,403)		(N=67,608)		(N=19,795)	
	mean	sd	mean	sd	mean	sd
30+	13,290	15.2	10,947	16.2	2,343	11.8
Missing	30,500	34.9	22,870	33.8	7,630	38.6
Smoking						
Ever	9,633	11.0	7,130	10.6	2,503	12.6
Never	56,527	64.7	44,063	65.2	12,464	63.0
Missing	21,243	24.3	16,415	24.3	4,828	24.4
District Group						
Northern Israel	15,098	17.3	11,631	17.2	3,467	17.5
Central Israel	59,690	68.3	46,160	68.3	13,530	68.4
Southern Israel	12,615	14.4	9,817	14.5	2,798	14.1
Socioeconomic Status						
0–10	24,396	27.9	19,215	28.4	5,181	26.2
11–14	21,969	25.1	16,767	24.8	5,202	26.3
15+	22,097	25.3	16,737	24.8	5,360	27.1
Infertility Indication*						
Male infertility	18,721	21.4	17,982	26.6	739	3.7
Anovulation	13,394	15.3	12,201	18.1	1,193	6.0
Mechanical	5,748	6.6	4,595	6.8	1,153	5.8
PCOS	2,439	2.8	2,428	3.6	11	0.1
Pituitary-hypothalamic	261	0.3	229	0.3	32	0.2
Unspecified	73,933	84.6	56,525	83.6	17,408	87.9

* categories are not mutually exclusive

Table 2

Adjusted HRs for Breast and Gynecologic Cancers Associated with Fertility Treatments

	n cases	person-years	HR*	95% CI
Breast				
Any infertility treatment	389	566,539	0.87	(0.72, 1.06)
Any IVF	140	187,820	1.01	(0.83, 1.23)
1–3 cycles	77	106,206	1.00	(0.78, 1.27)
4–6 cycles	32	44,369	0.96	(0.67, 1.38)
7+ cycles	31	37,246	1.10	(0.76, 1.59)
GnRH	118	174,493	0.88	(0.72, 1.09)
Clomiphene	284	426,797	0.94	(0.79, 1.12)
Progestogen	278	450,928	0.77	(0.65, 0.92)
Ovarian				
Any infertility treatment	34	564,275	0.90	(0.45, 1.79)
Any IVF	21	186,918	2.34	(1.30, 4.22)
1–3 cycles	10	105,736	2.05	(0.98, 4.29)
4–6 cycles	7	44,161	3.18	(1.37, 7.40)
7+ cycles	4	37,021	2.12	(0.73, 6.12)
GnRH	11	173,641	0.99	(0.50, 1.96)
Clomiphene	20	425,227	0.65	(0.36, 1.19)
Progestogen	23	449,283	0.69	(0.38, 1.24)
Endometrial				
Any infertility treatment	34	564,934	1.26	(0.56, 2.86)
Any IVF	15	187,312	1.52	(0.80, 2.87)
1–3 cycles	10	105,892	1.83	(0.88, 3.80)
4–6 cycles	3	44,244	1.26	(0.38, 4.15)
7+ cycles	2	37,176	0.97	(0.23, 4.12)
GnRH	12	173,991	1.22	(0.62, 2.39)
Clomiphene	20	425,861	0.68	(0.37, 1.27)
Progestogen	27	449,807	1.14	(0.60, 2.19)
Cervix in situ				
Any infertility treatment	202	566,539	0.48	(0.38, 0.61)
Any IVF	54	187,820	0.62	(0.46, 0.83)
1–3 cycles	28	106,206	0.55	(0.37, 0.81)
4–6 cycles	12	44,369	0.60	(0.34, 1.07)
7+ cycles	14	37,246	0.87	(0.51, 1.49)
GnRH	45	174,493	0.53	(0.39, 0.73)
Clomiphene	140	426,797	0.54	(0.43, 0.67)
Progestogen	142	450,928	0.49	(0.39, 0.61)
Cervix invasive				
Any infertility treatment	21	566,539	0.57	(0.27, 1.19)
Any IVF	10	187,820	1.28	(0.60, 2.70)

	n cases	person-years	HR [*]	95% CI
1–3 cycles	4	106,206	0.91	(0.31, 2.64)
4–6 cycles	3	44,369	1.58	(0.47, 5.29)
7+ cycles	3	37,246	1.98	(0.59, 6.64)
GnRH	4	174,493	0.45	(0.16, 1.28)
Clomiphene	12	426,797	0.47	(0.23, 0.97)
Progestogen	10	450,928	0.30	(0.14, 0.64)

* Adjusted for age at entry, BMI, smoking, parity at exit, and SES

Table 3

Adjusted HRs for Breast and Gynecologic Cancers Associated with Fertility Treatments, Stratified by Parity at Study Exit

		Nulliparous at exit (n=23,291)			Parous at exit (n=64,112)		
		n cases	HR*	95% CI	n cases	HR*	95% CI
Breast							
Any infertility treatment		115	0.69	(0.49, 0.95)	274	0.97	(0.75, 1.25)
Any IVF		43	0.93	(0.66, 1.32)	97	1.01	(0.80, 1.27)
1–3 cycles		21	0.88	(0.55, 1.40)	56	1.01	(0.76, 1.35)
4–6 cycles		10	0.85	(0.45, 1.62)	22	0.99	(0.64, 1.54)
7+ cycles		12	1.14	(0.63, 2.06)	19	1.01	(0.63, 1.61)
GnRH		33	0.80	(0.55, 1.17)	85	0.88	(0.69, 1.12)
Clomiphene		73	0.77	(0.57, 1.05)	211	1.00	(0.80, 1.23)
Progestogen		83	0.67	(0.50, 0.91)	195	0.83	(0.67, 1.02)
Ovarian							
Any infertility treatment		19	0.71	(0.31, 1.64)	15	1.32	(0.38, 4.59)
Any IVF		11	1.81	(0.83, 3.92)	10	3.34	(1.31, 8.54)
1–3 cycles		6	1.93	(0.75, 4.96)	4	2.32	(0.70, 7.74)
4–6 cycles		4	2.50	(0.83, 7.52)	3	4.48	(1.18, 17.00)
7+ cycles		1	0.72	(0.09, 5.42)	3	5.14	(1.34, 19.75)
GnRH		5	0.74	(0.28, 1.96)	6	1.42	(0.53, 3.79)
Clomiphene		9	0.48	(0.21, 1.08)	11	1.05	(0.40, 2.70)
Progestogen		11	0.45	(0.21, 0.97)	12	1.26	(0.47, 3.39)
Endometrial							
Any infertility treatment		19	0.82	(0.32, 2.08)	15	3.73	(0.49, 28.31)
Any IVF		7	0.92	(0.38, 2.22)	8	2.82	(1.06, 7.56)
1–3 cycles		4	1.03	(0.35, 3.04)	6	3.65	(1.26, 10.55)
4–6 cycles		3	1.60	(0.47, 5.47)	0	--	--
7+ cycles		0	--	--	2	3.83	(0.81, 18.24)
GnRH		5	0.73	(0.27, 1.94)	7	2.30	(0.85, 6.20)
Clomiphene		10	0.56	(0.25, 1.26)	10	1.01	(0.36, 2.78)

	Nulliparous at exit (n=23,291)		Parous at exit (n=64,112)	
	n cases	HR* 95% CI	n cases	HR* 95% CI
Progestogen	17	1.18 (0.50, 2.77)	10	0.98 (0.35, 2.73)

* Adjusted for age at entry, BMI, smoking, and SES