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Cancer in Women after Assisted Reproductive Technology

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Abstract

Objective—To evaluate the risk of cancer after assisted reproductive technology (ART) therapy.

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Design—Longitudinal cohort of New York, Texas, and Illinois residents between 2004-09, treated with ART, and whose cycles were reported to the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System (SART CORS).

Setting—Not applicable

Patients—Cycles of 113,226 women, including 53,859 women without prior ART treatment, were linked to their respective Cancer Registries. Standardized incidence ratios (SIR) and their 95% confidence intervals were calculated, comparing the observed to expected cancer cases based on age-specific cancer rates in the general population of each State. Among the cohort of women without prior ART therapy, hazard ratios (HR) and 95% confidence intervals were calculated for treatment parameters and reproductive history factors.

Intervention—None

Main Outcome Measures—Diagnosis of cancer, as reported to the State Cancer Registry

Results—Mean follow-up was 4.87 years; among women without prior ART, 450 women developed 460 cancers. Women treated with ART had significantly lower risks for all cancers (for all women: SIR 0.78, 0.73-0.83; and women without prior ART: SIR 0.75, 0.68-0.82), breast cancer, and all female genital cancers; nonsignificant lower risks for endocrine and uterine cancer; and nonsignificant higher risks for melanoma and ovarian cancer. Among women without prior ART, there were no significant increased HRs by parity, number of cycles, cumulative FSH dosage, or cycle outcome.

Conclusions—These results suggest no greater risks for developing cancer after nearly 5 years of follow-up compared to the general population, and to other women treated with ART.

Capsule—These results suggest no greater short-term risks for developing cancer compared to the general population, and to other women treated with ART.

Keywords

cancer risk; assisted reproductive technology; pregnancy outcome; fertility

Introduction

Use of assisted reproductive technology (ART), defined as medical procedures involving the *ex vivo* manipulation of both male and female gametes to achieve conception, has risen steadily in the United States during the past two decades due to several reasons including childbearing at older maternal ages and increasing insurance coverage (1-3). The number of ART cycles in the United States has increased by 76% between 2000 and 2012 (from 99,629 to 176,247) (4, 5). Risk factors for both infertility and cancer often coexist, including low parity, early menarche and late menopause, older age at first birth, and lower incidence and duration of breastfeeding. The incidences of cancers with a hormonal etiology among infertile women who receive ART are of particular interest, because the therapy itself could potentially modify the hormonal environment and contribute to malignant cellular changes. Women with primary infertility (those who have never been able to conceive) are at an increased risk of uterine and ovarian cancers (6); studies suggest that the risk is attributable to the underlying cause of infertility. Specifically, a history of infertility, tubal factors,

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endometriosis, older age at first pregnancy, polycystic ovarian syndrome, and pelvic inflammatory disease have each been associated with greater risks of gynecologic cancers (7-18). Theoretically, ovulation-inducing drugs may exert a carcinogenic effect through incessant ovulation; the trauma to the ovarian surface epithelial cells caused by ovulation may render the ovaries sensitive to this process (19-22). The association between exogenous hormone use and breast cancer is well established (23-25). Ovarian epithelial dysplasia has been associated with ovulation induction therapy, which could be a precursor of invasive neoplastic disease (26, 27). Despite the available evidence from case-control and small clinical studies, there is a need for larger, population-based, contemporary prospective research to clarify the relationship between infertility, its treatment, and the risk of cancer. The purpose of this study was to compare the incidence of cancers among women treated for ART to the general population of women, with record linkage of the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database to the New York, Texas, and Illinois State Cancer Registries.

Methods and Methods

Study Data and Oversight

The SART CORS database contains comprehensive data from more than 90% of all clinics providing assisted reproductive technology in the United States (http://www.sart.org). Data were collected and verified by SART and reported to the Center for Disease Control and Prevention (CDC) in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). In 2004, after a contract change with the CDC, SART gained access to the SART CORS data system for the purposes of conducting research. The SART CORS database is left-censored at 2004, that is, ART treatment details for women prior to 2004 are not available. SART makes deidentified clinical data available for research purposes to persons or entities who have agreed to comply with SART research guidelines. Patients undergoing assisted reproductive technology at SART-associated clinics sign clinical consent forms that include permission to use their deidentified data for research. The data are submitted by individual clinics and verified by the practice director of each clinic. Approximately 10% of the clinics are audited each year by the CDC and SART to validate the accuracy of the reported data (5). The study was approved by the Institutional Review Boards at Michigan State University, the University of Minnesota, the New York State Department of Health, the Texas Department of State Health Services, and the Illinois Department of Public Health. Data were analyzed using SAS 9.2 software (Cary, NC).

New York, Texas, and Illinois maintain population-based Cancer Registries that have consistently received Gold certification by the North American Association of Central Cancer Registries during 2004-2009 (http://www.naaccr.org/Certification/USCert2011.aspx). Data available from the Cancer Registries included cancer site, morphology, International Classification of Disease for Oncology codes, age at diagnosis, and cancer stage at diagnosis.

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Linkage procedures

The SART CORS database is maintained by Redshift Technologies, Inc. for the Society for Assisted Reproductive Technology (SART). Cycles in the database to women who were residents of New York, Texas, or Illinois treated between January 1, 2004 and December 31, 2009 were linked by Redshift Technologies, Inc. Cycles for the same woman which occurred within one clinic were linked using the woman's birth date, first and last names, and social security number (when present). Cycles across clinics to the same woman were linked with the additional factors of partner's name and the sequence of ART outcomes. Cycles linked to individual women enabled the calculation of cumulative exposures (28-30). Redshift Technologies, Inc. also generated study-specific unique identifiers (for each woman and each cycle).

SART CORS data to State Cancer Registries

Redshift Technologies, Inc. sent a data file of women who were in the SART CORS and were residents of each State to the respective State Cancer Registries; the data file included the woman's first and last names, social security number (when present), date of birth, zip code of residence, and the unique identifiers. In order to achieve uniform results, all three States used probabilistic record linkage with Link Plus software, available through the Centers for Disease Control and Prevention (CDC)'s National Program of Cancer Registries (NCPR). Each of the three State Cancer Registries then linked reported cancers for each woman in the data file (linked SART CORS/cancer files). Identifying variables (including names, dates, and social security numbers) were then removed and the de-identified analytic file (which included the unique identifiers) was sent to the investigators. The final linked SART CORS/cancer files were stripped of any data elements that could identify an individual. For instance, the final file did not contain names, date of birth, or any geographic unit smaller than the State itself.

SART CORS data to Investigators

Redshift Technologies, Inc. sent the investigators a data file of the unique identifiers, woman's age, reproductive history, and ART treatment and outcome data to link to the SART CORS/cancer files received from each of the three States. The SART CORS data records for each woman were ordered by date of treatment at cycle initiation, regardless of cycle type (fresh or thawed, autologous or donor). The data from each woman was then summarized into a single record that included data from the initial ART treatment, such as patient age, as well as the total number of cycles, total FSH and clomiphene citrate doses over all ART cycles reported. Using the data from each State, the earliest malignancy and its site of occurrence were identified for each woman; three malignancies that were classified as 'unknown primary site' were deleted. The two files were then merged so that the final file included women with and without malignancies. Women identified as having a cancer diagnosis prior to ART and through six months post initiation of ART therapy, were excluded from this analysis.

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Independent Variables

Diagnoses were defined for data entry to SART CORS as follows: male factor was the presence of abnormal semen parameters or function; endometriosis was the presence of any stage of endometriosis whether treated or untreated; ovulation disorders could have several differing definitions including multiple cysts affecting fertility, oligoovulation, or anovulation; diminished ovarian reserve was defined as high follicle stimulating hormone or estradiol in the early follicular stage as measured on a clomiphene challenge test, or reduced ovarian volume, but could also have been defined by advanced maternal age for some earlier cycles in our cohort; tubal factor was any condition affecting the patency of the Fallopian tubes; uterine factor included any uterine abnormality. The category of other factors included immunologic, chromosomal, cancer, and any other conditions not listed in the previously defined categories. Unexplained was intended to be an absence of any defined male and female diagnoses in a couple with at least one year of unprotected intercourse without conception.

Independent variables included State (New York, Texas, or Illinois), year of ART treatment (2004, 2005, 2006, 2007, 2008, 2009), age at cycle start in years (categorized as 18-29, 30-34, 35-37, 38-40, 41-43, and 44-64), parity (0, 1, ≥2), infertility diagnosis (male factor, endometriosis, ovulation disorders, diminished ovarian reserve, tubal factors, other factors, and unexplained), number of infertility diagnoses (1 or >1), number of ART cycles (1, 2, 3, 4, or ≥5), cumulative follicle stimulating hormone (FSH) dosage (none, <2,000 IU, 2,000-3,999 IU, 4,000-6,999 IU, and ≥7,000IU), cumulative clomiphene citrate dosage (none, 1-499 mg, and ≥500 mg), and ART outcome (live birth, conception but no live birth, or no conception).

Follow-Up Periods

Follow-up periods after date of last treatment were until December, 2010 for New York, and December, 2012 for Texas and Illinois. Years of follow-up were rounded (i.e., 1 year = 6-18 months) as month of diagnosis was not provided for all records. For women who were diagnosed with cancer, the follow-up period was censored at the time of diagnosis.

Statistical Analysis

For each woman, the expected probability of cancer incidence was computed using age and State of residence. Because race/ethnicity was unknown for many women in the SART CORS database, the rates used were for the entire State population. These expected probabilities were then summed over all subjects or all in a specified cohort to produce an estimate of the expected count of cancers. Standardized incidence ratios (SIRs) and their 95% confidence intervals (CIs) were calculated for the observed/expected ratios for all women and for women without prior ART, both with and without the ART diagnosis of Other, since that diagnosis may include a history of prior cancer. Within the cohort of women treated with ART we examined associations with treatment parameters (including cumulative treatment), pregnancy, and reproductive history.

Hazard ratios can only be computed for subjects for whom the length of exposure is known; therefore, the primary analyses and data presentation are limited to the 53,859 women

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without ART treatment prior to their first cycle recorded in the SART CORS database. These data were analyzed using Cox proportional hazards regression (reported as hazard ratios, HR, and 95% confidence intervals), with person-time beginning at the first cycle of ART and extending until diagnosis of cancer or the end of the follow-up period.

When estimating the hazard ratios by the Cox proportional hazard models, we adjusted variables that could be determined earlier in the treatment cycle; i.e., age at cycle start was adjusted for State and year of ART treatment; the variables of parity, infertility diagnosis, and number of infertility diagnoses were adjusted for age at cycle start, State, and year of ART treatment; number of ART cycles was adjusted for infertility diagnosis and number of infertility diagnoses, parity, age at cycle start, and year of ART treatment; cumulative FSH dosage was adjusted for infertility diagnosis, number of ART cycles and diagnoses, parity, age at cycle start, State, and year of ART treatment; and ART outcome was adjusted for cumulative FSH dosage, infertility diagnosis, number of ART cycles and diagnoses, parity, age at cycle start, State, and year of ART treatment.

Results

The study population included 114,601 women, including 63,642 from New York, 23,888 from Texas, and 27,071 from Illinois. Records were eliminated for women who had data from more than one State (654 women), those with a diagnosis of cancer prior to ART treatment (717), one with missing age, and 3 with an unknown type of cancer. The final study population included 113,226 women, of whom 53,872 did not have prior ART (26,837 from New York, 12,231 from Texas, and 14,804 from Illinois). Of these 53,872 women, 450 were subsequently diagnosed with cancer; 10 women were also diagnosed with a second cancer, with 263,457 person-years of follow-up (mean 4.87 ± 2.01 years). The number of cancers reported was 460 overall, including 71 endocrine, 42 melanoma, 185 breast, 21 ovarian, 26 uterine, and 67 all-female genital (cervix, uterus, other female genitalia, ovary, vagina, and vulva). The number of women with cancer by State was: New York: 228, Texas: 85, and Illinois: 137. For all cancers, 25% were diagnosed an average of one year after ART, 21% two years after, and 54% three or more years after ART; for the cancers of breast, endocrine, female genitalia, and melanoma, these proportions were 24%, 28%, and 48%, respectively. The mean age at cancer diagnosis was 40.8 ± 5.7 years. Among women treated with ART, those who were diagnosed with cancer were significantly older at the start of ART treatment (37.8 ± 5.4 years vs 35.3 ± 5.3 years, $p<0.0001$), but did not differ in parity, number of ART cycles, or ART outcome. They were more likely to have the diagnosis of diminished ovarian reserve (31.1% vs 22.1%, $p<0.0001$), more than one infertility diagnosis (29.3% vs 24.6%, $p=0.02$), and to have received a lower cumulative dose of FSH. A description of the study population is shown in Table 1. Less than 3.5% of women received any dosage of clomiphene citrate; these results are not shown.

A comparison of SIRs and 95% CIs for all women, women without prior ART, and by age at cycle start is presented in Table 2. Women treated with ART had significantly lower risks than the general population of women for all cancers (SIRs of 0.71 to 0.78), breast cancer (SIRs of 0.74 to 0.83), and all female genital cancers (SIRs of 0.63 to 0.72); nonsignificant risks for endocrine (SIRs of 0.88 to 1.02), uterine cancer (SIRs of 0.73 to 0.82), melanoma

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(SIRs of 1.07 to 1.15) and ovarian cancer (SIRs of 0.96 to 1.18). Among women without prior ART, the risk of cancer was lower at the same age group of cycle start compared to women in the general population for all cancers (SIRs of 0.66 to 0.84), and not significant within specific cancers. Excluding women with the diagnosis of Other (which may include cancer) did not substantially change the SIRs among all women or among women without prior ART.

The hazard ratios (HR) and 95% CIs for the risk of cancer within the cohort of women treated with ART by age of cycle start are presented in Table 3. Older age at start of ART therapy was associated with a significantly increased HR for all cancers, and breast and female genital cancers. However, since the SIRs associated with age (Table 2) are similar, this was most likely due to increasing age and not related to ART.

The hazard ratios (HR) and 95% CIs for the risk of cancer within the cohort of women treated with ART are shown in Table 4. Women with the diagnosis of uterine factor were at increased risk for melanoma (HR 2.86, 95% CI 1.15-7.22). Women with the diagnosis of male factor infertility or endometriosis were at increased risk for breast cancer (HR 1.57, 95% CI, 1.10-2.24, and HR 1.68, 95% CI 1.02-2.78, respectively), and women with the diagnosis of other factors were at increased risk for all cancers (HR 1.35, 95% CI 1.04-1.75) and breast cancer (HR 1.60, 95% CI 1.07-2.39). Women with more than one infertility diagnosis were at increased risk for breast cancer (HR 1.44, 95% CI 1.06-1.97). Women with an ART outcome of no conception or conception but no live birth were at increased risk for uterine cancer (HR 3.71, 95% CI 1.19-11.85, and HR 5.54, 95% CI 1.36-23.30, respectively) compared to women who had a live birth outcome. Overall, there were no other increased risks by parity, ART outcome, number of diagnoses or ART cycles, or cumulative FSH dosage.

Discussion

In this large study of women who initiated ART between 2004 and 2009 in New York, Texas, and Illinois, we observed no evidence of increased risk of cancers after nearly 5 years of follow-up relative to age-specific general population rates. These three States were chosen for this study because they are large and ethnically diverse, ranking 1st, 4th, and 5th in number of ART cycles in the US, respectively, in 2012 (5). The advantage of this study over prior reports is the population-based design, follow-up of contemporary ART regimens (2004-09), large sample size (more than 50,000 women treated with ART), and the use of a national ART database with validated exposure data.

Our findings of a lower risk of breast cancer after ART compared to the general population confirm results from other population-based studies in Sweden (31, 32), the United States (33, 34), and two recent meta-analyses (35, 36). The lack of associations between ART and risks of ovarian or uterine cancer are consistent with the findings from a recent review and two meta-analyses (37-39). Although our study included a larger number of incident cases than many other reports (n = 21 for ovarian cancer, and n =26 for uterine cancer), our findings showed no significant associations for either type of cancer by age at cycle start, parity, infertility diagnosis, number of ART cycles, cumulative FSH dosage over all cycles

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of treatment, or ART outcome. Our findings, though, are limited by a relatively short period of follow-up and small numbers in strata by ART and patient characteristics.

As a subset of all subfertile and infertile women, those who receive ART therapy may differ from other women in several important aspects. Women who receive ART treatment are on average significantly more affluent and with higher educational attainment, are leaner, have a lower intake of alcohol, are less likely to smoke, and are more likely to exercise vigorously than those with infertility who do not seek or cannot obtain treatment, factors which may indicate a low risk population for cancer relative to the general population (1, 40).

While this study is the largest prospective study of the association between ART and cancer risk to date, it is subject to several limitations in addition to those expressed above. The SART CORS database lacks information on family history of cancer, age at menarche and first birth, breastfeeding history, and the use of contraceptive drugs and hormone replacement therapy. In addition, the use of the SIR has inherent limitations, due to the absence of data on the reproductive factors listed above in both the ART group and women in the general population. Since the diagnosis of Other may include women with cancer diagnosed in another state, we recalculated the SIRs without women who had this diagnosis; this exclusion did not substantially change the SIRs (Table 2). There was a difference in follow-up among the three States in this study (New York through December, 2010, and Texas and Illinois through December, 2012). We are planning on continuing and expanding this study, with longer and more consistent periods of follow-up in the future.

One of the greatest challenges in conducting an evaluation of cancer risk after ART exposure is the changing nature of ART therapy. Since the 1960s, clomiphene citrate has been the primary medication to treat ovulatory disorders (41, 42). GnRH agonists were introduced in 1987 and GnRH antagonists became clinically available in 1999; these are currently the most commonly used medications in IVF protocols. Most recently, aromatase inhibitors have gained wider acceptance, in combination with follicle stimulating hormone (43). Therefore, studies with follow-up of treatments prior to 1990 (45, 33, 34, 44-56) are evaluating the long-term effects of regimens and dosages which are no longer in use. Likewise, the potential adverse long-term effects of the newest protocols will not be known for years, or even decades from now.

Perhaps of greatest importance to interpretation of these data is the small number of incident cases of cancer among this cohort of greater than 50,000 exposed women. This is, in part, due to the relatively short duration of follow-up and low expected rate of cancer among women who on average remain within their 40s during the full duration of person-time contribution. It may be that the effect of ART on cancer risk is not evident until the postmenopausal years, when cancer incidence due to all causes increases. The observation that cancer risk, overall and breast and genital cancers in particular, may be lower among women who have undergone ART is of interest and requires replication in expanded large national and international populations. Future investigation of associations by subtypes of cancer is warranted, particularly with respect to the endogenous hormonal milieu, which differs by estrogen and progesterone receptor status (57).

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In conclusion, this large contemporary study suggests that the short-term risk of cancer is not increased among women of reproductive age who have had ART treatment. ART, or the characteristics of women who receive it, may be associated with a lower risk overall and for breast and female genital cancers. Future studies should include expansion to a broader geographic catchment regions and greater duration of follow-up after ART therapy.

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Table 1

Characteristics of 53,859 Women Without Prior ART Treatment Undergoing ART in New York Texas, and Illinois between 2004 and 2009

	All	Women	Women	Person-years	P Value*
	Women	Without Cancer	With Cancer	Of Follow-up	Between groups
(N)	53,859	53,409	450	262,309	
Age at cancer diagnosis (mean years, SD)			40.8 ± 5.7		
Age at Start of ART Treatment (mean years, SD)	35.3 ± 5.3	35.3+5.3	37.8 ± 5.4		<0.0001
(%) <30	14.4	14.4	7.1	38,841	
31-34	30.0	30.1	19.1	81,164	
35-37	20.4	20.4	19.6	54,091	
38-40	17.7	17.7	24.4	44,910	
41-42	11.8	11.8	16.4	29,477	
≥43	5.7	5.7	13.3	13,826	
(%) Parity					
0	77.5	77.6	74.9	202,859	
1	14.1	14.0	16.7	37,289	0.27
≥2	8.4	8.4	8.4	22,161	
Infertility Diagnosis (%), more than one is possible					
Male factor	32.8	32.8	31.8	86,981	0.69
Endometriosis	9.1	9.2	8.4	25,379	0.68
PCOS	12.7	12.7	10.7	35,538	0.91
Diminished Ovarian Reserve	22.2	22.1	31.1	54,714	<0.0001
Tubal factors	20.2	20.2	17.1	54,322	0.11
Uterine factors	5.2	5.2	6.2	13,267	0.34
Other factors	14.9	14.9	20.9	39,626	0.0007
Unexplained	12.3	12.4	10	32,837	0.15
(%) Number of Diagnoses					
1	75.3	75.4	70.4	195,396	0.02
>1	24.7	24.6	29.3	66,913	
Number of Cycles (%)					
1	51.1	51.1	48	126,957	
2	26.1	26.2	25.6	69,729	
3	12.4	12.4	14.7	34,680	0.45
4	5.5	5.5	6.4	16,259	
≥5	4.9	4.8	5.3	14,684	
Cumulative dose of FSH Stimulation (%)					
none	7.7	7.7	12.2	20,017	0.0003
<2,000 IU	19	19.0	14.4	49,525	

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	All	Women	Women	Person-years	P Value*
2,000-3,999 IU	29.8	29.9	26	76,791	
4,000-6,999 IU	21.6	21.6	22.4	56,061	
7,000+ IU	21.8	21.8	24.9	59,915	
ART Outcome: Live birth	49.1	49.2	44.4	132,594	
Conception, no live birth	7.5	7.5	8.9	19,459	0.12
No conception	43.3	43.3	46.7	110,256	

*P-values calculated from chi-square test or two-sample t-test (age)

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Table 2

Comparison of Standardized Incidence Ratios (SIRs) and 95% Confidence Intervals (CI) by Study Group and Exclusions

		All Cancers				Endocrine				Melanoma				Breast				Ovary				Uterus				All Female Genital Cancers			
		# Cancers				# Cancers				# Cancers				# Cancers				# Cancers				# Cancers				# Cancers			
Group	**Categories**	**Exp**	**Obs**	**SIR**	**95% CI**	**Exp**	**Obs**	**SIR**	**95% CI**	**Exp**	**Obs**	**SIR**	**95% CI**	**Exp**	**Obs**	**SIR**	**95% CI**	**Exp**	**Obs**	**SIR**	**95% CI**	**Exp**	**Obs**	**SIR**	**95% CI**	**Exp**	**Obs**	**SIR**	**95% CI**
All women	All Diagnoses	1,232.11	955	**0.78**	0.73, 0.83	147.06	150	**1.02**	0.86, 1.20	70.76	76	**1.07**	0.85, 1.34	487.93	404	**0.83**	0.75, 0.91	40.67	48	**1.18**	0.87, 1.56	64.13	49	**0.76**	0.57, 1.01	186.20	128	**0.69**	0.57, 0.82
All women	Excluding Dx of Other	1,023.05	767	**0.75**	0.70, 0.80	125.27	120	**0.96**	0.79, 1.15	59.50	64	**1.08**	0.83, 1.37	402.65	323	**0.80**	0.72, 0.89	33.64	39	**1.16**	0.82, 1.58	52.79	39	**0.74**	0.53, 1.01	154.78	98	**0.63**	0.51, 0.77
No prior ART	All Diagnoses	613.69	460	**0.75**	0.68, 0.82	75.28	71	**0.94**	0.74, 1.19	36.55	42	**1.15**	0.83, 1.55	239.93	185	**0.77**	0.66, 0.89	20.21	21	**1.04**	0.64, 1.59	31.56	26	**0.82**	0.54, 1.21	93.61	67	**0.72**	0.55, 0.91
No prior ART	Excluding Dx of Other	508.21	363	**0.71**	0.64, 0.79	63.99	56	**0.88**	0.66, 1.14	30.72	35	**1.14**	0.79, 1.58	197.22	145	**0.74**	0.62, 0.87	16.67	16	**0.96**	0.55, 1.56	25.92	19	**0.73**	0.44, 1.14	77.66	50	**0.64**	0.48, 0.85
No prior ART	All Diagnoses																												
Age at cycle start	18-29	38.94	32	**0.82**	0.56, 1.16	8.27	9	**1.09**	0.50, 2.06	3.87	6	**1.55**	0.57, 3.37	9.19	4	**0.44**	0.12, 1.11	1.28	1	**0.78**	0.02, 4.35	1.43	1	**0.70**	0.02, 3.90	6.70	4	**0.60**	0.16, 1.53
	30-34	130.18	87	**0.67**	0.54, 0.82	21.85	18	**0.82**	0.49, 1.30	9.77	11	**1.13**	0.56, 2.01	43.77	25	**0.57**	0.37, 0.84	4.13	5	**1.21**	0.39, 2.83	5.90	6	**1.02**	0.37, 2.21	21.76	14	**0.64**	0.35, 1.08
	35-37	122.69	89	**0.73**	0.58, 0.89	16.04	15	**0.94**	0.52, 1.54	7.63	6	**0.79**	0.29, 1.71	48.94	32	**0.65**	0.45, 0.92	3.84	6	**1.56**	0.57, 3.40	5.97	1	**0.17**	0.00, 0.93	18.94	12	**0.63**	0.33, 1.11
	38-40	137.96	116	**0.84**	0.69, 1.01	14.23	16	**1.12**	0.64, 1.83	7.33	9	**1.23**	0.56, 2.33	59.53	52	**0.87**	0.65, 1.15	4.46	3	**0.67**	0.14, 1.96	7.07	4	**0.57**	0.15, 1.45	19.99	13	**0.65**	0.35, 1.11
	41-43	112.92	75	**0.66**	0.52, 0.83	9.88	6	**0.61**	0.22, 1.32	5.23	7	**1.34**	0.54, 2.76	49.15	37	**0.75**	0.53, 1.04	3.92	3	**0.77**	0.16, 2.24	6.30	9	**1.43**	0.65, 2.71	15.96	15	**0.94**	0.53, 1.55
	44-64	71.01	61	**0.86**	0.66, 1.10	4.99	7	**1.40**	0.56, 2.89	2.71	3	**1.11**	0.23, 3.23	29.35	35	**1.19**	0.83, 1.66	2.57	3	**1.17**	0.24, 3.41	4.89	5	**1.02**	0.33, 2.39	10.25	9	**0.88**	0.40, 1.67

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Table 3

Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Risk of Cancer after ART among Women without Prior ART Treatment by Age at Cycle Start*

		All Cancers			Endocrine			Melanoma			Breast			Ovary			Uterus			All Female Genital		
N (number of cancers)		(460)			(71)			(42)			(185)			(21)			(26)			(67)		
		HR	**95% CI**	**P Value***	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**
Age at	18-29	**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference	
Cycle Start	30-34	**1.27**	0.85, 1.92		**0.96**	0.43, 2.16		**0.88**	0.32, 2.42		**2.95**	1.02, 8.65		**1.88**	0.21, 17.57		**2.74**	0.33, 23.74		**1.52**	0.49, 4.76	
	35-37	**1.92**	1.28, 2.90	<0.0001	**1.16**	0.51, 2.70	0.59	**0.71**	0.23, 2.25	0.75	**5.59**	1.98, 16.15	<0.0001	**4.05**	0.49, 35.18	0.31	**0.66**	0.04, 11.10	0.01	**2.06**	0.66, 6.54	0.01
	38-40	**2.86**	1.92, 4.27		**1.36**	0.59, 3.16		**1.28**	0.45, 3.68		**10.43**	3.76, 29.51		**1.64**	0.15, 19.08		**3.06**	0.34, 28.72		**2.25**	0.72, 7.26	
	41-43	**2.87**	1.89, 4.39		**0.81**	0.29, 2.32		**1.49**	0.50, 4.57		**11.61**	4.13, 33.31		**3.54**	0.37, 35.88		**10.01**	1.26, 82.78		**4.55**	1.51, 14.09	
	44-64	**4.88**	3.17, 7.59		**1.90**	0.70, 5.24		**1.36**	0.34, 5.65		**23.20**	8.23, 66.86		**7.68**	0.79, 78.24		**9.30**	1.03, 87.78		**5.24**	1.57, 17.95	

*Models adjusted for State, and year of ART treatment

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Table 4

Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Risk of Cancer after ART among Women without Prior ART Treatment

		All Cancers			Endocrine			Melanoma			Breast			Ovary			Uterus			All Female Genital		
N (number of cancers)		(460)			(71)			(42)			(185)			(21)			(26)			(67)		
		HR	**95% CI**	**P Value***	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**
Parity[1]	0	**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference	
	1	**1.10**	0.86, 1.42	0.57	**1.35**	0.73, 2.52	0.54	**0.78**	0.30, 2.03	**0.81**	**1.24**	0.85, 1.82	0.43	**2.07**	0.72, 6.03	0.40	**0.71**	0.21, 2.43	0.60	**0.88**	0.43, 1.83	0.71
	≥ 2	**0.90**	0.64, 1.27		**0.82**	0.33, 2.11		**0.76**	0.23, 2.57		**0.89**	0.53, 1.51		**1.39**	0.31, 6.49		**0.41**	0.05, 3.15		**0.67**	0.24, 1.89	
Diagnosis[1]	Male factor	**1.14**	0.90, 1.45		**1.17**	0.65, 2.14		**0.52**	0.22, 1.27		**1.57**	1.10, 2.24		**1.25**	0.39, 4.03		**0.35**	0.10, 1.30		**1.07**	0.58, 2.01	
	Endometriosis	**1.05**	0.74, 1.50		**0.57**	0.20, 1.66		**1.56**	0.61, 4.07		**1.68**	1.02, 2.78		**0.70**	0.09, 5.78		**0.48**	0.06, 3.85		**0.62**	0.19, 2.09	
	Ovulation Disorders	**0.92**	0.67, 1.26		**1.30**	0.64, 2.68		**0.96**	0.34, 2.74		**0.73**	0.41, 1.30		**0.39**	0.05, 3.24		**2.11**	0.76, 6.00		**1.26**	0.61, 2.63	
	Dim. Ovarian Res.	**1.07**	0.82, 1.40	0.15	**0.72**	0.34, 1.54	0.73	**0.79**	0.31, 2.07	0.16	**1.37**	0.93, 2.03	0.03	**2.49**	0.69, 9.14	0.69	**0.68**	0.24, 1.97	0.25	**1.32**	0.67, 2.62	0.56
	Tubal factors	**0.79**	0.26, 2.43		**0.48**	0.03, 7.16		--	--		**0.97**	0.16, 6.29		**1.00**	0.02, 69.31		--	--		**0.64**	0.03, 15.76	
	Uterine factors	**1.07**	0.72, 1.58		**0.48**	0.12, 2.03		**2.86**	1.15, 7.22		**1.30**	0.75, 2.29		--	--		**1.89**	0.55, 6.71		**0.83**	0.26, 2.76	
	Other factors	**1.35**	1.04, 1.75		**1.27**	0.64, 2.55		**0.98**	0.39, 2.51		**1.60**	1.07, 2.39		**1.81**	0.50, 6.71		**1.39**	0.53, 3.72		**1.72**	0.91, 3.29	
	Unexplained	**1.07**	0.72, 1.58		**0.59**	0.20, 1.77		**1.31**	0.44, 3.99		**1.51**	0.85, 2.72		**1.04**	0.16, 6.86		**0.30**	0.03, 2.78		**0.78**	0.27, 2.31	
Number of	1	**1.00**	Reference	0.22	**1.00**	Reference	0.85	**1.00**	Reference	0.75	**1.00**	Reference	0.02	**1.00**	Reference	0.91	**1.00**	Reference	0.32	**1.00**	Reference	0.21
Diagnoses[1]	>1	**1.14**	0.93, 1.40		**1.05**	0.62, 1.81		**1.12**	0.57, 2.23		**1.44**	1.06, 1.97		**1.06**	0.38, 3.04		**1.53**	0.67, 3.54		**1.41**	0.83, 2.42	
Number of	1	**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference	
ART cycles[2]	2	**0.95**	0.76, 1.20		**0.96**	0.53, 1.76		**1.65**	0.80, 3.46		**0.94**	0.66, 1.35		**0.69**	0.21, 2.25		**1.33**	0.52, 3.46		**0.69**	0.37, 1.31	
	3	**1.07**	0.81, 1.42	0.86	**1.73**	0.93, 3.26	0.27	**1.38**	0.53, 3.66	0.58	**0.68**	0.41, 1.14	0.55	**0.65**	0.14, 3.10	0.64	**1.91**	0.69, 5.43	0.71	**0.94**	0.46, 1.94	0.85
	4	**0.98**	0.66, 1.46		**0.74**	0.22, 2.50		**1.00**	0.23, 4.54		**1.16**	0.67, 2.03		**2.08**	0.56, 7.90		**0.61**	0.08, 5.01		**0.97**	0.37, 2.54	
	≥5	**0.83**	0.54, 1.28		**0.52**	0.12, 2.27		**2.10**	0.68, 6.66		**0.84**	0.45, 1.61		--	--		--	--		---	---	
Cumulative	None	**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference	
FSH dosage[3]	<2,000	**1.01**	0.67, 1.53		**2.61**	0.75, 9.23		**1.82**	0.41, 8.31		**0.75**	0.38, 1.51		**0.44**	0.09, 2.34		**2.59**	0.53, 13.09		**1.19**	0.45, 3.20	
	2,000-3,999	**1.07**	0.73, 1.56	0.96	**2.30**	0.69, 7.85	0.55	**1.58**	0.38, 6.83	0.72	**1.11**	0.64, 1.95	0.74	**0.07**	0.01, 0.72	0.17	**1.95**	0.42, 9.39	0.20	**0.80**	0.32, 2.05	0.59
	4,000-6,999	**1.02**	0.71, 1.48		**1.81**	0.54, 6.23		**0.88**	0.20, 4.08		**1.08**	0.64, 1.85		**0.25**	0.05, 1.30		**2.16**	0.52, 9.28		**0.68**	0.27, 1.72	
	≥7,000	**0.94**	0.65, 1.39		**1.59**	0.46, 5.61		**1.27**	0.30, 5.43		**1.08**	0.62, 1.89		**0.56**	0.12, 2.70		**0.47**	0.08, 2.71		**0.63**	0.24, 1.68	

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		All Cancers			Endocrine			Melanoma			Breast			Ovary			Uterus			All Female Genital		
N (number of cancers)		**(460)**			**(71)**			**(42)**			**(185)**			**(21)**			**(26)**			**(67)**		
		HR	**95% CI**	**P Value***	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**
ART	Live birth	**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference		**1.00**	Reference	
Outcome[4]	Conception, no live birth	**1.17**	0.83, 1.66	0.67	**1.07**	0.47, 2.45	0.11	**1.38**	0.51, 3.83	0.73	**1.30**	0.76, 2.25	0.57	**2.03**	0.54, 7.80	0.26	**5.54**	1.36, 23.30	0.04	**1.80**	0.77, 4.31	0.39
	No conception	**1.01**	0.82, 1.25		**0.57**	0.33, 1.00		**0.92**	0.46, 1.85		**1.14**	0.81, 1.59		**0.62**	0.21, 1.85		**3.71**	1.19, 11.85		**1.21**	0.69, 2.15	

[1] Models adjusted for age at cycle start, State, and year of ART treatment

[2] Models adjusted for infertility diagnosis and number of diagnoses, parity, age at cycle start, State, and year of ART treatment

[3] Models adjusted for number of cycles, infertility diagnosis and number of diagnoses, parity, age at cycle start, State, and year of ART treatment

[4] Models adjusted for cumulative FSH dosage, number of cycles, infertility diagnosis and number of diagnoses, parity, age at cycle start, State, and year of ART treatment

* P-values, Wald statistic.