Research Article

Cancer Epidemiology, Biomarkers & Prevention

Cancer Risk in Women Treated with Fertility Drugs According to Parity Status—A Registry-based Cohort Study

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Abstract

Background: Long-term safety of assisted reproductive techniques (ART) is of interest as their use is increasing. Cancer risk is known to be affected by parity. This study examined the risk of cancer after fertility treatment, stratified by women's parity.

Methods: Data were obtained from all women ($n = 1,353,724$) born in Norway between 1960 and 1996. Drug exposure data (2004–2014) were obtained from the Norwegian Prescription Database (drugs used in ART and clomiphene citrate). The Medical Birth Registry of Norway provided parity status. HRs were calculated for all site cancer, breast, cervical, endometrial, ovarian, colorectal, central nervous system, thyroid cancer, and malignant melanoma.

Results: In 12,354,392 person-years of follow-up, 20,128 women were diagnosed with cancer. All-site cancer risk was 1.14 [95% confidence interval (95% CI), 1.03–1.26] and 1.10 (95% CI, 0.98–1.23) after clomiphene citrate and ART exposure, respectively. For ovarian cancer, a stronger association was observed for both exposures in nulliparous (HR, 2.49; 95% CI, 1.30–4.78; and HR, 1.62; 95% CI, 0.78–3.35) versus parous women (HR, 1.37; 95% CI, 0.64–2.96; and HR, 0.87; 95% CI, 0.33–2.27). Elevated risk of endometrial cancers was observed for clomiphene citrate exposure in nulliparous women (HR, 4.49; 95% CI, 2.66–7.60 vs. HR, 1.52; 95% CI, 0.67–3.42). Risk was elevated for breast cancer in parous women exposed to clomiphene citrate (HR, 1.26; 95% CI, 1.03–1.54) for thyroid cancer and among nulliparous women after ART treatment (HR, 2.19; 95% CI, 1.08–4.44).

Conclusions: Clomiphene citrate appears associated with increased risk of ovarian and endometrial cancer. Elevations in risks of breast and thyroid cancer were less consistent across type of drug exposure and parity.

Impact: Continued monitoring of fertility treatments is warranted. *Cancer Epidemiol Biomarkers Prev; 26(6); 953–62. ©2017 AACR.*

Introduction

Pregnancy is known to protect against ovarian (1), breast (2), and endometrial (3) cancers, and nulliparity is consequently an established risk factor for these cancers. Furthermore, some studies have suggested that older ages at first birth may relate to increased risk of cutaneous malignant melanoma (CMM; ref. 4) and increasing parity to an elevated risk of thyroid cancer (5).

A continuing expansion of the use of assisted reproductive techniques (ART) means that growing numbers of women are exposed to a variety of fertility drugs (6), and monitoring the safety of these relatively new drugs is of importance. Some studies have found associations between fertility drug use and risks of ovarian (7, 8) breast (9–11), and other cancers (12, 13), whereas others have not (14–17), including two meta-analyses (18, 19). With reproductive factors being modifiers of cancer risk at several sites, a question that remains is whether effects of fertility drugs are different among nulliparous and parous women. Only a limited number of studies have been able to perform analyses stratified by parity (8, 20, 21), and even fewer have been able to look separately at risks in women who remain nulliparous after treatment (22).

We previously examined cancer risk associated with ART in parous women in Norway and found elevated risks of breast (11) and central nervous system cancers (23). We attempted in the current study to expand on our previous studies by examining risks in both parous and nulliparous women, and by analyzing exposure to both ART and clomiphene citrate. The novelty of this study is that we were able to present results for treated nulliparous women alone, to assess whether these women harbor an especially high risk of cancer compared to parous women.

The aim of the study was to compare cancer risk in nulliparous women exposed to fertility drugs to nulliparous women not treated with fertility drugs. By using data from four nationwide registries, we were able to establish a nationwide cohort of considerable size. For comparison, analyses on parous women were also included. The study assessed all-site cancer risk, and the risk of breast, cervical,

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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doi: 10.1158/1055-9965.EPI-16-0809

endometrial, ovarian, colorectal, central nervous system (CNS) thyroid cancers, and cutaneous malignant melanoma (CMM).

Materials and Methods

Data sources and study population

This population-based study includes all women born in Norway between 1960 and 1996 registered in the National Registry. Additional nationwide registries provided data on dispensed fertility drugs (the Norwegian Prescription Database), pregnancies and births (the Medical Birth Registry of Norway), and cancer diagnoses (the Cancer Registry of Norway). Since 2004, the Norwegian Prescription Database has included data on all prescribed drugs dispensed to individuals in ambulatory care (24). Drugs are classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification (25). The Medical Birth Registry of Norway was established in 1967 and contains information on all births in Norway, and is based on compulsory notification of every birth, from 16 completed weeks of gestation onwards (26). The Cancer Registry of Norway was established in 1952, and contains information on all persons diagnosed with cancer since 1953 (27). A unique personal identity number (PID) is assigned to each resident at birth or immigration, enabling data linkage across the registries. Reporting to the registries is mandatory and regulated by national legislation.

Ascertainment of exposure of fertility drugs

Exposure to ART. Controlled ovarian hyperstimulation (COH) is the process of using drugs to obtain several mature oocytes in a single menstrual cycle for use in *in vitro* fertilization (IVF). Hormone protocols used for COH in ART vary widely, but mostly the standard protocols include the following three medications: gonadotropin-releasing hormone (GnRH) analogues (agonists or antagonists), gonadotropins (follicle-stimulating hormone or human menopausal gonadotropin), and finally human chorionic gonadotropin (hCG; ref. 28). Study subjects were considered as exposed to a cycle of ART treatment either when they had been prescribed either a combination of all three medications, or only the first two (GnRH analogues and other gonadotropins) within a 2-month time period. Number of cycles of ART were categorized: 1, 2, and 3 or more ART cycles.

Exposure to clomiphene citrate. Clomiphene citrate is a nonsteroidal ovarian stimulant used for ovulation induction since the 1960s. It binds to hypothalamic estrogen receptors and by negative feedback induces pulsatile GnRH secretion, increased gonadotrophin secretion, and increased ovarian follicular activity (29). All women with at least one prescription of clomiphene citrate were considered as exposed to clomiphene citrate, all others were denoted non-clomiphene citrate women. Each treatment cycle consists of 50 mg for 5 consecutive days, and dose was categorized as $\leq$ 3 cycles, 3–6 cycles, or <6 cycles.

The drugs and ATC codes included in the analyses are displayed in Supplementary Table S1.

Cancer diagnoses

Cancers were categorized according to the International Classification of Diseases version 10 (ICD-10), (C00-96, up to 12 per individual).

Analyses of all-site cancer risk considered the first cancer (at any site) and in site-specific analyses, the first case of the cancer of interest was used. Women diagnosed with a cancer before 2004 were excluded from the analyses.

Analyses were conducted for the same sites as in our previous studies on parous women, namely breast (C50), cervical (invasive cancers only; C53), endometrial (C54-55), ovarian (C56), colorectal (C18-20) CNS (C70–72) thyroid cancers (C73), and CMM (C43). Separate analyses were made for ovarian cancer subgroups, and for borderline ovarian tumors (see Supplementary File for histology codes).

Potential confounding factors

We adjusted for region of residence because there may be regional differences in both use of fertility treatment and cancer incidence. We adjusted for birth year to account for potential cohort effects on cancer incidence. In the analyses of all women, adjustment was made for parity by splitting the data at the date of each woman's first birth. When assessing ART exposure, adjustments were made for clomiphene citrate exposure (ever/never), and vice versa.

Follow-up

Follow-up started on January 1, 2004 for all women born between 1960 and 1985. Women who were born in 1986 or later started follow-up on turning 18 years because receiving fertility treatment before this age was deemed unlikely. Women born before 1960 were not included as it was considered likely that they would be too old for fertility treatment during in the observational period 2004 to 2014. Follow-up ended upon diagnosis of the first cancer of interest, death, emigration, or December 31, 2014 (the latest update of the The Cancer Registry of Norway).

Statistical analyses

We used Cox regression models to compute hazard ratios (HR) and 95% confidence intervals (CI) for cancer risk in exposed versus unexposed women. Separate analyses were made for ART and clomiphene citrate exposure, and for parous and nulliparous women. Age was used as the timescale (30). Parity was treated as a time-dependent variable, with women switching classification from nulliparous to parous at the time of their first birth.

Analyses were stratified by doses of ART and clomiphene citrate, with dose as a time-varying covariate (31). Stratified analyses were also made on age at follow-up (below and above 30 years), and age at inclusion (below and above 40 years). Sensitivity analyses were made excluding those receiving other hormones (such as progesterone, or monotherapy with GnRH analogues). Risk of all-site cancer was made after omitting any cancer sites with elevated risks. Testing for heterogeneity was done using a likelihood-ratio test to test any observed differences between groups (P values below 0.05 were considered statistically significant). We attempted to analyze risk according to time since diagnosis to assess potential surveillance bias.

The proportional hazards assumption was tested using the Schoenfeld residuals (32). Analyses were made using the STATA software package, version 14.0, and the STROBE guidelines for reporting observational studies were adhered to (33).

Ethics

The Regional Ethics Committee of the South Eastern Health Region and the Norwegian Data Inspectorate approved the study.

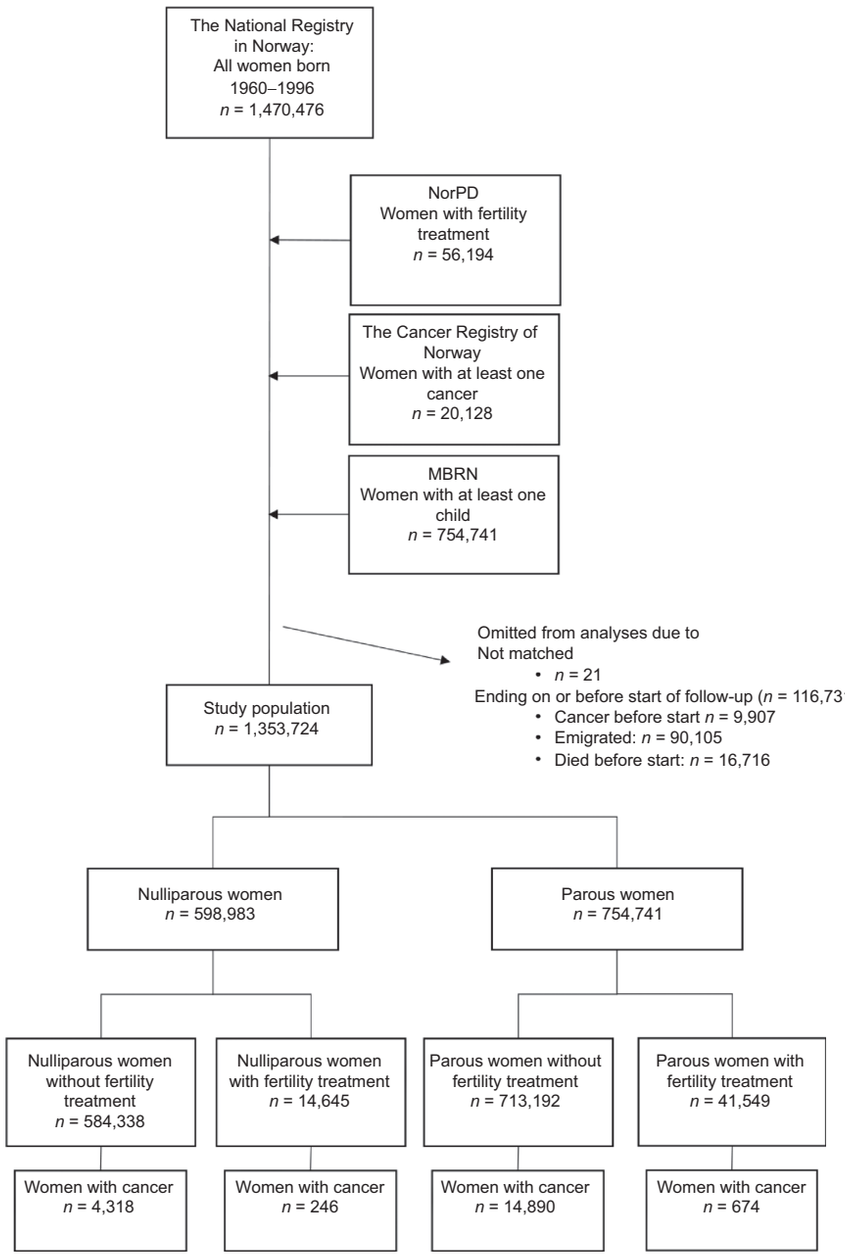

Figure 1.
Establishment of the study cohort. NR, National Registry; NorPD, Norwegian Prescription Database; MBRN, The Medical Birth Registry of Norway.

Results

Cohort

In the National Registry, 1,470,476 women were registered as born between 1960 and 1996, of which 1,353,724 (92%) women were eligible for study (Fig. 1).

The total follow-up time was 12,354,392 person-years, median 11 years and median exposure time for exposed women was 5.8. Apart from region of residence (485, <0.1% missing), no other variables had any missing values. A total of 598,983 (44%) women were classified as nulliparous, of which 14,645 (2.4%) had received fertility treatment (Table 1). The corresponding number of parous women with fertility treatment was 41,549 (5.5%, Fig. 1). Of those receiving fertility drugs, 33,431 received treatment with ART and 38,927 with clomiphene citrate.

Median age at entry was 27 years for nulliparous women with fertility treatment, and 18 years for nulliparous women without fertility treatment (Table 1). Nulliparous women with cancer were younger at diagnosis (median 40 years and 37 years for those without and with fertility treatment, respectively) compared with parous women (median 43 and 38 years).

Of the total cohort, 20,128 women were registered with at least one cancer diagnosis, with 920 (4.6%) of these occurring in exposed women (Table 1).

Exposure to ART

The risk of all-site cancer in ART exposed compared with unexposed women was 1.10 (95% CI, 0.98–1.23). For nulliparous

Table 1. Demographic data of study subjects registered in the Norwegian Prescription Database as having been prescribed and dispensed any fertility drug between January 1, 2004 and December 31, 2014

	Nulliparous women[a]		Parous women[b]		
	No fertility treatment	**Any fertility treatment**	**No fertility treatment**	**Any fertility treatment**	**Total cohort**
Total number of persons	584,338	14,645	713,192	41,549	1,353,724
Persons with cancer during follow-up (*n*)	4,318	246	14,890	674	20,128
Age at entry, years (median, IQR)	18 (18–24)	27 (21–33)	31 (24–37)	28 (23–32)	31 (24–37)
Age at exit, years (median, IQR)	27(22–34)	38 (32–43)	42 (35–48)	39 (34–43)	42 (35–48)
Age at first ART exposure (median, IQR)	—	35 (31–38)	—	33 (30–36)	—
Age at first CC exposure (median, IQR)	—	33 (28–38)	—	31 (28–36)	—
Age at cancer diagnosis (median, range)	40 (18–55)	37 (19–52)	43 (18–55)	38 (18–53)	43 (18–55)
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Birth year					
1960–1969	65,591 (11)	2,757 (19)	278,876 (39)	6,214 (15)	353,438 (26)
1970–1979	83,287 (14)	6,508 (44)	255,396 (36)	23,498 (57)	368,689 (27)
1980–1989	209,148 (36)	4,927 (34)	160,399 (22)	11,548 (28)	386,022 (29)
1990–1996	226,312 (39)	453 (3)	18,521 (3)	289 (1)	245,575 (18)
Total	584,338 (100)	14,645 (100)	713,192 (100)	41,549 (100)	1,353,724 (100)
Region of present residence					
South East	185,935 (32)	5,368 (37)	279,331 (39)	15,825 (38)	486,459 (36)
Oslo	132,427 (23)	3,254 (22)	75,416 (11)	5,983 (14)	217,080 (16)
South	80,240 (14)	2,029 (14)	108,130 (15)	7,171 (17)	197,570 (15)
West	92,423 (16)	2,094 (14)	119,304 (17)	6,741 (16)	220,562 (16)
Middle	46,753 (8)	866 (6)	63,513 (9)	3,049 (7)	114,181 (8)
North	46,338 (8)	1,025 (7)	67,257 (9)	2,767 (7)	117,387 (9)
Missing or unknown	222 (0)	9 (0)	241 (0)	13 (0)	485 (0)
Total	584,338 (100)	14,645 (100)	713,192 (100)	41,549 (100)	1,353,724 (100)
Number of children, at entry					
None	—	—	674,834 (95)	39,719 (96)	714,553 (95)
One	—	—	25,883 (4)	1,347 (3)	27,230 (4)
Two	—	—	7,728 (1)	320 (1)	8,048 (1)
Three or more	—	—	4,747 (1)	163 (0)	4,910 (1)
Missing	—	—	0 (0)	0 (0)	0 (0)
Age at start of follow-up			713,192 (100)	41,549 (100)	754,741 (100)
Below 25	446,658 (76)	6,036 (41)	201,364 (28)	14,169 (34)	668,227 (49)
25–29	43,266 (7)	3,265 (22)	120,958 (17)	12,535 (30)	180,024 (13)
30–35	35,891 (6)	3,113 (21)	141,408 (20)	10,234 (25)	190,646 (14)
More than 35	58,523 (10)	2,231 (15)	249,462 (35)	4,611 (11)	314,827 (23)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	584,338 (100)	14,645 (100)	713,192 (100)	41,549 (100)	1,353,724 (100)
Age at first cancer					
Below 30	1,043 (24)	41 (17)	990 (7)	84 (12)	2,158 (11)
30–39	1,068 (25)	123 (50)	3,897 (26)	339 (50)	5,427 (27)
40–49	1,757 (41)	76 (31)	8,066 (54)	240 (36)	10,139 (50)
More than 50	450 (10)	6 (2)	1,937 (13)	11 (2)	2,404 (12)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	4,318 (100)	246 (100)	14,890 (100)	674 (100)	20,128 (100)
Types of treatment					
Any fertility drug		14,645 (92)		41,549 (90)	56,194 (90)
Only ART	—	5,032 (31)	—	12,235 (26)	17,267 (28)
Only Clomiphene citrate	—	6,012 (38)	—	18,507 (40)	24,519 (39)
Both	—	3,601 (23)	—	10,807 (23)	14,408 (23)
Ever ART	—	8,633 (54)	—	23,042 (50)	31,675 (51)
Ever CC	—	9,613 (60)	—	29,314 (63)	38,927 (62)
Other medications[c]	—	1,347 (8)	—	4,848 (10)	6,195 (10)
Any treatment in the NorPD	—	15,992 (100)	—	46,397 (100)	62,389 (100)
Number of cycles of ART					
One	—	3,372 (39)	—	9,716 (42)	13,088 (41%)
Two	—	2,097 (24)	—	5,957 (26)	8,054 (25%)
Three	—	1,600 (19)	—	3,634 (16)	5,234 (17%)
Four	—	762 (9)	—	1,877 (8)	2,639 (8%)
Five	—	418 (5)	—	911 (4)	1,329 (4%)
Six or more	—	384 (4)	—	947 (4)	1,331 (4%)
Total	—	8,633 (100)	—	23,042 (100)	31,675 (100%)
Dose of clomiphene citrate					
Up to 84 mg	—	7,955 (83)	—	24,639 (84)	32,594 (84)
84–168 mg	—	1,441 (15)	—	4,048 (14)	5,489 (14)
Above 168 mg	—	217 (2)	—	627 (2)	844 (2)
Total	—	9,613 (100)	—	29,314 (100)	38,927 (100)

[a]This column includes all women who gave birth by the end of follow-up, that is women who remain childless throughout the study period. Some women may have been nulliparous, but have had children after some years of nulliparity, and therefore end up in the right column.
[b]This column includes all women who gave birth by the end of follow-up, that is, they may have been nulliparous at the start.
[c]Such as GnRH monotherapy or progesterone only.

Table 2. HRs with 95% CIs of cancer in women receiving ART as registered in the Norwegian Prescription Database compared with women not receiving ART

Cancer site	ICD 10 code	ART women cases	Unexposed cases	HR[a] (95% CI)	*P*[b]
All-site cancer	C00–99				
Nulliparous		108	5,159	1.00 (0.81–1.24)	
Parous		277	14,584	1.14 (1.00–1.29)	
All women[c]		385	19,743	1.10 (0.98–1.23)	0.5
Breast cancer	C50				
Nulliparous		29	1,262	1.11 (0.75–1.66)	
Parous		83	5,316	0.96 (0.76–1.22)	
Total		112	6,578	1.00 (0.81–1.22)	0.6
Cervical Cancer	C53				
Nulliparous		8	466	0.78 (0.37–1.67)	
Parous		24	1,331	0.95 (0.62–1.46)	
All women		32	1,797	0.91 (0.62–1.32)	0.8
Endometrial cancer	C54–55				
Nulliparous		5	224	0.39 (0.15–1.03)	
Parous		7	341	1.62 (0.70–3.85)	
All women		12	565	0.76 (0.40–1.45)	0.4
Ovarian cancer	C56				
Nulliparous		11	222	1.62 (0.78–3.35)	
Parous		5	393	0.87 (0.33–2.27)	
All women		16	615	1.29 (0.73–2.28)	0.05
Borderline ovarian tumors	N/A				
Nulliparous		12	245	1.69 (0.75–3.79)	
Parous		8	374	2.12 (1.11–4.04)	
All women		20	619	1.95 (1.18–3.23)	0.9
Colorectal cancer	C18–20				
Nulliparous		3	263	0.63 (0.19–2.10)	
Parous		12	874	0.88 (0.47–1.63)	
All women		15	1,137	0.81 (0.47–1.41)	0.5
CNS	C70–72				
Nulliparous		4	424	0.43 (0.15–1.23)	
Parous		22	1,072	1.25 (0.79–2.00)	
All women		26	1,496	0.99 (0.65–1.51)	0.1
Thyroid cancer	C73				
Nulliparous		10	286	2.19 (1.08–4.44)	
Parous		19	622	1.31 (0.78–2.19)	
All women		29	908	1.53 (1.01–2.31)	0.6
Malignant melanoma	C43				
Nulliparous		10	543	0.77 (0.39–1.54)	
Parous		30	1,717	1.06 (0.72–1.54)	
All women		42	2,260	0.97 (0.70–1.36)	0.8

[a]Adjusted for region of residence, birth cohort, and concomitant exposure to clomiphene citrate.
[b]Test for heterogeneity between parous and nulliparous women.
[c]Adjustments for parity are made in the analyses of all women together.

women the HR was 1.00 (95% CI, 0.81–1.24), compared with 1.14 (95% CI, 1.00–1.29) among parous women (Table 2).

ART was not associated with an elevated risk of breast cancer, either in nulliparous (HR, 1.11; 95% CI, 0.75–1.66) nor parous women (HR, 0.96; 95% CI, 0.76–1.22).

ART women (both parous and nulliparous) appeared to have a lower risk of cervical cancer although neither risk was statistically significant. Risk of endometrial cancer was slightly but not statistically significantly elevated in parous women exposed to ART (HR, 1.62; 95% CI, 0.70–3.85). No elevation was observed among nulliparous women (HR, 0.39; 95% CI, 0.15–1.03).

Women exposed to ART did not have a significantly elevated risk of ovarian cancer (HR, 1.29; 95% CI, 0.73–2.28) compared with those unexposed to ART. For nulliparous women, risk was slightly higher, although not statistically significant, (HR, 1.62; 95% CI, 0.78–3.35). For parous women alone, no risk elevation was observed (HR, 0.87; 95% CI, 0.33–2.27). A *P* value of 0.05 indicates a borderline-significant difference in risk between nulliparous and parous women for ART and ovarian cancer.

Risk of borderline ovarian tumors was elevated for all ART-exposed women, (HR, 1.95; 95% CI, 1.18–3.23). The stratified analyses on parity showed that there was no significant difference in risk between nulliparous (HR, 1.69; 95% CI, 0.75–3.79) and parous women (HR, 2.12; 95% CI, 1.11–4.04; $P = 0.9$). No differences in risk were observed with increasing number of cycles of ART (Supplementary Table S2).

The risk of thyroid cancer was elevated for all women exposed to ART compared with non-ART women (HR, 1.53; 95% CI, 1.01–2.31), with significant risks in nulliparous women (HR, 2.19; 95% CI, 1.08–4.44) and nonsignificant risk in parous women (HR, 1.31; 95% CI, 0.78–2.19).

ART treatment was not associated with elevated risk of colorectal cancer, CNS tumors, or CMM in exposed women, regardless of parity and dose (Tables 2, 3 and Supplementary tables S2 and S3).

Exposure to clomiphene citrate

Clomiphene citrate exposure was associated with an elevated risk of all-site cancer, (HR, 1.14; 95% CI, 1.03–1.26), and the

Table 3. HRs with 95% CIs of cancer in women receiving clomiphene citrate, as registered in the Norwegian Prescription Database, compared with women not receiving clomiphene citrate

Cancer site	ICD 10 code	CC women cases	Unexposed cases	HR[a] (95% CI)	*P*[b]
All-site cancer	C00–99				
Nulliparous		130	5,137	1.21 (0.99–1.46)	
Parous		334	14,527	1.11 (0.98–1.25)	
All women[c]		464	19,664	1.14 (1.03–1.26)	0.09
Breast cancer	C50				
Nulliparous		24	1,267	0.73 (0.47–1.12)	
Parous		116	5,283	1.26 (1.03–1.54)	
All women		140	6,550	1.12 (0.93–1.35)	0.02
Cervical cancer	C53				
Nulliparous		11	463	1.12 (0.59–2.14)	
Parous		26	1,329	0.74 (0.49–1.13)	
All women		37	1,792	0.83 (0.62–1.18)	0.4
Endometrial cancer	C54–55				
Nulliparous		18	211	4.49 (2.66–7.60)	
Parous		8	340	1.52 (0.67–3.42)	
All women		26	551	2.91 (1.87–4.53)	0.06
Ovarian cancer	C56				
Nulliparous		14	219	2.49 (1.30–4.78)	
Parous		8	390	1.37 (0.64–2.96)	
All women		22	609	1.93 (1.18–3.16)	0.04
Borderline ovarian tumors	N/A				
Nulliparous		7	246	1.16 (0.49–2.73)	
Parous		9	377	0.87 (0.41–1.82)	
All women		16	623	0.97 (0.56–1.70)	0.6
Colorectal cancer	C18–20				
Nulliparous		4	262	0.83 (0.29–2.37)	
Parous		18	868	1.20 (0.72–2.00)	
All women		22	1,130	1.12 (0.71–1.76)	0.4
CNS	C70–72				
Nulliparous		10	418	1.63 (0.83–3.17)	
Parous		23	1,071	0.93 (0.59–1.46)	
All women		33	1,489	1.10 (0.75–1.60)	0.5
Thyroid cancer	C73				
Nulliparous		6	290	0.68 (0.28–1.68)	
Parous		25	616	1.47 (0.93–2.31)	
All women		31	906	1.24 (0.82–1.85)	0.3
Malignant melanoma	C43				
Nulliparous		17	536	1.71 (1.01–2.92)	
Parous		35	1,714	0.90 (0.63–1.30)	
All women		53	2,250	1.06 (0.79–1.43)	0.1

Abbreviation: CC, clomiphene citrate.

[a]Adjusted for region of residence, birth cohort and concomitant exposure to clomiphene citrate.

[b]Test for heterogeneity between parous and nulliparous women.

[c]Adjustments for parity are made in the analyses of all women together.

risk estimates were similar for parous and nulliparous women (Table 3).

Clomiphene citrate exposure was associated with increased risk of breast cancer in parous women (HR, 1.26; 95% CI, 1.03–1.54; $P = 0.02$), but no dose–response relationship was seen for clomiphene citrate and breast cancer (Supplementary Table S3).

For clomiphene citrate–exposed women, the risk of cervical cancer was the same as in unexposed women, although slightly but not statistically significantly lower in the parous group (HR, 0.83; 95% CI, 0.62–1.18).

The risk of endometrial cancer was elevated in women treated with clomiphene citrate (HR, 2.91; 95% CI, 1.87–4.53) and risk was highest for nulliparous women (HR, 4.49; 95% CI, 2.66–7.60; $P = 0.04$; Table 3), and among parous women with more than 6 cycles (HR, 4.68; 95% CI, 1.74–12.6); P_{trend} was 0.011.

Clomiphene citrate–exposed nulliparous women had increased risk of ovarian cancer (HR, 2.49; 95% CI, 1.30–4.78), while risk was not increased in parous women (HR, 1.37; 95% CI, 0.64–2.96; $P = 0.04$; Table 3). The magnitude of the HRs appeared to increase with increasing doses of clomiphene citrate, 1.76 (95% CI, 0.68–4.58) at the lowest dose versus 3.46 (95% CI, 1.19–10.0) with the highest dose, although a test for trend revealed a $P = 0.269$.

Clomiphene citrate exposure was not associated with the risk of borderline tumors, thyroid cancers, colorectal cancer, CNS tumors, or CMM.

Secondary analyses

When stratifying on different histologic subtypes of ovarian cancer, clomiphene citrate exposure was associated with a risk of endometrioid ovarian cancers (HR, 4.75; 95% CI, 1.95–11.6; data not shown). No differences were seen for risk of neither serous nor mucinous tumors (data not shown). When stratifying on age above and below 30 and 40 years at start of follow-up, no differences were observed for ovarian, breast, or endometrial cancer. When looking at time since diagnosis, no differences

could be seen due to few cases of cancers in the exposed group (data not shown). When removing ovarian and thyroid cancers from analyses of ART, the estimate for all-site cancer was unchanged (HR, 1.08; 95% CI, 0.96–1.21). Neither did removing ovarian and endometrial cancers change estimates for clomiphene citrate exposure (HR, 1.12; 95% CI, 1.01–1.25; data not shown).

Discussion

This population-based registry study is one of the largest to date to assess risk of cancer in women receiving fertility treatments. We observed elevated risk of ovarian and endometrial cancer, and the risk appeared to be highest among nulliparous women following exposure to clomiphene citrate. An enhanced risk of thyroid cancer was observed for for nulliparous women exposed to ART. Furthermore, a modest increase in risk of breast cancer was observed with clomiphene citrate treatment, of similar magnitude as in our previous study on breast cancer risk after ART among parous women (11).

Ovarian cancer

Results demonstrate elevated risk of ovarian cancer after clomiphene citrate exposure, and also suggest that ART exposure may be associated with elevated risk, albeit among nulliparous women. For clomiphene citrate, the risk among nulliparous women increased with increasing drug dosage. Fathalla suggested in 1971 that repeated involvement of the ovarian surface epithelium during ovulation could be related to the development of ovarian neoplasms, coining the term "incessant ovulation" (34). Subsequent research has suggested that ovulatory pauses such as oral contraceptives, pregnancy, and lactation could reduce ovarian cancer risk (35). Our results indicate that an additional risk pertains to nulliparous women treated with fertility drugs, due not only to the lack of ovulatory pause associated with pregnancy, but also possibly due to exposure to COH.

One of the first studies looking at fertility drugs and ovarian cancer also found that women who remained childless had a higher risk than women conceiving after fertility treatment (36). Later, two U.S.-based studies reported higher risks associated with clomiphene citrate in women remaining nulliparous (37, 38). An Australian study also found nonsignificantly elevated risk of ovarian cancer in nulliparous IVF women (21). Two further studies, one from Sweden (8), and another from the Netherlands, both detected elevated risk of ovarian cancers after treatment with ART (7), but none provided separate estimates for nulliparous women. In our previous study, we found higher risk of ovarian cancer in women with primary infertility and those conceiving only one child (23). On the other hand, several other studies observe no increase in risk of ovarian cancers (39–41), and/or no difference in risk between nulliparous and parous women with fertility treatment (20, 41).

Our results suggest highest risk of ovarian cancer among those with the highest doses of clomiphene citrate. Although one earlier study also found an association between ovarian cancer and 12 or more cycles of clomiphene citrate (42), most other investigators observe no dose–response relationships with clomiphene citrate (16) nor ART (7, 20) and ovarian cancer. Although our findings are noteworthy, it is important to keep in mind that women receiving multiple doses of fertility drugs may be a selected group of women. It may well be that women exposed to many treatment rounds suffer resistant infertility, for example, for women with polycystic ovarian syndrome, only 20% become pregnant with each cycle of clomiphene citrate on average (43, 44). These women require many cycles of clomiphene citrate, but may indeed have elevated risks of ovarian cancer due to their ovulation disorders, and not the treatment itself. Finally, it is important to mention that the dose–response analyses are based on few cases, possibly representing a chance finding.

We found elevated risk of borderline ovarian tumors in women treated with ART, in line with two previous studies (7, 45), but in contrast to a further three (41, 46, 47). In our study, we could not observe difference in risk among nulliparous and parous women. This was in line with findings from an Australian study (45), but contrary to a Dutch study that found highest risk among nulliparous women (7). In Norway, these nonmalignant tumors are systematically registered in the The Cancer Registry of Norway. Elevated risks of borderline tumors in women treated with fertility hormones have been suggested to reflect surveillance bias, and not a biological explanation, which may explain the absence of risk with increasing number of cycles of ART. In the current study, we did not have sufficient data to evaluate potential surveillance bias in terms of time since diagnosis.

Endometrial cancer

We found elevated risk of endometrial cancers in women exposed to clomiphene citrate, highest among nulliparous women, and for those with more than 6 treatment cycles. In contrast to this, a recent meta-analysis consisting of six studies found no elevation in risk connected to neither fertility drugs nor ART (48). Notably, one of the studies in the meta-analysis (49) was unable to replicate their earlier findings (50) where they had demonstrated increased risk of endometrial cancer associated with clomiphene citrate for six or more cycles.

It is worth mentioning that body mass index (BMI) and anovulatory infertility (PCOS) have been shown associated with endometrial cancer (51), and may cause confounding of our results, as this information is unavailable.

Thyroid cancer

Our study suggests thyroid cancer to be associated with ART treatment, with risks highest in the nulliparous group. Two other studies made similar findings, one detecting elevated risks among nulliparous women with use of clomiphene citrate (22, 52), whereas another discovered increased risk among parous women (12).

Thyroid tumors are more frequent in women than in men (53), giving reason to believe that female sex hormones may be involved. Ovarian stimulation has been shown to cause elevated levels of TSH (54), which promotes cellular proliferation in the gland. Both the normal thyroid gland and thyroid tumors exhibit estrogen receptors (55), although the exact mechanisms by which tumor growth is promoted are unclear (56). Thyroid cancer incidence has increased in recent years, possibly due to incidental findings of tumors with increased use of ultrasound, CT, and MRI; however, when correcting for this in our analyses, risk was still elevated among ART women.

Breast cancer

We found an increased risk of breast cancer associated with clomiphene citrate treatment, but not with ART. The risk increase

associated with clomiphene citrate use was restricted to parous women, and the magnitude of the estimate similar to our previous study of parous women (11). Although Brinton and colleagues reported an elevated risk of breast cancer in women exposed to multiple cycles (>12) of clomiphene citrate (15), we did not observe any relation of risk according to number of clomiphene citrate cycles. A recent meta-analysis concluded that the association between infertility treatment (any hormonal treatment) and the risk of breast cancer was weak, but underlined that extensive use of clomiphene citrate should be limited due to concerning findings relating to breast cancer (19).

Other cancers

No association was found between fertility treatment and risks of colorectal, CNS cancer, nor CMM. Reassuringly, the elevated risk of CNS tumors found in our previous study on parous women (11) could not be replicated presently, possibly reflecting the shorter follow-up in the current study, with data from the Norwegian Prescription Database only available from 2004. Two recent papers support our null findings on fertility drugs and CMM (13, 57). Two other studies conclude no association between use of clomiphene citrate and colorectal cancer (22, 58).

We observed a nonsignificant decrease in risk of cervical cancer among fertility-treated women, in line with others studies (16, 17, 49), possibly due to infertile women's regular gynecologic examinations, including cervical screening tests leading to reduced risk of invasive cervical cancer (59).

Strengths and limitations

The main strength of this study is its size. By using population-based registry data all the way back to 1960, we were able to obtain a nationwide study cohort that may be the largest to date addressing fertility drugs and cancer risk. In this study, collection of information on drug exposure from the Norwegian Prescription Database minimized the risk of recall bias (60, 61). Furthermore, the Prescription Database only records prescribed drugs that are dispensed and collected by patients, reducing the risk of primary noncompliance (24, 62) and subsequently the risk of misclassification. Moreover, the registry-based collection of data on cancer from the The Cancer Registry of Norway and childbirths from the Medical Birth Registry of Norway is advantageous as the mandatory reporting to both registries ensures high external validity and completeness (27). Another strength of the study is that we are able to look at both ART and clomiphene citrate as separate exposures. In contrast to several other studies data from Medical Birth Registry enabled us to separate nulliparous and parous women, accounting for the effects of childbearing on cancer risk.

The study is at risk of some misclassification of exposure, as the Norwegian Prescription Database only includes data from 2004. Thus, some women may be misclassified as unexposed if they only received fertility drugs before 2004. However, stratifying on age at inclusion did not reveal any differences in risk between women who were older compared with those that were younger in 2004. Misclassification of exposure may also occur if women receive fertility treatment abroad not recorded in the Norwegian Prescription Database (63). Using Prescription Database information does not provide the opportunity to assess the degree of adherence; although a drug is dispensed, the patient might not actually have taken it. However, infertile patients seeking to conceive are likely to have high drug adherence (64).

In the current study, comorbidity data are unavailable. First, this is important as nulliparous women may be more likely to suffer from chronic diseases including cancer, which prevent them from having children. However, then risk elevations would likely be observed for several cancer sites, not just the specific ones we observed. Second, with respect to comorbidity, information on fertility diagnoses are unavailable to us in the current study. This is an issue, for example, as endometriosis been suggested to be associated with an elevated risk of ovarian cancer (7, 21, 65, 66). In our study, we were unable to disentangle the effects of the fertility treatment from underlying causes of infertility themselves. It may be that some women harbor pathologic changes in the ovary leaving them prone to both infertility and ovarian neoplasms. Thus, confounding by indication may be driving some of the observed associations between fertility drugs and ovarian cancer. This may also be the case for thyroid cancer, as it has been demonstrated that thyroxin substitution treatment is used more frequently by ART pregnant women, than by those pregnant after natural conception (67). It may therefore be that the preexisting thyroid disease may be a common cause of both infertility and thyroid neoplasms.

Some factors associated with cancer and infertility were unavailable: BRCA mutations, socioeconomic factors, smoking, and BMI. BMI is a potential confounder associated with both infertility (68) and breast (69) and endometrial cancer (70), and may be the reason, at least in part, why we observe elevations in risk after clomiphene citrate exposure. Oral contraceptives are known to reduce risk of ovarian and endometrial cancers. If OC use is less in infertile than in fertile women, this factor may be mediating some of the observed effects of fertility drugs on ovarian cancer.

Women treated with fertility drugs may be subject to some degree of surveillance bias, which could be a possible explanation for our findings of elevated risk of thyroid and borderline tumors. This could have been clarified by examining the stage and mortality of cancers in exposed women in future studies.

It is also important to note that this study includes women of relatively young ages, and as a consequence the follow-up time is short. Thus, the median ages at cancer diagnosis were below the ages where cancer is prevalent, (37 years for exposed nulliparous women and 38 years for exposed parous women), and for some site-specific analyses, number of cases in the comparison groups are low. Another limitation is that correction for multiple analyses has not been performed. However, the need to do so may be subject for discussion. For example there is likely to be little correlation between breast cancer and malignant melanoma, both with respect to tumor biology, but also differences in etiology.

Conclusions

In this nationwide registry-based study, we used data on parity, drug exposure, and cancer outcomes, to compare cancer risks associated with fertility drug exposures among parous and nulliparous women. Findings were reassuring for most cancers, although fertility treatment, particularly with clomiphene citrate, appeared to increase the risk of ovarian and endometrial cancer especially in nulliparous women. For some sites, including breast, endometrium and thyroid, there were some elevations in risk, although less consistently according to treatment type and parity.

Although some risk elevations are observed, it must be kept in mind that the study population is young, and its absolute cancer

risk low. Future research should continue to monitor women treated for infertility as they grow older. Assessing ovarian cancer risk in women remaining childless after treatment, and risks associated with cumulative doses of fertility drugs is of importance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The interpretation and reporting of the Medical Birth Registry of Norway data is the sole responsibility of the authors, and no endorsement by the Registry is intended nor should be inferred.

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Acknowledgments

The authors thank the Medical Birth Registry of Norway and The Cancer Registry of Norway for supplying the data.

Grant Support

This study was supported by departmental funds (Oslo University Hospital) to support M.M. Reigstad throughout the study period and manuscript preparation.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received October 13, 2016; revised December 21, 2016; accepted December 22, 2016; published OnlineFirst January 20, 2017.

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