American Journal of Epidemiology

Vol. 160, No. 11
Printed in U.S.A.
DOI: 10.1093/aje/kwh315

A Case-Control Study of Ovarian Cancer in Relation to Infertility and the Use of Ovulation-inducing Drugs

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Received for publication March 22, 2004; accepted for publication August 23, 2004.

The authors conducted a population-based, case-control study among women aged 35–54 years to assess the influence of infertility and use of ovulation-inducing drugs on ovarian cancer risk. The study was conducted from 1994 to 1998 in three regions (metropolitan Atlanta, Georgia, Detroit, Michigan, and Seattle, Washington) and included 378 cases and 1,637 controls. Data were obtained through in-person interviews, and analysis was conducted using unconditional logistic regression. Among parous women, the authors observed no association of cancer risk with a history of infertility, medical evaluation for infertility, specific types of infertility, or use of ovulation-inducing drugs. Among nulliparous women, risk was increased among women with a history of infertility (odds ratio = 1.6, 95% confidence interval: 1.0, 2.6), particularly when infertility first became manifest relatively late in reproductive life (for first infertility at ≥30 years of age: odds ratio = 2.2, 95% confidence interval: 1.1, 4.5); risk was not associated with medical evaluation for infertility, specific types of infertility, or use of ovulation-inducing drugs. Findings were similar when borderline and invasive epithelial tumors were considered separately. While the results of this study support the hypothesis that a subset of nulliparous women who experience infertility may be at increased risk of ovarian cancer, the reasons for this increase in risk remain unclear.

Infertility; ovarian neoplasms

Abbreviations: CARE, Women's Contraceptive and Reproductive Experiences; CI, confidence interval; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results.

Studies that have thoroughly adjusted for the effects of confounding factors, including duration of oral contraceptive use and number of full-term pregnancies, have not noted a strong association between difficulty in conceiving and the risk of ovarian cancer among parous women (1–4). However, an increased risk among infertile women who remain childless despite long periods of unprotected intercourse has been reported in two large, pooled analyses (2, 4). It remains to be understood whether such women are at risk due to the primary basis for their infertility, some correlate of infertility such as exposure to ovulation-inducing drugs, a shared genetic susceptibility to ovarian cancer and infertility, or some other reason.

We conducted a population-based, multicenter, case-control study among women aged 35–54 years to assess the influence of infertility and use of ovulation-inducing drugs on risk of ovarian cancer. The limited age range of partipants reflected the availability of ovulation-inducing drugs during the reproductive ages of women during the years in which the study was conducted: clomiphene citrate was first approved for use in the United States in 1967 (5), and other regimens of ovulation induction came into use even more recently.

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MATERIALS AND METHODS

The current study was conducted in three geographic regions (metropolitan Atlanta, Georgia, Detroit, Michigan, and Seattle, Washington) served by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. Involvement of human subjects in this study was approved by the review board of the participating institution in each of these locations. The Women's Contraceptive and Reproductive Experiences (CARE) Study of breast cancer was conducted contemporaneously with this study and served as the source of controls. Details of control selection for the CARE Study have been described elsewhere (6). Eligible CARE Study controls were English-speaking women ascertained in five geographic regions, were born in the United States, were of White or Black race, had no prior history of breast cancer, and were aged 35–64 years at the reference date. They were selected using random digit telephone dialing with unclustered, equal-probability sampling of phone numbers. An estimated 82 percent of households were successfully screened through random digit dialing.

Women eligible to be interviewed as cases for this study included English-speaking, White or Black female residents of King County, Washington; Wayne, Oakland, or Macomb counties, Michigan; or Fulton, Cobb, or Dekalb counties, Georgia, who were 35–54 years of age when diagnosed with a SEER Program-reportable, first primary borderline ovarian tumor from July 1994 or first primary invasive ovarian cancer from July 1995 through June 1998. Women without a residential telephone at the time of diagnosis were considered ineligible, because random digit telephone dialing was used to select controls. Eligible case women were identified through the population-based SEER Program tumor registries in each area. The registries supplied information regarding the histologic type of cancer and the degree of invasiveness (i.e., borderline or invasive). Borderline ovarian tumors (also referred to as tumors of low malignant potential) considered reportable to the SEER Program during the years in which the study was conducted were those with *International Classification of Diseases for Oncology*, Second Edition (7), codes of 8442/3 (serous cystadenoma, borderline), 8451/3 (papillary cystadenoma, borderline), 8462/3 (papillary serous cystadenoma, borderline), 8472/3 (mucinous cystadenoma, borderline), or 8473/3 (papillary mucinous cystadenoma, borderline).

A total of 406 cases were interviewed of the 547 women eligible for interview (74.2 percent). Thirty-two women were not contacted because their physician declined permission for their contact, 63 chose not to participate, 22 were not located by the study staff, and 24 died before they could be interviewed. Because controls were women without a previous diagnosis of breast cancer and were required to be born in the United States, we excluded from these analyses interviewed case women who reported a prior history of breast cancer ($n = 16$) or who were foreign-born ($n = 12$), resulting in 378 cases available for analysis. Based on the tumor histologies recorded by the SEER Program registries and a published histologic grouping system (8), 355 (93.9 percent) cases had epithelial ovarian tumors, and of these, 213 (60.0 percent) were invasive. Serous tumors were the most common histologic subtype of epithelial tumors ($n = 201$; 56.6 percent), and 65 (18.3 percent of epithelial tumors) were mucinous.

Only those CARE Study controls who were residents of the Seattle, Atlanta, or Detroit metropolitan area counties listed above and were aged 35–54 years at reference were considered potentially eligible ($n = 2,228$). Of those women, interviews were obtained from 1,828 (82.0 percent). After the exclusion of interviewed women who reported having had a bilateral oophorectomy ($n = 176$) or ovarian cancer ($n = 6$) prior to the reference date and nine women who were uncertain whether they retained at least one ovary at that date, 1,637 women were included in this study as controls.

Cases and controls received a letter of approach that described the study and invited their participation. The letter was followed by telephone contact with an interviewer who scheduled an in-person interview with the subject if she was willing. All participants signed a consent form prior to interview. Information collected at interview pertained to the period of time before ovarian cancer diagnosis (for cases) or before an assigned, comparable reference date (for controls) and covered the following: demographic and lifestyle characteristics; medical history; family history of cancer; and detailed reproductive history, including menstrual, pregnancy, and contraceptive history, use of noncontraceptive hormones, and testing and treatment for infertility. To aid recall, interviewers used a calendar to record major life events as well as time intervals of pregnancy, breastfeeding, and use of various contraceptive methods. In addition, interviewers provided lists and photographs of commonly used oral contraceptive and hormone replacement preparations and lists of fertility medications. Cases and controls were administered nearly identical questionnaires, except for the addition of questions regarding the circumstances that led to the diagnosis of ovarian cancer and deletion of questions regarding detailed mammographic history among cases. Control interviews were conducted from September 1994 through December 1998; because of later availability of funding for case interviews, these were conducted from January 1996 through July 1999.

To identify women with possible fertility problems, interviewers examined the life-events calendar for time periods at least 12 months long (after menarche and before the first occurrence of tubal ligation, hysterectomy, or last reported menstrual period) when the study participant was not pregnant, breastfeeding, or using birth control (including male contraceptive methods) or noncontraceptive hormones. For each of these intervals, women were asked whether they were at risk of becoming pregnant, that is, having regular sexual intercourse (three or more times per month) with a male partner. The dates of all such intervals were recorded. Moreover, women were asked if they had ever visited a physician, clinic, or hospital because of a problem becoming pregnant or to seek help in becoming pregnant. For women who reported that they had sought such medical attention, information was collected on whether they or their partner had had infertility testing performed, the basis for their infertility, and the types and durations of infertility medications received. Information regarding use of assisted reproductive

TABLE 1. Characteristics of ovarian cancer cases and controls: Atlanta, Georgia, Seattle, Washington, and Detroit, Michigan, metropolitan areas, 1994–1998

Characteristic	Cases (n = 378)		Controls (n = 1,637)		Odds ratio*	95% confidence interval
	No.	%	No.	%		
Study site						
Atlanta	68	18.0	545	33.3		
Seattle	114	30.2	616	37.6		
Detroit	196	51.9	476	29.1		
Race						
White	327	86.5	1,193	72.8		
Black	51	13.5	444	27.1		
Age (years)						
35–39	56	14.8	342	20.9		
40–44	90	23.8	453	27.7		
45–49	134	35.4	451	27.6		
50–54	98	25.9	391	23.9		
Marital status						
Never married	38	10.1	132	8.1	1.0	
Ever married	340	89.9	1,505	91.9	0.6	0.4, 0.9
Education						
High school or less	118	31.2	471	28.8	1.0	
Some college	138	36.5	527	32.2	1.2	0.9, 1.6
College graduate	122	32.3	639	39.0	0.9	0.6, 1.2
Cigarette smoking						
Never smoked	178	47.2	804	49.1	1.0	
Former smoker	123	32.6	469	28.7	1.1	0.8, 1.4
Current smoker	76	20.2	363	22.2	1.0	0.7, 1.3
Missing	0		1			
Age at menarche (years)						
<12	104	27.5	424	25.9	1.0	
12	106	28.0	463	28.3	1.0	0.7, 1.3
13	99	26.2	436	26.7	1.0	0.7, 1.3
≥14	69	18.3	311	19.0	1.0	0.7, 1.4
Missing	0		3			
Oral contraceptive use (months)						
Never	65	17.4	171	10.5	1.0	
<6	45	12.1	141	8.6	0.9	0.6, 1.4
6–59	133	35.7	645	39.4	0.6	0.4, 0.8
≥60	130	34.9	678	41.5	0.5	0.4, 0.8
Missing	5		2			

Table continues

technologies, such as artificial insemination, in vitro fertilization, and gamete intrafallopian transfer, was also collected. At interview, female causes of infertility were classified into the following types of abnormalities: cervical mucous; fallopian tube; ovarian, including cysts or anovulation; hormonal, including luteal phase defect; uterine; endometriosis; or other.

Unconditional logistic regression was used to calculate odds ratios as estimates of the relative risk of ovarian cancer associated with the exposures of interest while controlling for the confounding effects of other variables. Parameter estimates were computed by maximum likelihood techniques, and 95 percent confidence intervals were based on the standard error of the coefficients and the normal approximation (9). We assessed the odds ratio of ovarian cancer associated with various definitions and aspects of infertility separately among nulliparous and parous women. All analyses were adjusted for the CARE Study frequency-matching

TABLE 1. Continued

Characteristic	Cases (n = 378)		Controls (n = 1,637)		Odds ratio*	95% confidence interval
	No.	%	No.	%		
No. of pregnancies						
0	71	18.8	212	13.0	1.0	
1	62	16.4	223	13.6	0.9	0.6, 1.3
2	107	28.3	412	25.2	0.7	0.5, 1.0
3	81	21.4	384	23.5	0.6	0.4, 0.9
≥4	57	15.1	403	24.7	0.4	0.3, 0.6
Missing	0		3			
No. of births						
0	108	28.6	343	21.0	1.0	
1	69	18.3	291	17.8	0.7	0.5, 1.0
2	125	33.1	559	34.2	0.6	0.5, 0.9
≥3	76	20.1	441	27.0	0.5	0.3, 0.7
Missing	0		3			
Duration of breastfeeding (among women with a livebirth)						
Never	116	43.3	451	35.1	1.0	
<6 months	80	29.9	335	26.0	0.9	0.7, 1.3
6–12 months	38	14.2	211	16.4	0.8	0.5, 1.2
>1 year	34	12.7	289	22.5	0.5	0.3, 0.7
Missing	0		1			
Body mass index (kg/m^2)						
<25	215	57.3	1,030	63.3	1.0	
25–<30	85	22.7	355	21.8	1.2	0.9, 1.5
≥30	75	20.0	243	14.9	1.5	1.1, 2.1
Missing	3		9			
Family history of ovarian cancer (first degree)						
No	354	97.0	1,571	98.7	1.0	
Yes	11	3.0	20	1.3	2.7	1.2, 6.0
Missing	13		46			
Family history of breast cancer (first degree)						
No	333	91.2	1,441	90.6	1.0	
Yes	32	8.8	150	9.4	0.9	0.6, 1.4
Missing	13		46			

* Adjusted for age, race, and study site.

variables of age (5-year groups), race (White or Black), and study site. Analyses among nulliparous women were additionally adjusted for duration of oral contraceptive use and, among parous women, for duration of oral contraceptive use and number of full-term births. Other characteristics examined as potentially confounding or modifying the associations of interest included education, marital status, diagnosis/reference year, number of pregnancies, duration of breastfeeding, body mass index, tubal ligation, hysterectomy, family history of breast cancer, and family history of ovarian cancer. None of these latter variables importantly influenced relative risk estimates.

RESULTS

Slightly over half of the interviewed cases and 29.1 percent of controls were residents of the Detroit metropolitan area (table 1). Controls were more likely to be Black women.

TABLE 2. Odds ratios for ovarian cancer associated with measures of infertility* among nulliparous and parous women: Atlanta, Georgia, Seattle, Washington, and Detroit, Michigan, metropolitan areas, 1994–1998

Exposure	Nulliparous				Parous			
	No. of cases (*n* = 108)	No. of controls (*n* = 343)	Odds ratio†	95% confidence interval	No. of cases (*n* = 270)	No. of controls (*n* = 1,291)	Odds ratio‡	95% confidence interval
Infertility								
Never	66	243	1.0		169	779	1.0	
Ever	42	98	1.6	1.0, 2.6	101	512	0.9	0.6, 1.2
Missing	0	2			0	0		
Total years of infertility								
≤4	14	42	1.4	0.7, 2.8	64	352	0.8	0.6, 1.2
>4–<10	13	27	2.0	0.9, 4.2	22	104	0.9	0.5, 1.6
≥10	15	29	1.6	0.7, 3.3	15	56	1.1	0.5, 2.1
Age (years) at first infertility								
<20	9	23	1.2	0.5, 3.1	29	179	0.7	0.5, 1.2
20–29	17	42	1.4	0.7, 2.7	53	247	0.9	0.6, 1.3
≥30	16	33	2.2	1.1, 4.5	19	86	1.0	0.6, 1.8

* See text for definitions; table excludes three controls with unknown parity.
† Adjusted for age, race, study site, and duration of oral contraceptive use.
‡ Adjusted for age, race, study site, duration of oral contraceptive use, and number of births.

TABLE 3. Odds ratios for ovarian cancer associated with medical testing and diagnosis of infertility problems: Atlanta, Georgia, Seattle, Washington, and Detroit, Michigan, metropolitan areas, 1994–1998

Exposure	Nulliparous				Parous			
	No. of cases (*n* = 108)	No. of controls (*n* = 343)	Odds ratio*	95% confidence interval	No. of cases (*n* = 270)	No. of controls (*n* = 1,291)	Odds ratio†	95% confidence interval
Sought care for infertility problem								
Never	84	289	1.0		221	1,098	1.0	
Ever	24	53	1.5	0.9, 2.8	49	193	1.1	0.8, 1.6
Missing	0	1			0	0		
Testing done								
No	4	8	1.9	0.5, 7.2	14	51	1.3	0.7, 2.4
Yes	20	45	1.5	0.8, 2.8	35	142	1.0	0.7, 1.6
No cause identified	4	10	2.0	0.5, 7.0	10	41	1.0	0.5, 2.2
Male problem only	6	8	2.1	0.6, 6.8	5	20	0.9	0.3, 2.6
Female problem	9	26	1.1	0.5, 2.5	19	80	1.1	0.6, 1.9
Results unknown	1	1			1	1		
Type of female abnormality								
Cervical	1	2	0.9	0.1, 11.1	0	4		
Tubal	3	9	1.0	0.3, 4.4	9	31	1.5	0.7, 3.3
Ovarian	3	9	1.2	0.3, 4.7	3	19	0.5	0.2, 1.9
Endocrine	0	3			3	21	0.6	0.2, 2.2
Uterine	2	5	1.5	0.3, 8.4	3	16	0.8	0.2, 3.0
Endometriosis	0	4			1	18	0.3	0.03, 2.2

* Adjusted for age, race, study site, and duration of oral contraceptive use.
† Adjusted for age, race, study site, duration of oral contraceptive use, and number of births.

The body mass index of cases (assessed 5 years before the reference date) was generally greater than that of controls, and cases were more likely to be nulliparous and less likely to have had three or more births. Among women who had had a livebirth, cases were less likely to have breastfed, particularly for 1 year or longer. Cases were less likely to have used oral contraceptives and more likely to report a first-degree relative with ovarian cancer. After adjustment for age, race, and study site, cases and controls were fairly similar with respect to other characteristics such as education, cigarette smoking, and age at menarche.

A commonly used clinical criterion for infertility is an attempt to conceive for longer than 1 year without success. Among nulliparous women only, we observed an increased risk of ovarian cancer associated with infertility, defined as the occurrence of an interval of greater than 12 months during which a woman at risk of pregnancy (as described in Materials and Methods, above) reported engaging in regular intercourse without contraception or conception (table 2). This increase in risk was essentially identical in an analysis restricted to ever-married nulliparous women (results not shown). We observed no clear trend in risk according to the total number of months of infertility (counted as months during which a woman was at risk of conception, beyond the first year of each interval of unprotected intercourse recorded on the life-events calendar). Risk appeared greatest among nulliparous women whose infertility first became manifest relatively late in reproductive life (for first infertility at ≥30 years of age: odds ratio (OR) = 2.2, 95 percent confidence interval (CI): 1.1, 4.5) (table 2). These results were similar in analyses restricted to nonmucinous epithelial ovarian tumors.

While the risk of developing a borderline epithelial ovarian tumor among nulliparous women who were infertile (as defined in the preceding paragraph) was somewhat greater than the risk of an invasive tumor (adjusted ORs = 1.7 (95 percent CI: 0.8, 3.6) and 1.3 (95 percent CI: 0.7, 2.5) for borderline and invasive disease, respectively), risk estimates for borderline and invasive epithelial tumors were similar among nulliparous women whose infertility was first evident relatively late in reproductive life (for infertility at ≥30 years of age: adjusted ORs = 1.9 (95 percent CI: 0.7, 5.6) and 2.0 (95 percent CI: 0.9, 4.9) for borderline and invasive disease, respectively). Among parous women, we observed no increased risk of either borderline or invasive epithelial ovarian cancer associated with having had a history of infertility.

Among nulliparous women, the risk of ovarian cancer associated with a history of infertility was most apparent among women who had had one or more incomplete pregnancies (for infertility and infertility first identified at ≥30 years of age: adjusted ORs = 3.0 (95 percent CI: 1.3, 7.2) and 3.6 (95 percent CI: 1.3, 10.4), respectively). This elevation in risk was similar regardless of whether the termination of pregnancy was spontaneous or induced, or whether a pregnancy occurred before or after the last infertility episode. Among parous women, risk was not elevated among women who did or did not give birth after the last infertility episode.

We also assessed risk associated with alternative definitions of infertility, including the following: seeking medical care related to a problem in becoming pregnant; having medical testing related to infertility; diagnosis of female infertility (i.e., excluding infertility due only to a problem of the male partner); and diagnosis of specific types of female infertility. Among cases and controls who had never experienced infertility according to our initial definition of this condition (i.e., an interval of greater than 12 months during which a woman at risk of pregnancy reported engaging in regular intercourse without contraception or conception), 6 percent of each group reported seeking care for fertility problems. Among women who had experienced such infertility, 41.3 percent of cases and 31.1 percent of controls sought care. Among nulliparous women only, risk was somewhat elevated among women who had ever sought care for a fertility problem (OR = 1.5, 95 percent CI: 0.9, 2.8). However, risk of ovarian cancer was not associated with a woman's receipt of testing for infertility, the diagnosis of female infertility, or the diagnosis of any specific type of female abnormality leading to infertility (table 3). Similar results were obtained in analyses that compared women who had sought care for infertility with the subgroup of women who had neither sought care for infertility nor had had a greater than 12-month interval at risk of pregnancy. In addition, results were similar when analyses were conducted separately for borderline and invasive tumors and in analyses restricted to nonmucinous epithelial tumors. When the analyses shown in table 3 were conducted among the subgroup of women who had experienced infertility (again, defined as a >12-month interval at risk of pregnancy), the adjusted odds ratio among nulliparous women who sought care for infertility was 1.0 (95 percent CI: 0.4, 2.3), suggesting that nulliparous women who seek care for infertility are at no greater risk than nulliparous, infertile women who do not seek such care.

Use of ovulation-inducing medications as treatment for infertility was reported by 17 cases (4.5 percent) and 85 controls (5.2 percent). The large majority (over 80 percent of both cases and controls) of women who used ovulation-inducing drugs reported 12 or fewer menstrual cycles of use. Clomiphene citrate was the most commonly used ovulation-inducing drug, and only one case had used another type of ovulation-inducing drug. In an analysis of parous and nulliparous women combined, we observed no association of ovarian cancer risk with use of ovulation-inducing drugs; for example, the risk (relative to women who had never sought medical care related to infertility) among women who had ever used clomiphene citrate was 0.9 (95 percent CI: 0.5. 1.5) and, among those who had used the drug during more than 12 menstrual cycles, it was also 0.9 (95 percent CI: 0.2, 4.2). Because risk of ovarian cancer appeared elevated only among nulliparous, infertile women, we also examined the association of ovarian cancer risk and fertility drug use separately among nulliparous and parous women (table 4). Again, we observed no association of use of fertility drugs, ovulation-inducing drugs, or clomiphene citrate with risk of ovarian cancer (all types combined) among either parous or nulliparous women. Similar results were obtained in analyses that compared women who had taken fertility drugs

TABLE 4. Odds ratios for ovarian cancer associated with use of ovulation-inducing drugs: Atlanta, Georgia, Seattle, Washington, and Detroit, Michigan, metropolitan areas, 1994–1998

Exposure	Nulliparous				Parous			
	No. of cases (*n* = 108)	No. of controls (*n* = 343)	Odds ratio*	95% confidence interval	No. of cases (*n* = 270)	No. of controls (*n* = 1,291)	Odds ratio†	95% confidence interval
Never sought care for infertility	84	289	1.0		221	1,098	1.0	
Sought care, no fertility drugs used	18	33	1.9	1.0, 3.6	35	118	1.3	0.8, 1.9
Ever used any fertility drug	6	20	1.0	0.4, 2.8	13	75	0.8	0.4, 1.5
Missing	0	1			1	0		
Ever used ovulation-inducing drugs‡	5	18	1.0	0.4, 3.0	12	67	0.8	0.4, 1.6
Used <6 cycles	3	9	1.4	0.3, 5.5	6	32	1.0	0.4, 2.4
Used 6–12 cycles	1	6	0.5	0.1, 4.7	4	24	0.7	0.2, 2.3
Used >12 cycles	1	3	1.3	0.1, 13.7	1	9	0.5	0.1, 4.2
Missing	0	0			1	2		
Ever used clomiphene citrate	5	16	1.2	0.4, 3.5	11	66	0.8	0.4, 1.6
Used <6 cycles	3	7	1.9	0.4, 8.4	5	33	0.8	0.3, 2.2
Used 6–12 cycles	1	6	0.5	0.1, 4.7	4	25	0.7	0.2, 2.2
Used >12 cycles	1	3	1.3	0.1, 13.5	1	7	0.7	0.1, 6.4
Missing	0	0			1	1		

* Adjusted for age, race, study site, and duration of oral contraceptive use.
† Adjusted for age, race, study site, duration of oral contraceptive use, and number of births.
‡ Clomiphene citrate, human menopausal gonadotropins, or follicle-stimulating hormone.

with the subgroup of women who had neither sought care for infertility nor had had a greater than 12-month interval at risk of pregnancy. In addition, we observed no clear differences in risk associated with exposure to fertility drugs in analyses that separately examined borderline and invasive tumors or in analyses restricted to nonmucinous epithelial ovarian tumors, among either nulliparous or parous women.

DISCUSSION

Differences in the characteristics of women who did or did not choose to participate in this study may influence our results, as may errors in recall of various aspects of fertility history and use of ovulation-inducing drugs. However, the associations we observed of ovarian cancer with other factors generally believed to influence risk, such as parity and use of oral contraceptives, are quite consistent with those previously reported (2, 10), suggesting that the extent of selection or recall bias in this study is not likely to exceed that of previous research. Because our initial results (and those of some prior studies) suggested that any association of risk of ovarian cancer with infertility might be limited to nulliparous women, we assessed the role of specific types of infertility and use of ovulation-inducing drugs separately among nulliparous and parous women; however, our study had limited power to detect associations with such relatively uncommon exposures in these subgroups.

Many prior ovarian cancer studies have been restricted to epithelial types, which accounted for over 90 percent of our case group. Because this study was designed to assess risk associated with infertility and use of ovulation-inducing drugs, and because some previous studies suggested an association of fertility drug use with the occurrence of both epithelial and nonepithelial ovarian tumors (2, 11, 12), we included all histologic types of ovarian cancer. Our results were similar when restricted to epithelial tumors.

Infertility has been variously defined (13), and we analyzed risk according to multiple definitions of this condition. Based on the occurrence of one or more intervals of infertility, 37.4 percent of controls in the current study had a history of this condition, while 15.1 percent reported having sought care for fertility-related problems; 6.5 percent were diagnosed with a specific female-derived basis for infertility while, for 1.7 percent of women, a male abnormality was the only diagnosed cause. These proportions are similar to those reported in a prior population-based study of women aged 20–54 years (13).

Prior studies that have adjusted for confounding by oral contraceptive use and other factors have generally not found a strong overall association of infertility with risk of ovarian cancer. However, several studies have reported an increased risk among a subgroup of nulliparous or nulligravid women. In a combined analysis of case-control data, Whittemore et al. (2) suggested that a subgroup of infertile women with long periods of unprotected intercourse and/or prior use of infertility medications may be at increased risk. Ness et al. (4), in a subsequent combined analysis of case-control studies (including data from Risch et al. (1) discussed separately below), also reported an increased risk among women with a long lifetime duration of years of attempted conception. In both studies, the increased risk was more apparent among nulligravid than gravid women. In a prospective

cohort study of women who were unlikely to have been exposed to ovulation-inducing drugs, Rodriguez et al. (3) reported an increased risk of fatal ovarian cancer in nulligravid women who reported that their infertility was related to a female, rather than male, abnormality, while no increase in risk associated with infertility was observed in gravid women. Risch et al. (1) observed an increased risk associated with a late age at recognition of infertility among nulliparous, but not parous, women, in a population in which no cases and only two controls reported use of an ovulation-inducing drug.

Similar to other researchers, we observed an increased risk associated with infertility among nulliparous, but not parous, women. Among nulliparous women, risk associated with infertility was particularly evident among women whose infertility was first recognized at an older age and among women who had conceived but had not given birth. We observed no association with a particular type of female abnormality leading to infertility or with receipt of fertility drugs, among either nulliparous or parous women. While some prior studies have reported associations with infertility due to the female, but not male, partner (3) or with particular subtypes of female infertility (most studies reviewed by Klip et al. (14); see also Ness et al. (4)), these associations have been inconsistently observed. The results of studies examining the relation of fertility drug use with ovarian cancer have also been inconsistent (most studies reviewed by Glud et al. (15); see also Ness et al. (4)). In a prior cohort study (16), we observed an increased risk of developing a borderline or invasive ovarian tumor among women with long-term use of clomiphene (≥12 cycles), although this association was statistically imprecise (relative risk = 11.1, 95 percent CI: 1.5, 82.3). Most studies, including the current one, have had a very limited ability to assess the effect of long-term use of clomiphene or other ovulation-inducing drugs.

Nieto et al. (17) hypothesized that infertility and ovarian cancer might both be consequences of a common underlying genetic abnormality, particularly among nulliparous women. The suggestion in our data that risk was greatest among nulliparous women whose first infertility episode occurred relatively late in reproductive life does not readily support this hypothesis, as it seems unlikely that an inherited basis for infertility (that also increased ovarian cancer risk) would become manifest only at an older age. Further, a first-degree family history of ovarian or breast cancer was reported by similar proportions of cases with (2.1 percent and 7.9 percent, respectively) or without (3.6 percent and 9.3 percent) a history of infertility.

Low levels of progesterone during a woman's reproductive years have been proposed to increase the risk of ovarian cancer (18), and inability to carry a pregnancy to term late in reproductive life has been proposed as a marker of progesterone deficiency (19). Conceivably, the increased risk we observed in nulliparous women who experienced an infertility episode relatively late in reproductive life may reflect the occurrence or onset of a progesterone deficiency. However, while progesterone deficiency may in part account for the relatively greater increase in risk we observed among infertile nulliparous women who had been pregnant at least once, such women were at a similar risk regardless of whether their pregnancies ended in spontaneous or induced abortion.

The current study adds support to the hypothesis that a subset of women who experience infertility may be at increased risk of ovarian cancer. As in other studies, the proportion of women at increased risk appears to be fairly low. In this study, 6.0 percent of controls and 11.1 percent of cases were nulliparous women who were classified as infertile on the basis of a joint consideration of their reproductive, contraceptive, and sexual histories; even lower percentages of women elected to seek medical care for infertility. Although this study and other studies have attempted to determine whether the observed increase in risk of ovarian cancer among nulliparous, infertile women is related to the pathologic basis for the infertility, the use of ovulation-inducing drugs, shared genetic susceptibility to infertility and ovarian cancer, or some other unrecognized factor, the reason for this increase in risk remains unclear.

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