Ovarian Cancer Risk After the Use of Ovulation-Stimulating Drugs

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OBJECTIVE: To assess the long-term effects of ovulation-stimulating drugs on the risk of ovarian cancer.

METHODS: A retrospective cohort study of 12,193 eligible study subjects (median age 30 years) who were evaluated for infertility during the period of 1965–1988 at 5 clinical sites identified 45 subsequent ovarian cancers in follow-up through 1999. Standardized incidence ratios compared the risk of cancer among the infertile patients to the general population, whereas analyses within the cohort allowed the derivation of rate ratios for drug usage compared with no usage after adjustment for other ovarian cancer predictors.

RESULTS: The infertility patients had a significantly elevated ovarian cancer risk compared with the general population (standardized incidence ratio 1.98, 95% confidence intervals [CI] 1.4, 2.6). When patient characteristics were taken into account and risks assessed within the infertile women, the rate ratios associated with ever usage were 0.82 (95% CI 0.4, 1.5) for clomiphene and 1.09 (95% CI 0.4, 2.8) for gonadotropins. There were higher, albeit nonsignificant, risks with follow-up time, with the rate ratios after 15 or more years being 1.48 (95% CI 0.7, 3.2) for exposure to clomiphene (5 exposed cancer patients) and 2.46 (95% CI 0.7, 8.3) for gonadotropins (3 exposed cancer patients). Although drug effects did not vary by causes of infertility, there was a slightly higher risk associated with clomiphene use among women who remained nulligravid, based on 6 exposed patients (rate ratio 1.75; 95% CI 0.5, 5.7).

CONCLUSION: The results of this study generally were reassuring in not confirming a strong link between ovulation-stimulating drugs and ovarian cancer. Slight but nonsignificant elevations in risk associated with drug usage among certain subgroups of users, however, support the need for continued monitoring of long-term risks. (Obstet Gynecol 2004;103:1194–203. © 2004 by The American College of Obstetricians and Gynecologists.)

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It is well recognized that nulliparous women are at an increased risk for ovarian cancer.[1] It has been suggested that infertile women who receive ovulation-stimulating drugs may be at particularly high risk. The association has biologic credibility, given that "incessant ovulation" and excess gonadotropin levels during reproductive years appear to be likely explanations for a number of the recognized risk factors for ovarian cancer, such as nulliparity and oral contraceptive usage[2–4] Contributing to the concern regarding the possible adverse effects of ovulation-stimulating drugs are several studies that have observed elevated risks associated with the use of these drugs.[5,6] However, not all studies have observed similar relationships,[7–19] leading to scrutiny regarding the methodologies of the previous studies. The retrospective nature of data collection in interview-based case–control studies has led to questions regarding the validity of the reported drug exposures. Concerns regarding prospective studies have focused on the small numbers of events, short and incomplete follow-up, and absence of information on other predictors of ovarian cancer risk. In addition, most of the investigations have been unable to account for the indications for drug usage, notably anovulation, and for the effects of other causes of infertility, which could independently affect ovarian cancer risk.[5,20–24]

To evaluate further the effects of drug usage and causes of infertility on subsequent cancer risk, we undertook a large, retrospective cohort study among women treated for infertility at 5 specialized practices. Our study has a number of strengths over previous investigations,

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including detailed medical record abstraction (enabling accurate classification of causes of infertility and drug exposures), extended follow-up (on average nearly 20 years), subsequent collection of questionnaires from patients (which elicited information on other factors that could affect cancer risk), and identification and medical verification of cancer outcomes through multiple sources. We report here the results relating to the risk of developing ovarian cancer among this cohort of women evaluated for infertility.

MATERIALS AND METHODS

Patients for this study comprised women who had sought advice for infertility at 1 of 5 large reproductive endocrinology practices in the following areas: Boston, Massachusetts; New York, New York; Chicago, Illinois; Detroit, Michigan; and the San Francisco Bay Area, California. These practices were chosen because they had retained all original records and evaluated large numbers of infertile patients, many of whom received high doses of ovulation-stimulating drugs. To allow extended follow-up, only patients evaluated during 1965–1988 were eligible for study. The study was approved by the institutional review boards at the collaborating centers as well as at the National Cancer Institute.

Trained abstractors reviewed medical records of all patients evaluated for infertility at these practices to determine eligibility. Patients were eligible for inclusion in the study if they were evaluated for infertility at 1 of the participating clinics between 1965 and 1988, had a U.S. address at the time of evaluation, and were seen more than once or had been referred by another physician who provided relevant medical information. Patients with either primary or secondary infertility were eligible for inclusion, but those who were evaluated for reversal of a tubal ligation were not. A total of 12,193 met eligibility criteria. Using standardized software, trained abstractors entered data directly into laptop computers. This included patient identifiers as well as information on the work-up for infertility, medications prescribed, menstrual and reproductive histories, and other factors that might affect health status. Drug information abstracted included clomiphene citrate (hereafter referred to as clomiphene) and a variety of human gonadotropins, namely, Pergonal (Serono, Rockland, MA), Humegon (Organon, West Orange, NJ), or Metrodin (Serono, Rockland, MA). Details from the clinical work-up were used to define 6 causes of infertility (endometriosis, anovulation, tubal disease/pelvic adhesions, male factor, cervical disorders, and uterine disorders), with each patient coded as having no evidence, evidence, or an incomplete evaluation for each cause.

Location information was sought through a variety of sources, including clinic records, telephone directories, credit bureaus, postmasters, and motor vehicle records. Additional information about vital status and development of cancers was obtained by administering questionnaires to located, living subjects and through linkage of the cohort against selected cancer registries and the National Death Index. As detailed in Figure 1, a total of 9,751 (80%) of the patients was traced 1 or more years after first clinic registration. A total of 1,319 (10.8%) of the patients indicated upon contact that they did not want to participate in the study and would not allow access to data in their medical records. Only descriptive information, that is, calendar year and age at registration, and race, was retained for these patients.

A total of 272 of the patients was traced as deceased. For the living patients, information on the development of cancers was obtained from questionnaires, clinic records, and cancer registries. Questionnaires were mailed to patients beginning in early 1998, with telephone follow-up attempted for nonrespondents. A total of 5,597 of the patients completed the questionnaire. The questionnaires ascertained information on demographic factors, updated health status, and lifestyle factors that could affect health, including menstrual, pregnancy and breast-feeding history; the use of exogenous hormones; anthropometric factors; cigarette smoking; alcohol consumption; and breast and ovarian disease screening histories. An additional 216 patients had follow-up visits 1 or more years beyond their initial clinic visit. For 2,347 patients for whom we were unable to obtain questionnaires, we had location information that enabled tracing through cancer registries in the states in which the majority of patients were last known to reside–namely, California, Florida, Illinois, Massachusetts, Michigan, New Jersey, New York, and Texas.

Attempts were made to medically verify cancers reported in the questionnaires by obtaining discharge summaries and operative and pathology reports from the institutions where the diseases had been diagnosed and/or treated. Six self-reported ovarian cancers found to be non-neoplasms were excluded. Additional information on cancers was obtained from the cancer registries or the National Death Index or from death certificates obtained from individual state vital statistics registries. Death certificates, which noted cancer as a cause of death, were searched for information on the duration of the disease to define approximate diagnostic dates.

For the women who were followed for subsequent cancer diagnoses, person-years were accrued beginning 1 year after clinic registration and continuing through the earliest date of cancer diagnosis, death, or date last known alive and free of cancer. Patients living in states

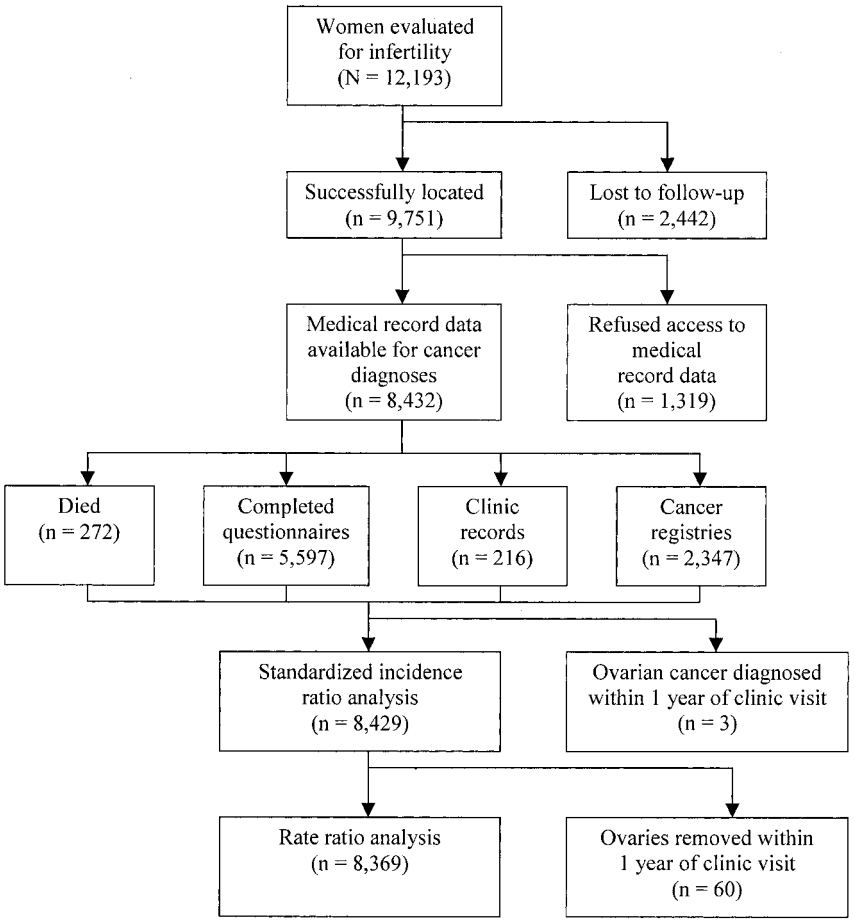

Figure 1. Field and analytic status of eligible study subjects, women evaluated for infertility, 1965–1988.

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involving cancer registry searches had variable study ending dates, depending on the completeness of registration, which ranged from 1997 to 1999. Otherwise, December 31, 1999 defined the end of the study period.

To explore the relationship between ovulation-stimulating drugs and ovarian cancer risk, we used 2 analytic approaches with 2 predominantly overlapping subsets of the eligible study population. We first established the ovarian cancer risk associated with different medications by comparing ovarian cancer rates among infertile women to rates from the U.S. population (155,624 person-years). For this analysis, exclusions comprised patients whose date of last contact was within 1 year of their initial clinical visit, those who denied access to their records, and 3 women who were diagnosed with ovarian cancer during the first year of follow-up, leaving 8,429 study subjects (Figure 1). The second analytic approach assessed ovarian cancer risk according to medication usage within the cohort, which allowed for multivariable adjustment of potential confounders. For this analysis, person-years were additionally truncated at the time of removal of both ovaries. A total of 60 women who had both ovaries removed within 1 year of their first clinic visit were excluded, leaving 8,369 study subjects (148,318 person-years). Both analyses included 45 women who developed ovarian cancer; medical or cancer registry records confirmed 21 of these, death certificates defined 10, and 14 were reported via questionnaires.

Standardized incidence ratios and 95% confidence intervals (CIs) compared ovarian cancer risk among the cohort of infertile women to that of U.S. women. Standardized incidence ratios were computed as the number of observed cancers divided by the expected numbers based on age, race, and calendar year-specific incidence disease rates for females available through the Surveillance, Epidemiology, and End Results Program. Standardized mortality ratios (SMRs) were similarly calculated by using U.S. mortality rates to generate expected values. For this analysis, subjects who were located but did not respond to the questionnaire were assumed alive and their person-years accrued until the end of follow-up.

Rate ratios for developing ovarian cancer associated with various drug exposures and their 95% CIs were

Table 1. Selected Demographic Factors of Women Evaluated for Infertility

	Subjects in follow-up analysis (N = 8,429)		Subjects excluded from analysis (N = 3,764)	
	n	%	n	%
Calendar years of initial clinic evaluation				
< 1970	260	3.1	153	4.1
1970–1974	1,898	22.5	848	22.5
1975–1979	2,908	34.5	1,378	36.6
1980–1984	2,516	29.8	1,048	27.8
1985–1988	847	10.1	337	9.0
Age at initial clinic evaluation (y)				
< 25	688	8.2	415	11.0
25–29	3,314	39.3	1,371	36.4
30–34	3,071	36.4	1,301	34.7
35–39	1,124	13.3	557	14.8
≥ 40	232	2.8	117	3.1
Unknown	0		3	
Race				
White	6,658	79.0	2,280	60.6
African-American	392	4.6	164	4.3
Other	471	5.6	191	5.1
Unknown	908	10.8	1,129	30.0

estimated by Poisson regression using standard likelihood ratio methods.[25] The rate ratios were adjusted for age (< 40, 40–49, ≥ 50) and calendar year of follow-up (before 1980, 1980–1989, 1990 or later). Other factors, such as study site and causes of infertility, were included in the regression models, as necessary, to evaluate their roles as potential confounding factors or to examine variations of the rate ratios. In addition, we used questionnaire data to assess influences of other ovarian cancer predictors (eg, gravidity, oral contraceptive usage, education).

RESULTS

Table 1 shows the distribution of the entire cohort and that of the subjects excluded from analyses according to selected patient characteristics. The medians for year and age of first evaluation were 1978 and 30 years, respectively. Nearly 80% of the subjects were known to be Caucasian. There were no significant differences according to year or age at first evaluation between the subjects included in the analyses and those excluded; however, a larger proportion of the excluded subjects had missing information on race. The median length of follow-up among subjects was 18.8 years (range 1–34 years), with more than 80% followed for 15 or more years.

The infertile study subjects were found to have a significantly higher risk of developing ovarian cancer than the general population (standardized incidence ratio = 1.98; 95% CI 1.4, 2.6; Table 2). A total of 3,277 (38.4%) of the study subjects was prescribed clomiphene, whereas 866 (10.3%) received gonadotropins. Ovarian

Table 2. Standardized Incidence Ratios Comparing Ovarian Cancer Among Infertile Patients With the General Population,* Overall and Stratified by Usage of Clomiphene and Gonadotropins

	Person-years of follow-up	Number of observed events	Number of expected events	Standardized incidence ratio†	95% confidence interval
All subjects	155,624	45	22.7	1.98	1.4, 2.6
Ever exposed to clomiphene					
No	96,976	30	14.3	2.09	1.4, 3.0
Yes	58,648	15	8.4	1.79	1.0, 3.0
Ever exposed to gonadotropins					
No	140,605	40	20.5	1.95	1.4, 2.7
Yes	15,019	5	2.2	2.26	0.7, 5.3

* Cancer incidence rates based on data from the Surveillance, Epidemiology, and End Results Program.

† Number of observed cancers divided by the expected number based on age, race, and calendar year–specific Surveillance, Epidemiology, and End Results Program incidence rates.

Table 3. Distribution of Demographic and Other Determinants of Ovarian Cancer Risk

	No cancer (N = 8,324)		Cancer (N = 45)		
	n	%	n	%	*P*
Age at first clinic visit (y)					.82
< 25	684	8.2	2	4.5	
25–29	3,269	39.3	21	46.7	
30–34	3,037	36.5	15	33.3	
35–39	1,106	13.3	6	13.3	
≥ 40	228	2.7	1	2.2	
Race					.62
White	6,567	88.5	40	93.0	
African-American	385	5.2	1	2.3	
Other	466	6.3	2	4.7	
Gravidity > 0 at first clinic visit	4,803	57.7	19	42.2	.04*
Cause of infertility[†]					
Anovulation	2,292	27.6	12	26.7	.88
Endometriosis	1,880	35.8	13	40.6	.57
Tubal disease/pelvic adhesions	2,938	42.8	16	38.1	.54
Uterine disorders	935	18.6	6	18.8	.98
Cervical disorders	573	11.4	2	8.7	.68
Male factor	1,932	31.8	10	31.3	.95
Ever breastfed[‡§]	2,450	73.4	8	80.0	.64
Oral contraceptive use[§]	5,394	85.2	33	91.7	.27
Family history of ovarian cancer[§]	96	1.9	0	. . .	.49
Hysterectomy[§]	287	3.5	2	4.4	.11
Tubal ligation[§]	644	13.8	3	12.0	.79
Years of education[§]					.31
< High school	517	11.0	5	20.8	
Some college	1,374	29.4	7	29.2	
College graduate	1,381	29.5	8	33.3	
Graduate work	1,409	30.1	4	16.7	

P values were estimated from Pearson χ^2 statistic, which was calculated for each variable after excluding subjects with missing data.

* $P < .05$.

† Causes of infertility are not mutually exclusive. Percentages for each cause of infertility are restricted to patients with workups sufficiently complete to allow a valid diagnosis for each condition.

‡ Among parous women.

§ Information from questionnaires, available for 5,597 patients.

cancer risks were similar for unexposed and exposed subjects. The standardized incidence ratio for subjects unexposed to clomiphene was 2.09 (95% CI 1.4, 3.0), as compared with 1.79 (1.0, 3.0) for those exposed. Comparable standardized incidence ratios for gonadotropins were 1.95 (1.4, 2.7) and 2.26 (0.7, 5.3).

Cohort members also were compared with the general population with respect to their mortality experience. There were 11 deaths caused by ovarian cancer, resulting in a SMR of 1.94 (95% CI 0.9, 3.5). There was no evidence of higher mortality among subjects exposed to infertility medications (SMR = 1.42; 95% CI 0.3, 4.2 versus SMR of 2.25; 95% CI 0.9, 4.4 for those unexposed).

To assess drug usage effects after accounting for other factors that might influence ovarian cancer risk, we focused subsequent analyses on internal comparisons to derive adjusted rate ratios. The distribution of risk factors by ovarian cancer status is shown in Table 3. Significantly fewer of the ovarian cancer patients as compared with the noncancer patients had ever been pregnant at first clinic visit. Although ovarian cancer patients more often had histories of oral contraceptive usage or diagnoses of endometriosis, and they were somewhat less educated than others, these differences were not statistically significant. Other postulated risk factors, including breast-feeding, tubal ligation, and hysterectomy, did not show substantial differences between the 2 groups of patients.

Despite the above differences, gravidity at entry was the only risk factor that had any impact on the risks associated with drug usage. After adjustment for this factor, as well as age at follow-up, calendar time, and study site, the rate ratio associated with use of clomiphene was 0.82 (95% CI 0.4, 1.5; Table 4). Dosage appeared unrelated to risk (eg, rate ratio = 0.80 for ≥ 2,251 mg of clomiphene). However, there was some evidence of a slightly elevated risk for women with either 12 or more cycles of exposure (rate ratio = 1.54, 95% CI

Table 4. Rate Ratios of Ovarian Cancer Among Infertile Women According to Clomiphene and Gonadotropin Exposures

	Person-years of follow-up	No. of ovarian cancers	Rate ratio*	95% confidence interval
Clomiphene				
Never	92,236	30	1.00	
Ever	56,082	15	0.82	0.4, 1.5
Dosage (mg)				
1–900	19,501	6	0.94	0.4, 2.3
901–2,250	17,532	4	0.71	0.2, 2.0
≥ 2,251	19,049	5	0.80	0.3, 2.1
Cycles				
< 6	36,298	10	0.85	0.4, 1.7
6–11	13,621	2	0.44	0.1, 1.9
≥ 12	6,163	3	1.54	0.5, 5.1
Years since first exposure				
< 15	38,752	9	0.47	0.2, 1.2
≥ 15	13,139	5	1.48	0.7, 3.2
Unknown		1		
Gonadotropins				
Never	133,680	40	1.00	
Ever	14,638	5	1.09	0.4, 2.8
Dosage (amps)†				
1–24	4,861	2	1.36	0.3, 5.7
≥ 25	9,777	3	0.96	0.3, 3.1
Cycles				
1–2	6,892	2	0.95	0.2, 3.9
≥ 3	7,746	3	1.21	0.4, 3.9
Years since first exposure				
< 15	11,015	2	0.67	0.2, 2.8
≥ 15	2,746	3	2.46	0.7, 8.3
Combination of clomiphene and gonadotropins				
Neither	89,677	29	1.00	
Clomiphene only	44,003	11	0.78	0.4, 1.6
Gonadotropins only	2,559	1	1.16	0.1, 8.2
Both	12,079	4	1.02	0.3, 2.8

* Adjusted for age at follow-up, calendar time, study site, and gravidity at first clinic visit.

† Each ampule of Pergonal or Humegon consisted of 75 IU of follicle stimulating hormone and 75 IU of luteinizing hormone; each ampule of Metrodin consisted of 75 IU of follicle stimulating hormone.

0.5, 5.1) or 15 or more years of follow-up (rate ratio = 1.48; 0.7, 3.2). Both of these risks, however, were based on few exposed cancers (3 and 5, respectively). Exposure to gonadotropins was associated with a rate ratio of 1.09 (95% CI 0.4, 2.8). Although there was no evidence of any trends in risk according to dose or cycles of exposure, these analyses were limited by the fact that only 5 exposed women developed ovarian cancer. A higher risk among women with 15 or more years since first use of gonadotropins was based on only 3 exposed cancer patients (rate ratio = 2.46, 95% CI 0.7, 8.3). There was no indication that patients who had been exposed to both clomiphene and gonadotropins were at an unusual risk of developing ovarian cancer compared to women who had never used either drug (rate ratio = 1.02).

Further analyses focused on whether clomiphene-associated risks varied by other ovarian cancer risk factors (Table 5). Subjects who never became pregnant had a somewhat higher risk associated with clomiphene (rate ratio = 1.75; 95% CI 0.5, 5.7, based on 6 exposed cancer patients) than those who eventually became pregnant (rate ratio = 0.77), but the differences were not significant. Although there was some variation in risks associated with clomiphene according to causes of infertility, usage was not substantially related to risk in any of the subgroups. There were no ovarian cancers among drug-exposed women with a first-degree family history of ovarian cancer, precluding evaluation of whether clomiphene might have differential effects depending on a woman's genetic predisposition.

We also attempted to assess whether effects of gonadotropins were modified by other ovarian cancer risk factors. Although limited by the small numbers of ovarian cancers that developed among those exposed to these drugs, we did not observe any patterns that would suggest strong interrelationships (data not shown).

Given that the ovarian cancers were defined in a number of different ways (self-reports followed by med-

Table 5. Rate Ratios of Ovarian Cancer Among Infertile Women for Ever Versus Never Use of Clomiphene According to Other Ovarian Cancer Risk Factors

	Person-years of follow-up*	No. of ovarian cancers	Rate ratio†	95% confidence interval
Age at follow-up (y)				
< 40	41,441	2	0.40	0.1, 1.9
40–49	24,663	10	0.97	0.4, 2.1
≥ 50	5,318	3	1.06	0.3, 4.3
Gravidity at follow-up‡				
Nulligravid	7,327	6	1.75	0.5, 5.7
Gravid	41,122	8	0.77	0.3, 1.8
Cause of infertility§				
Endometriosis	14,536	4	0.54	0.2, 1.8
Anovulation	22,310	6	1.02	0.3, 2.9
Tubal disease/pelvic adhesions	17,939	4	0.60	0.2, 1.9
Uterine disorders	5,742	1	0.31	0.0, 2.7
Cervical disorders	5,376	2	No cancer in referent group	
Male factor	13,029	3	0.72	0.2, 2.8
Ever used oral contraceptives‡				
No	6,702	0	. . .	
Yes	38,079	13	1.00	0.5, 2.0

* Among clomiphene users.
† Adjusted for age at follow-up and calendar time.
‡ Information from questionnaires, available for 5,597 patients.
§ Causes of infertility are not mutually exclusive.

ical validation, identification through cancer or death registries, self-reports only), additional analyses considered the influence of these sources on derived risks. Analyses, which were restricted to cancers that were validated against medical records, cancer registry records, or death certificates showed results similar to those for the total series (eg, rate ratio for ever use of clomiphene was 0.77; 95% CI 0.4, 1.6). Because several previous studies have found a preponderance of borderline ovarian cancers among clomiphene-exposed women, we also conducted analyses in which we eliminated the 6 such identified cancers. The resulting rate ratios were nearly identical to the total series (rate ratio for clomiphene = 0.73; 95% CI 0.4, 1.4). For the invasive cancers for which histology was available (n = 20), epithelial tumors were the predominant cell type, with only one cancer specifically noted as a granulosa cell tumor.

Because the retrospective nature of the study resulted in our inability to include the complete cohort for analyses, we also conducted a number of analyses to define the impact that losses might have had on our results. Because we were unable to obtain completed questionnaires from many of the subjects, we had to rely on identification of cancer outcomes on the basis of linkage against cancer registries. However, if the last known address was incorrect, we might have missed the true identification of cancers among these subjects and incorrectly assigned person-years until the end of the study. We were also unable to account for bilateral oophorectomy among these patients, which may have led to a false inflation of person-years. We therefore conducted alternative analyses in which we limited the analysis to patients with questionnaire data or a definite diagnosis of ovarian cancer confirmed by medical records, cancer registries, or death registries. Although the number of person-years substantially decreased, the rate ratios associated with drug exposures changed little. For example, the resultant rate ratios for clomiphene exposure was 0.78 (95% CI 0.4, 1.5).

DISCUSSION

This study assessed the relationship of ovarian cancer risk to parameters of exposure to ovulation stimulating drugs, including type of medication and dosage. Strengths of our study included a large cohort of women from different clinical sites, extended follow-up, and available information on other predictors of ovarian cancer risk, including specific causes of infertility and gravidity. Although the results generally were reassuring as compared with several studies that have seen strong associations between infertility drugs and ovarian cancer risk, some of our results suggest the need for further monitoring of this exposure, particularly given that many of our subjects were just beginning to enter the usual age range for the development of ovarian cancer. Notable were some slight increases in risk for both clomiphene and gonadotropins among the subjects followed for 15 or more years, results that were difficult to

evaluate because they were based on small numbers and not statistically significant.

Although the majority of previous studies on this topic have failed to document a relationship of ovulation-stimulating drugs to the risk of ovarian cancer,[7–19] most have suffered from a number of methodologic shortcomings. Prospective studies[5,7,10,11,15,16,18,19] have been limited by small numbers of ovarian cancers, with the number of patients ranging from 2 in the smallest study[15] to 15 in the largest study.[10] These studies also usually had limited information on causes of infertility or on other factors (such as parity, oral contraceptive usage, and socioeconomic status) that could independently influence ovarian cancer risk. In addition, most of the previous studies have not had an unexposed comparison group, and none has been able to censor patients with bilateral oophorectomies who are no longer at risk of developing ovarian cancer. Case-control studies,[6,9,12–14,17] which have the advantage of large numbers of cases, must rely on subject reports of past exposure to infertility medications, as well as on reasons for their having been prescribed. This information could be subject to a variety of sources of bias, which has led to considerable concern over results deriving from such investigations.[26,27]

Two investigations, which have noted effects of ovulation-stimulating drugs on subsequent ovarian cancer risk, are noteworthy. These include a retrospective cohort study conducted by Rossing and colleagues[5] and a meta-analysis of 12 case-control studies conducted by Whittemore and others.[6]

In the Rossing study,[5] which focused on 3,837 women evaluated in the Seattle area between 1974 and 1985, clomiphene use was associated with a 2.3-fold increased risk (95% CI 0.5, 11.4), based on 9 ovarian cancers. Use of the drug for less than 1 year was not associated with an increased risk, but 5 of the 9 women had taken the drug for 12 or more monthly cycles, resulting in a relative risk of 11.1 (95% CI 1.5, 82.3). A large proportion of the tumors were considered borderline, and there was some evidence that clomiphene risks were most apparent among women without apparent ovulatory problems. However, information on other predictors of ovarian cancer risk among cohort members was limited.

The other major positive study was a combined analysis of 12 U.S. case-control studies.[6] Interpretation of results was limited by the absence of information on the types of drugs used or their durations of usage. Among gravid women, there was little evidence of risk associated with drug usage (rate ratio = 1.4; 95% CI 0.5, 3.6), whereas among nulligravid women risk was substantially increased (rate ratio = 27; 95% CI 2.3, 315.6). These results have received considerable scrutiny (Caro JJ, Johanees CB, Hartz SC, Marrs R, Miettinen OS. Re: "Characteristics relating to ovarian cancer risk: collaborative analysis of 12 U.S. case-control studies. II. Invasive epithelial ovarian cancers in white women" [letter]. Am J Epidemiol 1993;137:928–9 *and* Shapiro S. Risk of ovarian cancer after treatment for infertility [letter]. N Engl J Med 1995;332:1301), with concerns focusing on the accuracy of recalled drug exposures.

In contrast to the findings of the Rossing and Whittemore studies, our findings were reassuring. Thus, we found that ever use of clomiphene or gonadotropins were not associated with any elevations in risk. However, given that the largest increases in risk in these 2 previous studies were either among women with multiple cycles of exposure or nulligravid women, we also assessed risks within these subgroups. It was notable that the risks that we observed for those with 12 or more cycles of use (or 15 or more years since follow-up) as well as among those who remained nulligravid at follow-up were somewhat elevated (rate ratios for clomiphene between 1.5 and 1.7). However, these risks were based on relatively small numbers of exposed cancer patients and were not statistically significant. Thus, although our study cannot totally rule out an effect of these drugs on ovarian cancer risk in select groups of users, the results do not confirm the substantial risks of 11- to 27-fold observed in the previous positive studies. Nonetheless, the exposure appears to be one that should continue to be monitored for long-term effects in future investigations.

As noted, the Rossing study found an enhancement of ovulation-stimulating drugs on the risk of borderline tumors. Several other individual investigations[17,28] and meta-analyses[13,29] have also noted an elevated risk of borderline tumors associated with fertility drugs, although these were case-control studies involving patient reports of prior drug exposures. In 1 study, the relationship was restricted to nulligravid women[13] and in another the relationship with infertility drugs pertained only to gonadotropins.[17] These findings, in conjunction with case reports of ovarian cancer developing in women during treatment with follicular stimulants (Dietl J. Ovulation and ovarian cancer [letter]. Lancet 1991;338:445),[30–37] have led to speculations that ovarian stimulation may induce highly differentiated indolent tumors. Alternatively, the findings could reflect more intensive surveillance among infertile women. Although we had a limited ability to evaluate drug effects on borderline tumors given their rare occurrence (we observed only 6 such cancers), we did not observe an unusual occurrence of these tumors in the large number of patients included in our investigation.

Although our study had a number of strengths, there were some notable limitations. Although the number of

ovarian cancer cancers was larger than any single previously published study, the total number (n = 45) was still limited. Furthermore, given the retrospective nature of the study, we were unable to locate 20% of the study population and, among those that we did locate as alive, 41% did not complete our questionnaire. Thus, a variety of selection biases could have affected our results. However, we were unable to detect any systemic biases in the analyses undertaken to assess relationships according to sources of subject inclusion or loss. In addition, a number of women had incomplete workups, leading to uncertainty regarding causes of infertility. However, among women with complete workups, adjustment for causes of infertility did not substantially change the risks associated with drug exposures. Furthermore, information on ovulation-stimulating drugs, although more complete than in most studies, was still less than optimal. Although information about later drug use was obtained via the questionnaire, we could not account for drugs subsequently prescribed by other providers among the women who did not complete the questionnaire. Finally, the pattern and dose of drug exposures for many women that we evaluated were quite different from those in current use (including in vitro fertilization). However, the drug exposures that we evaluated for women registered in the years 1965–1988 included women who subsequently underwent assisted reproductive technology procedures. In the early years, some women received prolonged cycles and very high doses of clomiphene, yet were found not to be at an overall increased risk of ovarian cancer.

Our findings were reassuring in not confirming a strong link between use of infertility medications and risk of subsequent ovarian cancer. Although it was clear from the derived standardized incidence ratios in the study, that infertile patients are at a higher risk of ovarian cancer than the general population, our study emphasized the importance of accounting for characteristics of infertile patients in assessing drug effects. Thus, in comparisons with other infertile patients, there was no evidence that ever use of either clomiphene or gonadotropins had an adverse effect on ovarian cancer risk. However, our study could not rule out the possibility that certain subgroups of users might experience some slight elevation in risk, supporting the need for additional studies to evaluate long-term effects.

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