

# Ovarian cancer risk associated with varying causes of infertility

Louise A. Brinton, Ph.D.,<sup>a</sup> Emmet J. Lamb, M.D.,<sup>b</sup> Kamran S. Moghissi, M.D.,<sup>c</sup> Bert Scoccia, M.D.,<sup>d</sup> Michelle D. Althuis, Ph.D.,<sup>a</sup> Jerome E. Mabie, B.S.,<sup>e</sup> and Carolyn L. Westhoff, Ph.D.<sup>f</sup>

National Cancer Institute, Bethesda, Maryland; Stanford University, Stanford, California; Wayne State University, Detroit, Michigan; University of Illinois at Chicago, Chicago, Illinois; Information Management Services, Rockville, Maryland; and Columbia University, New York, New York

**Objective:** To evaluate the risk of ovarian cancer as related to underlying causes of infertility.

**Design:** Retrospective observational cohort study.

**Setting:** Five large reproductive endocrinology practices.

**Patient(s):** A total of 12,193 women evaluated for infertility between 1965 and 1988.

**Intervention(s):** None.

**Main Outcome Measure(s):** Ovarian cancer ascertained through 1999.

**Result(s):** With 45 identified ovarian cancers, this cohort of infertility patients demonstrated a significantly higher rate of ovarian cancer than the general female population (standardized incidence ratio [SIR] = 1.98; 95% confidence interval [CI], 1.4–2.6). The risk was higher for patients with primary infertility (SIR = 2.73) than for those with secondary infertility (SIR = 1.44), and it was particularly high for patients who never subsequently conceived (SIR = 3.33). Women with endometriosis had the highest risk (SIR = 2.48; 95% CI, 1.3–4.2), with a further elevated risk among those with primary infertility (4.19, 2.0–7.7). Comparisons among the infertile women, which allowed calculation of rate ratios (RRs) after adjustment for multiple factors, also showed links with endometriosis. Compared with women with secondary infertility without endometriosis, patients with primary infertility and endometriosis had a RR of 2.72 (95% CI, 1.1–6.7).

**Conclusion(s):** Determination of ovarian cancer risk should take into account the type of infertility (primary vs. secondary) and underlying causes. Further study of endometriosis may provide insights into ovarian carcinogenesis. (*Fertil Steril*® 2004;82:405–14. ©2004 by American Society for Reproductive Medicine.)

**Key Words:** Ovarian cancer, risk, epidemiology, infertility, endometriosis, anovulation

Although extensively studied, the etiology of ovarian cancer remains unresolved, with few recognized risk factors that would allow its early detection. One established risk factor is nulliparity, with childless women having between a two- and three-fold increased risk compared with parous women (1, 2). A number of studies have indicated that this association may largely be attributable to infertility problems (2–4), but whether specific causes of infertility predispose more than others remains unknown. The studies that have attempted to assess relationships with specific causes of infertility have largely relied on patient reports, which are recognized as having serious limitations (5). Thus, studies that have medically documented information on specific problems that lead to infertility are needed and may

provide insights into mechanisms of ovarian carcinogenesis.

The need for such studies is further supported by recent observations that certain causes of infertility may be linked with the occurrence of ovarian cancer. This includes clinical reports of simultaneous occurrences of endometriosis and ovarian cancer (6–15) as well as several epidemiologic studies that have shown high risks of ovarian cancer after a diagnosis of endometriosis (16, 17). Anovulation is another condition meriting attention with respect to the risk of ovarian cancer. A follow-up study of infertile women found a nearly two-fold increased risk of ovarian cancer when patients with ovulatory abnormalities were compared with patients with other infer-

Received October 2, 2003; revised and accepted February 12, 2004.

Supported by National Cancer Institute intramural funds.

Presented at the 59th Annual Meeting of the American Society for Reproductive Medicine, which was held in San Antonio, Texas, October 11–15, 2003.

Reprint requests: Louise A. Brinton, Ph.D., National Cancer Institute, 6120 Executive Blvd., Room 7068, Rockville, Maryland 20852-7234 (FAX: 301-402-0916; E-mail: Brinton@nih.gov).

<sup>a</sup> Hormonal and Reproductive Epidemiology Branch, National Cancer Institute.

<sup>b</sup> Department of Obstetrics and Gynecology, Stanford University.

<sup>c</sup> Department of Obstetrics and Gynecology, Wayne State University.

<sup>d</sup> Department of Obstetrics and Gynecology, University of Illinois at Chicago.

<sup>e</sup> Information Management Services, Inc.

<sup>f</sup> Department of Obstetrics and Gynecology, Columbia University.

0015-0282/04/\$30.00  
doi:10.1016/j.fertnstert.2004.02.109

tility diagnoses (18). In addition, studies have reported that patients with polycystic ovarian syndrome may have a high risk of ovarian cancer (19, 20), possibly because of alterations in anthropometry, endogenous hormones, or growth factors. Finally, recent speculation regarding a possible etiologic role of inflammation in the etiology of ovarian cancer (21) has raised concern about effects of certain infectious processes that could lead to tubal disease/pelvic adhesions. Of note in this regard are several studies that have found elevated ovarian cancer risks among patients with a history of pelvic inflammatory disease (22–24).

To gain a better understanding of the etiology of ovarian cancer, we undertook a large retrospective cohort study of infertile patients for whom abstracted medical record data enabled careful characterization of causes of infertility. The collection of additional information relating to other reproductive, medical, and lifestyle factors enabled an evaluation of the relationship of ovarian cancer risk with specific causes of infertility independent of other predictors of ovarian cancer risk.

## MATERIALS AND METHODS

The patients for this study were women who had sought advice for infertility at one of five large reproductive endocrinology practices in the following metropolitan areas: Boston, New York City, Chicago, Detroit, and the San Francisco Bay area. These practices were chosen because they retained all original records and had 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 the period 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 one of the participating clinics between 1965 and 1988, if they had a U.S. address at the time of evaluation, and if they 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 patients met the eligibility criteria.

Using standardized software, trained abstractors entered data directly into laptop computers. These included patient identifiers as well as information on the workup for infertility (including details on all procedures and tests), medications prescribed, menstrual and reproductive histories, and other factors that might affect health status. Information on the clinical workup was used to define a number of discrete causes of infertility according to an algorithm presented in Appendix 1.

Location information was sought through a variety of sources, including clinic records, telephone directories, credit bureaus, postmasters, and motor vehicle administration records. Additional information about vital status and development of cancers was obtained by questionnaires that were sent 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 (80.0%) of the patients were successfully traced one 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 the data available in their medical records. Only descriptive information, i.e., calendar year at registration, age at registration, and race, was retained for these patients.

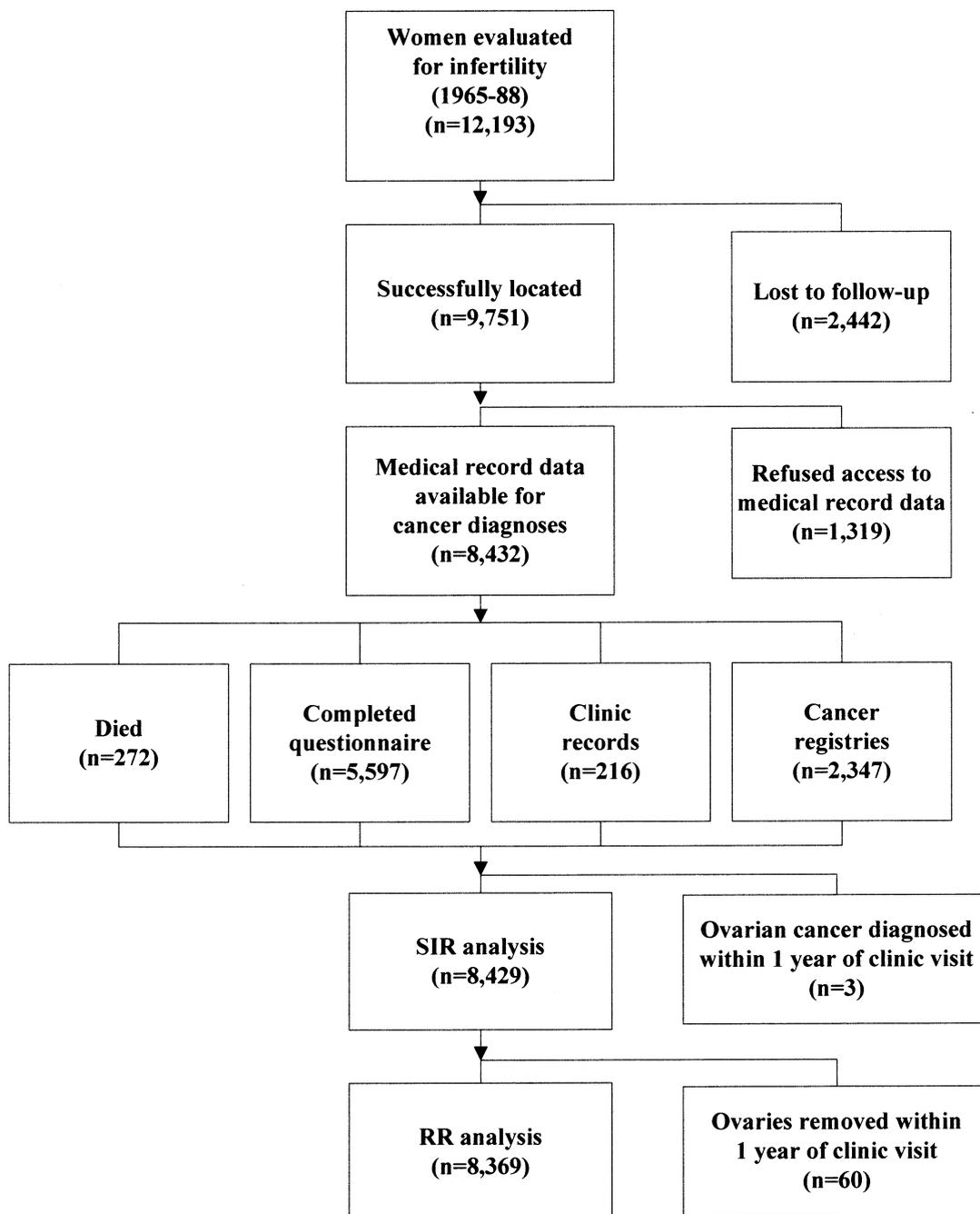
A total of 272 of the patients were traced as deceased. For the patients traced as alive, information on the development of cancers was obtained from completed questionnaires, clinic records, and cancer registries. Questionnaires were initially mailed to patients beginning in early 1998, with telephone 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 breastfeeding history; use of exogenous hormones; anthropometric factors; cigarette smoking; alcohol consumption; and breast and ovarian disease screening history.

An additional 216 patients had follow-up visits 1 year or more beyond their initial clinic visit. For the 2,347 patients for whom we were unable to obtain questionnaires, we had location information that enabled tracing through cancer registries, which was pursued 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 that were found to be benign or not neoplasms were excluded. Additional information on cancers was obtained from the cancer registries, causes of death available from the National Death Index, or copies of 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 an approximate diagnostic date.

For the women with available medical records who were followed for subsequent cancer diagnoses, person-years were accrued beginning 1 year after first clinic registration and continuing through the earliest date of cancer diagnosis, death, or date last known alive and free of cancer (as indicated by the last clinic visit, questionnaire completion, or

**FIGURE 1**

Field and analytic status of eligible study subjects, women evaluated for infertility, 1965–88.



Brinton. Causes of infertility and ovarian cancer. *Fertil Steril* 2004.

linkage against cancer registry data). Patients living in states involving cancer registry searches had variable study ending dates, depending on the completeness of registration, which ranged from the end of 1997 to 1999. Otherwise, December 31, 1999, defined the end of the study period.

To explore different aspects of the relationship between infertility and ovarian cancer, we used two analytic approaches with two predominantly overlapping subsets of the eligible study population. We first established the ovarian cancer risk associated with infertility by comparing ovarian

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
1970–74	1,898	22.5	848	22.5
1975–79	2,908	34.5	1,378	36.6
1980–84	2,516	29.8	1,048	27.8
1985–88	847	10.1	337	9.0
Age at initial clinic evaluation				
<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	4.4
Other	471	5.6	191	5.1
Unknown	908	10.8	1,129	30.0

Brinton. Causes of infertility and ovarian cancer. *Fertil Steril* 2004.

cancer rates among women evaluated for infertility with rates from the U.S. population (155,624 person-years accrued). For this analysis, exclusions comprised patients lost to follow-up, those who denied access to their medical records, and three women who were diagnosed with ovarian cancer during the first year of follow-up, leaving 8,429 study subjects (see Fig. 1).

The second analytic approach assessed ovarian cancer risk according to specific causes of infertility within the cohort of infertile women, allowing for multivariate adjustment of potential confounders. This analysis comprised an internal comparison of cancer risk among women with a specific cause of infertility compared with those with no evidence of that cause. 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 accrued). Both analyses included 45 women who developed ovarian cancers; medical or cancer registry records confirmed 21 of these, death certificates defined 10, and the remainder were self-reported via questionnaires.

Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) compared ovarian cancer risk in this cohort of infertile women with that of U.S. women. Standardized incidence ratios were computed as the number of observed cancer events divided by the expected number of events based on age, race, and calendar year-specific incidence

rates for females from cancer registry rates available through the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. The SEER program has population-based catchment areas and is widely used to estimate cancer burden in the United States. An SIR >1 indicates that the disease rate in the study group exceeds that expected in the U.S. population, while an SIR <1 indicates a lower disease rate in the study population compared with that expected.

Rate ratios (RRs) for developing ovarian cancer associated with various causes of infertility and 95% CIs on the risks were estimated by Poisson regression using standard likelihood ratio methods (25). For all analyses, the RRs were adjusted for both age at follow-up (<40, 40–49, 50+ years) and calendar year of follow-up (before 1980, 1980–89, 1990 or later). Other factors, such as study site and infertility medications prescribed, were included in the regression models, as necessary, to evaluate their roles as potential confounding factors or to examine variations of the RRs. In addition, we used data obtained through questionnaires to assess confounding and modifying influences of other predictors of ovarian cancer, including gravidity and parity at follow-up, education, and oral contraceptive usage.

## RESULTS

Table 1 shows the distribution of the analytic cohort and that of the subjects excluded from analyses according to selected demographic factors. The median year of first eval-

TABLE 2

Cause of infertility diagnoses among women evaluated for infertility (1965–88).

Cause of infertility <sup>a</sup>	Women diagnosed	Among women evaluated for each condition		Among all women in the analytic cohort	
	n	n <sup>b</sup>	% <sup>c</sup>	n	% <sup>d</sup>
Endometriosis	1,919	5,532	34.7	8,429	22.8
Anovulation	2,320	8,398	27.6	8,429	27.5
Tubal disease/pelvic adhesions	2,998	6,972	43.0	8,429	35.6
Male factor	1,952	6,144	31.8	8,429	23.2
Cervical disorder	575	5,061	11.4	8,429	6.8
Uterine disorder	954	5,120	18.6	8,429	11.3

<sup>a</sup> See Appendix 1 for further details as to means of classifying women into these causes of infertility groupings.

<sup>b</sup> Women with workups sufficiently complete to allow diagnosis of stated condition.

<sup>c</sup> Percentage of women with complete workups who showed evidence of each condition (no. of women diagnosed/no. of women evaluated for each condition<sup>2</sup>).

<sup>d</sup> Percentage of women in the total analytic cohort diagnosed with each condition (no. of women diagnosed/no. of women in total analytic cohort).

Brinton. Causes of infertility and ovarian cancer. *Fertil Steril* 2004.

uation was 1978, while the median age of the study subjects at first evaluation was 30 years. Nearly 80% of the subjects were known to be white. There were no substantial differences according to calendar year or age at first evaluation between the subjects included in the analyses and those excluded; however, a larger proportion of the subjects excluded from analysis had missing information on race. The median length of follow-up among subjects included in analyses was 18.8 years, with over 80% of the study population followed for 15 or more years.

Causes of infertility were classified into six different categories according to a standardized algorithm (Appendix 1). These categories included endometriosis, anovulation, tubal disease/pelvic adhesions, male factor, cervical disorders, and uterine disorders. As shown in Table 2, the number of subjects who had clinical workups sufficient to either rule in or out a specific condition varied by the cause of infertility, with the largest number of patients adequately evaluated for anovulation (which was based on the menstrual history along with other tests) and the least number of subjects evaluated for cervical or uterine disorders. When percentages were calculated in relation to the number of women adequately evaluated for each condition, a total of 34.7% showed evidence of endometriosis; 27.6%, anovulation; 43.0%, tubal disease/pelvic adhesions; 31.8%, male factor; 11.4%, cervical disorders; and 18.6%, uterine disorders. These percentages were considerably lower when calculated in relation to all study subjects.

The SIR analyses focused on comparisons of infertile women with the general population (Table 3). The total group of infertile subjects was found to have a significantly higher risk of developing ovarian cancer than the general population (SIR = 1.98; 95% CI, 1.4–2.6). When compared with the general population, which comprised both gravid and

nulligravid women, the risk was substantially higher for patients evaluated for primary infertility (i.e., nulligravid women; SIR = 2.73; 95% CI, 1.8–4.0) than those evaluated for secondary infertility (gravid women; SIR = 1.44, 0.9–2.3). Subjects who were known to not subsequently conceive were at even higher risk (SIR = 3.33; 95% CI, 1.7–6.0). When risks were examined by causes of infertility, the cause associated with the highest (and statistically significant) risk was that of endometriosis (SIR = 2.48; 95% CI, 1.3–4.2). Most other causes of infertility were associated with SIRs of 2 or less.

Given the difference in risk for primary versus secondary infertility, we stratified causes of infertility by this parameter and pursued further comparisons with the general population (Table 4). Given the small numbers of patients with either cervical or uterine disorders, this analysis focused on other causes of infertility. Patients evaluated for primary infertility who were found to have endometriosis were at a particularly high risk (SIR = 4.19; 95% CI, 2.0–7.7). Patients with primary infertility and tubal disease/pelvic adhesions also had a notably elevated risk (SIR = 3.24; 95% CI, 1.6–6.0). Among the patients with secondary infertility, high risks were noted for patients with anovulation (SIR = 2.12; 95% CI, 0.9–4.2) and uterine disorders (SIR = 1.97; 95% CI, 0.4–5.8), although this latter risk was based on only three cancers.

To clarify the effects of causes of infertility independent of each other and other predictors of ovarian cancer risk, subsequent analyses focused on comparisons within the cohort of infertile patients (Table 5). After adjustment for completeness of evaluation, evidence for other causes of infertility, and gravidity at entry, patients with endometriosis were found to be at highest risk compared with other infertility patients (RR = 1.26; 95% CI, 0.6–2.6). Adjustment for other factors found to be related to ovarian cancer risk in this population (race, education, oral contraceptive usage) as

TABLE 3

Standardized incidence ratios comparing ovarian cancer among infertile patients with the general population (based on cancer incidence data from the Surveillance, Epidemiology, and End Results program), by type and cause of infertility.

	Person-years of observation	Observed no. of events	Expected no. of events	SIR	95% CI
All subjects	155,624	45	22.7	1.98	1.4–2.6
Type of infertility					
Primary	66,561	26	9.5	2.73	1.8–4.0
Never conceived	21,806	11	3.3	3.33	1.7–6.0
Pregnancy during follow-up	20,215	6	2.7	2.20	0.8–4.8
Pregnancy during follow-up unknown	24,540	9	3.5	2.57	1.2–4.9
Secondary	89,063	19	13.2	1.44	0.9–2.2
Evidence for specific causes of infertility					
Endometriosis	35,196	13	5.2	2.48	1.3–4.2
Anovulation	43,952	12	6.2	1.94	1.0–3.4
Tubal disease/pelvic adhesions	53,013	16	7.8	2.04	1.2–3.3
Male factor	36,886	10	5.3	1.88	0.9–3.5
Cervical disorder	10,640	2	1.5	1.32	0.2–4.8
Uterine disorder	16,992	6	2.7	2.20	0.8–4.8

Note: CI = confidence interval; SIR = standardized incidence ratio.

Brinton. Causes of infertility and ovarian cancer. *Fertil Steril* 2004.

well as other factors found to be associated with ovarian cancer risk in other studies (age at menarche, breastfeeding, use of ovulation-stimulating drugs, tubal ligation, hysterectomy, age at menopause, and menopausal hormone use) had a minimal impact on this risk estimate or risks associated with other causes of infertility. Patients with anovulatory problems were not at increased or decreased risk compared with other infertile patients, while those with other causes (tubal disease/pelvic adhesions or male factor) were at a somewhat lower risk.

Given previous observations of higher risk among patients with primary than with secondary infertility, we also

calculated RRs specific to women with primary infertility, comparing their risks with those with secondary infertility who had no evidence of a specific causes of infertility. This showed a 2.7-fold excess risk (95% CI, 1.1–6.7) for patients with endometriosis, a risk considerably higher than that observed for the other causes of infertility.

## DISCUSSION

Although it is well established that nulliparous women are at an increased risk of ovarian cancer, it is unresolved whether certain conditions associated with infertility predis-

TABLE 4

Standardized incidence ratios comparing ovarian cancer among infertile patients with the general population (based on cancer incidence data from the Surveillance, Epidemiology, and End Results program), by combined classification of type and cause of infertility.

Evidence for specific causes of infertility	Primary infertility		Secondary infertility	
	Observed no. of events	SIR (95% CI)	Observed no. of events	SIR (95% CI)
Endometriosis	10	4.19 (2.0–7.7)	3	1.05 (0.2–3.1)
Anovulation	4	1.65 (0.4–4.2)	8	2.12 (0.9–4.2)
Tubal disease/pelvic adhesions	10	3.24 (1.6–6.0)	6	1.27 (0.5–2.8)
Male factor	7	2.66 (1.1–5.5)	3	1.12 (0.2–3.3)
Cervical disorder	1	1.56 (0.0–8.7)	1	1.14 (0.0–6.4)
Uterine disorder	3	2.48 (0.5–7.2)	3	1.97 (0.4–5.8)

Note: CI = confidence interval; SIR = standardized incidence ratio.

Brinton. Causes of infertility and ovarian cancer. *Fertil Steril* 2004.

TABLE 5

Rate ratios<sup>a</sup> of ovarian cancer for all patients and for those with primary infertility by cause of infertility, comparisons among women with infertility (n = 8,369).

Cause of infertility	All study subjects <sup>b</sup>		Patients with primary infertility <sup>c</sup>	
	No. of ovarian cancers	RR (95% CI)	No. of ovarian cancers	RR (95% CI)
Endometriosis	13	1.26 (0.6–2.6)	10	2.72 (1.1–6.7)
Anovulation	12	1.03 (0.5–2.0)	4	1.41 (0.4–4.4)
Tubal disease/pelvic adhesions	16	0.88 (0.4–1.6)	10	1.56 (0.7–3.7)
Male factor	10	0.94 (0.4–2.0)	7	1.66 (0.6–4.3)

Note: CI = confidence interval; RR = rate ratio.

<sup>a</sup> Adjusted for age at follow-up, calendar time, study site (Boston/New York, Chicago, Detroit, San Francisco Bay Area), gravidity at entry, and causes of infertility.

<sup>b</sup> Relative to patients with no evidence of the specified cause of infertility and adjusting for women who were not medically evaluated.

<sup>c</sup> Relative to patients with secondary infertility without evidence of a specific cause of infertility.

Brinton. Causes of infertility and ovarian cancer. *Fertil Steril* 2004.

pose more than others to this excess risk. We sought answers to this question by classifying causes of infertility among a large cohort of women that had been clinically evaluated and followed for extended periods of time. Our results, for the most part, indicated that risk is more influenced by the ability to bear children than by specific causes of infertility. However, similar to several other studies, we observed that women with a diagnosis of endometriosis might be at higher ovarian cancer risk than women with other causes of infertility.

The study took several different approaches to assess the relationship of causes of infertility to ovarian cancer risk. The first approach, which compared patients with the general population, was used because most previous investigations of infertile patients have relied on such comparisons. However, in this approach, it must be recognized that infertility patients are being compared with a group of patients who have very different fertility patterns, including more often giving birth and having greater numbers of offspring. Thus, any differences in risk could easily reflect the influence of different reproductive patterns rather than specific causes of infertility.

In the present investigation, comparisons with the general population showed a two-fold increased SIR. This risk was similar to what has been observed in several other smaller follow-up studies, including those of Rossing et al. (18) (SIR = 2.5, 11 ovarian cancers), Ron et al. (26) (SIR = 2.1, four ovarian cancers), and Modan et al. (27) (1.6, 12 ovarian cancers). One strength of our study was that the larger number of observed ovarian cancer cases (45 total) enabled risks to be separated according to the gravidity status of patients at the time of infertility evaluation. Importantly, this showed much higher risks for patients evaluated for primary infertility (SIR = 2.7) than for those evaluated for secondary

infertility (SIR = 1.4) and particularly high risks for patients who were known to not subsequently conceive (SIR = 3.3).

Defining causes of infertility can be a difficult task. The evaluations that women (and their partners) receive vary, depending on the symptoms, the treating physicians, and a variety of other factors. There is little agreement on the diagnostic criteria for various causes of infertility. We chose a different approach than other studies by assigning causes of infertility only to women who had received clinical work-ups sufficient to definitively assign diagnoses.

Our population of infertile patients was similar to others in terms of the proportions diagnosed with certain conditions (28, 29). However, the more restrictive assignment of causes of infertility used in our study may have contributed to some differences in ovarian cancer risks associated with infertility as compared with previous investigations. When only those with complete evaluations were considered, the percentages of women who had such conditions as male factor, endometriosis, and tubal disease/pelvic adhesions rose to between 30% and 40%. Cervical and uterine disorders were considerably less common, perhaps because of the strict diagnostic criteria used.

The other difference in our study as compared with previous investigations was that through internal comparisons of the infertility patients we were able to adjust for effects of multiple causes of infertility (common among patients presenting to infertility clinics) (28) as well as other ovarian cancer risk predictors that may be associated with the different causes of infertility. Thus, dissimilar to several previous studies, we found no unusually increased risk associated with ovulatory causes of infertility (18, 20, 33), fallopian tube dysfunction (30), or male factor/mechanical subfertility (27). What emerged from our analysis was a more important role for endometriosis, regardless of whether it occurred with

or without other causes of infertility. Thus, it was noteworthy in our investigation that patients with endometriosis were at a 4.2-fold increased risk compared with the general population if they presented with primary infertility. Patients with endometriosis who presented with primary infertility had a nearly three-fold increased risk compared with unaffected patients presenting with secondary infertility.

Several previous epidemiologic investigations have also supported a link between endometriosis and ovarian cancer. In a large Swedish record linkage study involving 20,686 women with hospital discharge diagnoses, Brinton et al. (16) found an SIR of 1.9 for ovarian cancer based on 29 observed cancers, with even further increases in risk among women with long-standing histories of ovarian endometriosis. In a survey conducted by the Endometriosis Association (31), over five-fold excesses of ovarian cancer were reported among a large series of self-referred women with endometriosis. Although neither of these studies was able to adjust for other ovarian cancer predictors, including parity and oral contraceptive usage, and had no information on ovarian removal before the development of cancer, strikingly similar risks associated with self-reported histories of endometriosis have derived from several case-control studies that were able to adjust for these factors (17, 22). In the largest of these endeavors (17), a pooling project involving data from eight case-control studies, the odds ratio associated with a history of endometriosis was identical to that derived from the Brinton et al. (16) study.

Although there are now extensive clinical and epidemiological as well experimental data linking endometriosis to an increased risk of ovarian cancer, little has been written on possible biological mechanisms involved in the malignant transformation process. Ness (32) has recently discussed similarities between the proposed etiology of ovarian cancer and the observed pathophysiology of endometriosis. Both conditions are promoted by estrogen excesses and progesterone (P) deficits, which may interact with a variety of immunological factors. Inflammatory mechanisms may also be involved. Future studies of ovarian carcinogenesis may therefore benefit from further exploration of the hormonal and immune environments that may promote the growth of endometriosis. These studies should focus specifically on the processes involved for endometrioid or clear cell ovarian carcinomas since these cancers have been most strongly linked with prior histories or concomitant occurrences of endometriosis (8, 11, 13, 15). Although we attempted to assess this relationship epidemiologically, we were hindered by the absence of information on the histologies of the observed ovarian cancers in our study, with only three of the 19 for whom we had histology information having these cell types.

Several previous studies have noted increases in risk among patients with ovulatory disorders (18, 20, 33). In the Rossing et al. (18) study, in which ovarian cancer risk was

compared between different subgroups of fertility disorders, the risk of ovarian cancer in women with oligomenorrhea, anovulation, or polycystic ovarian syndrome was about two-fold higher than that in women without ovulatory abnormalities. We did not identify an overall increased risk associated with anovulation but did observe an unexpected increase in the risk of ovarian cancer among subjects with secondary infertility due to anovulatory problems. Although the relationship was not statistically significant and may have been due to chance, the associated risk was striking with its variance with other categories of patients with secondary infertility. It is therefore interesting to speculate that these patients may have been unusual in some respect, including having a predisposition to diminished ovarian reserves through hormonal alterations that would relate to high ovarian cancer risks.

A substantial proportion of the patients in this study had tubal disease/pelvic adhesions. Since previous studies have suggested that patients with tubal ligations are at a substantially decreased risk of ovarian cancer (34–38), it might be hypothesized that blocked tubes would also predispose to decreases in ovarian cancer risk because of either compromised ovarian function or reduced blood supply to the ovaries (39). We found no evidence for a reduced risk of ovarian cancer among patients with tubal disorders and in fact observed that patients with primary infertility due to tubal problems were at elevated risk, although not statistically elevated when internal comparisons were considered. Our findings are consistent with several previous investigations that have found higher ovarian cancer risks among patients with fallopian tube dysfunction (30) or pelvic inflammatory disease (17, 23, 24), lending further support to the notion of inflammation as an important agent in ovarian carcinogenesis (22).

Several studies have noted increased risks of ovarian cancer among patients with unexplained infertility (17, 26, 27, 40). We were unable to reconcile our findings with these studies because our definition of infertility depended on assessing the adequacy of the clinical workups. Very few women in our population (notably 309, or 3.7%) had clinical workups that were sufficiently complete to rule out all of the categorized causes of infertility. Thus, it is possible that many of the women identified in previous studies as having unexplained infertility would have been found to have specific causes had they received more extensive workups. This was borne out in our study by the fact that the percentages of women with any condition increased substantially when proportions were calculated in reference to those adequately evaluated. It would be of particular interest to know what proportions of women with unexplained infertility may have had endometriosis, especially given hormonal studies that suggest that patients previously labeled as having unknown causes of infertility have disorders closely related to endometriosis (41).

Our study had a number of strengths over previous investigations in having long-term follow-up on a large series of women, well-defined causes of infertility, and information on many predictors of ovarian cancer risk (including ovarian status, an unaccounted factor in all previous prospective investigations).

There were, however, some limitations, particularly given that patients were evaluated for infertility during eras (beginning in the mid-1960s) when some of the more specific evaluative techniques and many of the current therapeutic modalities were unavailable. However, patients in earlier time periods had more complete evaluations, since it is now common for patients to be referred for IVF after fairly limited evaluations. We also had losses to follow-up and other necessary exclusions due to some patients denying access to their medical records and were unable to gather questionnaire data on all located subjects. We, however, did not identify any systematic differences between those included and excluded from analyses, other than race, a factor that we were able to adjust for in both the external (SIR) and internal (RR) analyses. Finally, while our numbers of observed ovarian cancers were an order of magnitude greater than all previous prospective investigations, we were hindered by this number when approaching analyses that stratified by several factors, such as type and cause of infertility.

In summary, this study with its careful characterization of causes of infertility among a large cohort of women emphasized the importance of type of infertility (primary vs. secondary) as a predictor of subsequent ovarian cancer risk. Although this appeared to be a more important predictor of risk than specific causes of infertility, an independent effect for endometriosis emerged. Given the consistency of this finding with previous observations, it would appear useful for further studies to focus on the common biologic mechanisms involved in both disease processes to gain a clearer understanding of preventive approaches to ovarian cancer.

---

*Acknowledgments:* The authors thank Drs. Melvin Cohen (Northwestern University, retired), Raymonde van de Wiele (now deceased), Raphael Jewelewicz (Columbia University), Robert Kistner (private practice, Boston, now deceased), and Michael Diamond (Wayne State University) for clinical expertise and scientific contributions to this study. The fieldwork for this study was directed by Dr. Rita Ouellet-Hellstrom of Survey Research Associates Life Sciences, with assistance and input from Dr. Rebecca Troisi (National Cancer Institute), Dr. Janet Engstrom (University of Illinois at Chicago), Karen Collins (Wayne State University), and Michael Payne (Stanford University). Additional support for the study was provided by Giannella Derienzo and Usha Singh (Westat, Inc.).

## APPENDIX 1: CRITERIA FOR DEFINING CAUSES OF INFERTILITY

The following criteria were used to categorize women into six categories of causes of infertility. Women could be categorized according to multiple causes.

**Endometriosis:** Women who had a pelvic laparoscopy, culdoscopy, or laparotomy at which endometriosis was found. Those categorized as having no endometriosis had one or more of these procedures and did not have endometriosis as a finding.

**Anovulation:** Primarily women who had an abnormal menstrual history (fewer than four periods per year or a minimum cycle length <20 or >50 days). In addition, patients were considered anovulatory if a P withdrawal test or an X-ray of the sella turcica had been done regardless of the outcome. Finally, a serum prolactin level >25 ng/mL was considered evidence of an ovulatory disturbance. Women categorized as not being anovulatory consisted of those who had a recorded menstrual history that did not meet these criteria and those who did not have a P withdrawal test, a sella X-ray, or elevated prolactin levels.

**Tubal Disorder/Pelvic Adhesions:** Women who had a hysterosalpingogram that showed one or two obstructed or non-filling tubes together with those who had a laparotomy or endoscopy that showed tubal obstruction, pelvic adhesions, or evidence of pelvic tuberculosis. Women categorized as not having a tubal disorder/pelvic adhesions had a hysterosalpingogram, endoscopy, or laparotomy that did not show any of these conditions.

**Male Factor:** Women whose partners had abnormal results in the semen analysis (<20 or >300 × 10<sup>6</sup> sperm/mL, progressive motility <25%, or normal morphology <30%), considering the highest count before any treatment of the male. Those categorized as not having a male factor had a normal semen analysis by the same criteria.

**Cervical Disorder:** Women who had three postcoital tests at time of ovulation that did not show motile sperm. Also included in this group were six patients with congenital absence of the cervix and 85 patients who had had a cervical conization. Women categorized as not having a cervical disorder included those who had at least one postcoital test with any result but did not have three abnormal ones at ovulation.

**Uterine Disorder:** Women who had a laparoscopy, culdoscopy, laparotomy, or hysteroscopy that showed a developmental abnormality or myomas. Women categorized as not having a uterine disorder were those who had one or more of these procedures that did not show a developmental abnormality or myoma.

### References

1. Hankinson SE, Colditz GA, Hunter DJ, Willett WC, Stampfer MJ, Rosner B, et al. A prospective study of reproductive factors and risk of epithelial ovarian cancer. *Cancer* 1995;76:284–90.

2. Risch HA, Marrett LD, Howe GR. Parity, contraception, infertility, and the risk of epithelial ovarian cancer. *Am J Epidemiol* 1994;140:585-97.
3. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. *Br J Cancer* 1989;60:592-8.
4. Whittemore AS, Wu ML, Paffenbarger RS Jr, Sarles D, Kampert JB, Grosser S, et al. Epithelial ovarian cancer and the ability to conceive. *Cancer Res* 1989;49:4047-52.
5. Klip H, Burger CW, Kenemans P, van Leeuwen FE. Cancer risk associated with subfertility and ovulation induction: a review. *Cancer Causes Control* 2000;11:319-44.
6. DePriest PD, Banks ER, Powell DE, van Nagell JR Jr, Gallion HH, Puls SE, et al. Endometrioid carcinoma of the ovary and endometriosis: the association in postmenopausal women. *Gynecol Oncol* 1992;47:71-5.
7. Heaps JM, Nieberg RK, Berek JS. Malignant neoplasms arising in endometriosis. *Obstet Gynecol* 1990;75:1023-8.
8. Jimbo H, Yoshikawa H, Onda T, Yasugi T, Sakamoto A, Taketani Y. Prevalence of ovarian endometriosis in epithelial ovarian cancer. *Int J Gynecol Obstet* 1997;59:245-50.
9. LaGrenade A, Silverberg SG. Ovarian tumors associated with atypical endometriosis. *Hum Pathol* 1988;19:1080-84.
10. Moll UM, Chumas JC, Chalas E, Mann WJ. Ovarian carcinoma arising in atypical endometriosis. *Obstet Gynecol* 1990;75:537-9.
11. Sainz de la Cuesta R, Eichhorn JH, Rice LW, Fuller AF Jr, Mikrui N, Goff BA. Histologic transformation of benign endometriosis to early epithelial ovarian cancer. *Gynecol Oncol* 1996;60:238-44.
12. Vercellini P, Parazzini F, Bolis G, Carinelli S, Dindelli M, Vendola N, et al. Endometriosis and ovarian cancer. *Am J Obstet Gynecol* 1993;169:181-2.
13. Modesitt SC, Tortolero-Luna G, Robinson JB, Gershenson DM, Wolf JK. Ovarian and extraovarian endometriosis-associated cancer. *Obstet Gynecol* 2002;100:788-95.
14. Oral E, Ilvan S, Tustas E, Korbeyli B, Bese T, Demirkiran F, et al. Prevalence of endometriosis in malignant epithelial ovary tumours. *Eur J Obstet Gynecol Reprod Biol* 2003;109:97-101.
15. Stern RC, Dash R, Bentley RC, Snyder MJ, Haney AF, Robboy SJ. Malignancy in endometriosis: frequency and comparison of ovarian and extraovarian types. *Int J Gynecol Pathol* 2001;20:133-9.
16. Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis. *Am J Obstet Gynecol* 1997;176:572-9.
17. Ness RB, Cramer DW, Goodman MT, Kruger Kjaer S, Mallin K, Mosgaard BJ, et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. *Am J Epidemiol* 2003;155:217-24.
18. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994;331:771-6.
19. Meirow D, Schenker JG. The link between female infertility and cancer: epidemiology and possible aetiologies. *Hum Reprod Update* 2003;2:63-75.
20. Schildkraut JM, Schwingl PJ, Bastos E, Evanoff A, Hughes C. Epithelial ovarian cancer risk among women with polycystic ovary syndrome. *Obstet Gynecol* 1996;88:554-9.
21. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. *J Natl Cancer Inst* 1999;91:1459-67.
22. Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology* 2000;11:111-7.
23. Risch HA, Howe GR. Pelvic inflammatory disease and the risk of epithelial ovarian cancer. *Cancer Epidemiol Biomark Prev* 1995;4:447-51.
24. Shu X, Brinton LA, Gao YT, Yuan JM. Population-based case-control study of ovarian cancer in Shanghai. *Cancer Res* 1989;49:3670-4.
25. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 2. The design and analysis of cohort studies. International Agency for Research on Cancer: Lyon, France, 1987.
26. Ron E, Lunenfeld B, Menczer J, Blumstein T, Katz L, Oelsner G, et al. Cancer incidence in a cohort of infertile women. *Am J Epidemiol* 1987;125:780-90.
27. Modan B, Ron E, Lerner-Geva L, Blumstein T, Menczer J, Rabinovici J, et al. Cancer incidence in a cohort of infertile women. *Am J Epidemiol* 1998;147:1038-42.
28. Brugo-Olmedo S, Chillik C, Kopelman S. Definition and causes of infertility. *Reprod Biomed Online* 2001;2:41-53.
29. Smith S, Pfeifer SM, Collins JA. Diagnosis and management of female infertility. *JAMA* 2003;290:1767-70.
30. Whittemore AS, Harris R, Itnyre J, the Collaborative Ovarian Cancer Group. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. *Am J Epidemiol* 1992;136:1184-1203.
31. Duczman L, Ballweg ML. Endometriosis and cancer: what is the connection? *Endometr Assoc Newsl* 1999:20.
32. Ness RB. Endometriosis and ovarian cancer: thoughts on shared pathophysiology. *Am J Obstet Gynecol* 2003;189:289-94.
33. Coulam CB, Annegers JF, Kranz JS. Chronic anovulation syndrome and associated neoplasia. *Obstet Gynecol* 1983;61:403-7.
34. Green A, Purdie D, Bain C, Siskind V, Russell P, Quinn M, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. *Int J Cancer* 1997;71:948-51.
35. Hankinson SE, Hunter DJ, Colditz GA, Willett WC, Stampfer MJ, Rosner B, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer. A prospective study. *JAMA* 1993;270:2813-8.
36. Kreiger N, Sloan M, Cotterchio M, Parsons P. Surgical procedures associated with risk of ovarian cancer. *Int J Epidemiol* 1997;26:710-5.
37. Miracle-McMahill HL, Calle EE, Kosinski AS, Rodriguez C, Wingo PA, Thun MJ, et al. Tubal ligation and fatal ovarian cancer in a large prospective cohort study. *Am J Epidemiol* 1997;145:349-57.
38. Rosenblatt KA, Thomas DB. Reduced risk of ovarian cancer in women with a tubal ligation or hysterectomy. The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. *Cancer Epidemiol Biomark Prev* 1996;5:933-5.
39. Ellsworth LR, Allen HH, Nisker JA. Ovarian function after radical hysterectomy for stage IB carcinoma of cervix. *Am J Obstet Gynecol* 1983;145:185-8.
40. Venn A, Watson L, Bruinsma F, Giles G, Healy D. Risk of cancer after use of fertility drugs with in-vitro fertilisation. *Lancet* 1999;354:1586-90.
41. Cahill DJ, Hull MGR. Pituitary-ovarian dysfunction and endometriosis. *Hum Reprod Update* 2000;6:56-66.