

MENOPAUSE AND OVARIAN CANCER

PATRICIA HARTGE,¹ ROBERT HOOVER,¹ LARRY MCGOWAN,² LINDA LESHER,²
AND HENRY J. NORRIS³

Hartge, P. (Environmental Epidemiology Branch, NCI, Bethesda, MD 20892), R. Hoover, L. McGowan, L. Leshner, and H. J. Norris. Menopause and ovarian cancer. *Am J Epidemiol* 1988;127:990-8.

Using data from a study of 296 patients diagnosed in greater Washington, D. C., from 1978 to 1981 with primary epithelial ovarian cancer and 343 patients hospitalized for other conditions, the authors estimated the rate ratios according to various characteristics of the menopause. Menopause induced by hysterectomy with preservation of both ovaries was associated with a 30 per cent reduction in risk of later development of ovarian cancer. Age at natural menopause was not consistently related to risk. Women who used menopausal estrogens showed a 40 per cent decreased risk.

estrogens; hysterectomy; menopause; ovarian neoplasms

The relations between ovarian cancer risk and various aspects of the menopause, including time, type, symptoms, and therapy, are not well understood. For example, many studies noted an apparently lower incidence of ovarian cancer among women who had an artificial menopause (1-6), but the observation remains unexplained. Some studies found that ovarian cancer patients have later menopause than usual (5), while others found that these cancer patients experienced menopause at early or normal ages (1). Using interview data, hospital records, and physician reports from a case-control study of ovarian cancer, we have estimated the relative incidence of

ovarian cancer according to various menopausal events.

MATERIALS AND METHODS

Cases

We attempted to identify all women aged 20-79 years residing in the Washington, D. C., metropolitan area who were first diagnosed at surgery with microscopically confirmed primary epithelial ovarian cancer from August 1978 to June 1981. We regularly checked the discharge lists of all 33 area hospitals that treated ovarian cancer. (Cases from one hospital were not available during the first year of the study; we estimate that two to three cases may have been lost.) Cases included women with tumors of low malignant potential and frankly malignant tumors. For all potential cases, we obtained microscopic slides made from the tumor tissue. One of us (H. J. N.) reviewed the slides. Those found not to have definite primary ovarian cancer of the epithelial type by clinical and microscopic evaluation were excluded from the study.

We identified 400 cases aged 20-79 years with histologically confirmed epithelial cancer, of whom we interviewed 296 (74 per

Received for publication September 4, 1986, and in final form November 2, 1987.

¹ Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD.

² Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, George Washington University Medical Center, Washington, D.C.

³ Armed Forces Institute of Pathology, Washington, D.C.

Reprint requests to Dr. Patricia Hartge, NCI, Landow Building, Room 3C06, NIH, Bethesda, MD 20892.

This work was supported by Contract NIH-NCI-NO1-CP-81051.

The authors acknowledge the statistical computing assistance of Joy Mele.

cent). The remaining 104 were not interviewed because of death ($n = 44$), disability ($n = 12$), physician's refusal ($n = 8$), patient's refusal ($n = 33$), or other reasons ($n = 7$). The histologic types of the cases' tumors, as classified by the reviewer, are shown in table 1.

Controls

Controls were identified from hospital discharge lists and were matched to cases according to age, race, hospital, and date of discharge. A woman was not eligible to be a control if her discharge diagnosis was potentially related to the exposures under study. Discharge diagnoses so excluded were breast disease, myocardial infarction, stroke, thromboembolism, gallbladder disease, osteoporosis, gynecologic complaints, melanoma, and colon cancer. We also excluded women with psychiatric diagnoses, as well as those who resided outside the Washington, D. C., metropolitan area.

For all potential controls, we also asked whether the physician's records showed that the woman had at least one ovary intact. Those women who had no ovaries were excluded from the control group since they could not be at risk of ovarian cancer. (Information gathered subsequently from hospital records was also used to exclude women who had had bilateral oophorectomies.)

We identified 439 women aged 20-79 years, eligible to be controls, of whom we

interviewed 343 (78 per cent). The remaining 96 were not interviewed because of death ($n = 13$), disability ($n = 8$), physician's refusal ($n = 11$), patient's refusal ($n = 50$), or other reasons ($n = 14$). The discharge diagnoses in the control group are presented in table 2. For this investigation, we excluded 11 controls with discharge diagnoses of osteoporosis or hip or forearm fracture because of the possibility that the underlying reason for hospitalization was osteoporosis, a condition related to estrogen use. A woman eligible to be a control was not excluded if the case to whom she was matched was found to be ineligible.

Data sources

For each identified case and control, we contacted the woman's physician to get permission to interview her. After the physician consented, we contacted the study subject to arrange a home interview. Trained, experienced medical interviewers administered a standardized questionnaire (available on request). The interview lasted about one hour and included questions about menstrual, sexual, reproductive, medical, and occupational histories and exposure to drugs, alcohol, and tobacco.

During the interview, respondents were shown photographs of hormone tablets. We categorized the subjects as users of menopausal estrogens if they 1) reported using one of the pictured replacement estrogens, 2) said they took menopausal estrogens but could not remember the brand, or 3) said they took a female hormone pill prescribed for menopausal symptoms.

The interviewers obtained a detailed history of all gynecologic surgery and elicited which organs were involved in each procedure. They asked for the name and address of the subject's gynecologist, surgeon, and hospital, from whom we sought confirmation and additional data on medical history, including pathology and operative reports from previous surgical procedures. We especially wished to distinguish hysterectomies with preservation of both ovaries from those with removal of some ovarian tissue.

TABLE 1
Ovarian cancer cases, according to histologic type

Histologic type	No.	%
Serous	84	28
Serous LMP*	35	12
Mucinous	17	6
Mucinous LMP	9	3
Endometrioid	76	26
Endometrioid LMP	8	3
Clear cell	12	4
Mixed epithelial	25	8
Undifferentiated	30	10
Total	296	100

* LMP, low malignant potential.

TABLE 2
Discharge diagnoses among controls

Disease category	No.	%
Infectious diseases	6	2
Benign neoplasms	8	2
Malignant neoplasms	13	3
Neoplasm (unspecified)	1	
Endocrine or metabolic diseases	19	5
Diseases of blood or blood-forming organs	4	1
Diseases of nervous system	20	8
Diseases of eye, ear, or mastoid	26	8
Varicose veins, hemorrhoids	5	1
Respiratory diseases	27	8
Digestive system diseases	55	16
Urinary diseases	18	5
Skin disorders	6	2
Musculoskeletal diseases*	75	22
Congenital anomalies	4	1
Symptoms, signs, ill defined conditions	18	5
Fractures†	18	5
Other injuries	20	6
Total	343	100

* Four controls were excluded for osteoporosis.

† Seven controls were excluded for fractures of the hip or forearm.

For 56 of the 65 controls reporting previous hysterectomy with both ovaries preserved, we obtained supporting documentation; for the remainder, permission was not given, or records were unavailable or insufficiently detailed. For all 34 cases reporting previous hysterectomy with both ovaries preserved, we obtained confirmation, but we would not have been certain of the ovarian status of 10 of these without documentation related to the diagnosis of ovarian cancer, since definitive records from the prior surgeries were not available. Since the controls underwent no diagnostic surgery equivalent to that of the cases, the 56 controls would be most comparable to the 24 cases for whom we had supporting documentation.

Analysis

Effects on ovarian cancer risk were measured by the estimated rate ratio, the ratio of ovarian cancer incidence in the exposed group to that in the unexposed. The estimates were adjusted for the effects of confounding variables by stratified contingency table analysis (7) and by logistic

regression models (8). The estimates presented in the tables were derived from logistic regression models. In this investigation of menopause-related variables, potential confounders included the other menopause-related variables, matching factors (age, hospital, race), protective factors (parity, recent oral contraceptive use), and risk factors (infertility, family history of ovarian cancer). Height and weight were not potential confounders because they were unrelated to risk. Twelve per cent of the cases and 14 per cent of the controls were black, and the remainder were white. The mean age at diagnosis of cases was 54.4 years, and the mean age of the controls was 54.7 years.

RESULTS

More cases than controls (31 per cent vs. 26 per cent) reported that they were still menstruating one year before diagnosis, and fewer cases (14 per cent vs. 24 per cent) reported surgical menopause) (one case reported drug-induced menopause). Using life table analysis of time to menopause (table 3), we estimated the median age at

TABLE 3
Age at menopause among cases and controls, from life table analysis

	All women*		All women†		Women without surgical menopause‡	
	Cases	Controls	Cases	Controls	Cases	Controls
25th percentile	45.1	43.3	47.4	48.0	47.2	47.9
Median	49.7	48.6	50.6	50.5	50.2	50.4
75th percentile	52.2	51.8	53.4	53.0	53.3	57.8
Number§	295	330	295	330	253	251
Mean	48.5	46.9	50.1	50.1	49.9	49.8
Standard error	1.3	1.7	0.9	0.8	1.0	1.0

* Time to menopause is the outcome; premenopausal women are considered censored at diagnosis minus one year.

† Time to natural menopause is the outcome; women are considered censored at surgical menopause or diagnosis minus one year.

‡ Time to natural menopause is the outcome; premenopausal women are considered censored at diagnosis minus one year.

§ Two controls were missing age at diagnosis.

menopause to be later in cases than in controls (49.7 vs. 48.6 years), a difference that was statistically significant ($p = 0.04$). When data from women with surgical menopause were either excluded from the comparison or considered as censored observations with natural menopause as the outcome, there was no difference in time to natural menopause between cases and controls. Thus, the apparent protection of early menopause was explained by a protective effect of early surgical menopause.

We further explored the protective effect of surgical menopause (table 4). Among the postmenopausal women, 11 cases and 23 controls reported unilateral oophorectomy with or without a hysterectomy (estimated rate ratio (RR) = 0.7). A reduced risk among women with only one ovary is not surprising. Hysterectomy was associated with a reduction in risk (estimated RR = 0.7) that was not statistically significant. Early hysterectomy with ovarian preservation was more protective than later hysterectomy, but hysterectomy after menopause was even more protective. (The hysterectomies after menopause were performed because of prolapsed uterus, hemorrhage, fibroids, bladder suspension, endometriosis, or cervical cancer.) Vaginal hysterectomies were slightly more protective than abdominal hysterectomies. Hysterectomies performed within the decade before diagnosis

were as protective as those performed earlier. For most of the hysterectomies, we obtained hospital and pathology records confirming the surgery. Analysis restricted to confirmed surgeries still showed protection.

Women reporting gynecologic surgery other than hysterectomy or oophorectomy were also at lower risk of developing ovarian cancer (estimated RR = 0.7), but the risk was not statistically significantly different from the null. Most of the surgeries other than hysterectomy or oophorectomy were performed 10 years before diagnosis or earlier. Too few were performed more recently to provide a stable estimate of the effect of recent surgery. The reduced risk following surgeries on fallopian tubes or ovarian cystectomies (procedures that would potentially involve both visualization of one or both ovaries and reduction of the blood supply to one or both ovaries) was about the same as the reduced risk following surgery on the uterus. Four cases had had unilateral surgery to a fallopian tube or an ovary (not including oophorectomies); all four involved the ovary contralateral to the tumor.

Ovarian cancer patients reported experiencing one or more symptoms at menopause slightly less frequently than did controls (82 per cent vs. 87 per cent) (table 5). A history of cramps at the time of meno-

TABLE 4
Estimated ovarian cancer incidence rate ratios among postmenopausal women, according to history of gynecologic surgery

Gynecologic surgery history	Cases (n)	Controls (n)	Estimated rate ratio*	95% confidence interval
No gynecologic surgery	138	128	1.0	
Unilateral oophorectomy (with or without hysterectomy)	11	23	0.6	0.3-1.3
Hysterectomy (no oophorectomy)	34	65	0.7	0.4-1.2
Surgical menopause at age <45	21	43	0.7	0.4-1.4
Surgical menopause at age ≥45	12	14	1.2	0.5-2.9
Hysterectomy after menopause	1	8	0.1	0.02-1.2
Abdominal hysterectomy	26	44	0.8	0.4-1.4
Vaginal hysterectomy	8	21	0.5	0.2-1.3
Hysterectomy <10 years ago	12	23	0.7	0.3-1.5
Hysterectomy ≥10 years ago	22	42	0.7	0.4-1.3
Confirmed by pathology or operative reports	24	56	0.6	0.3-1.1
Reports not available	10	9	1.5	0.6-4.1
Other gynecologic surgery	20	28	0.7	0.4-1.3
Other surgery <10 years ago	1	4	0.2	0.02-1.8
Other surgery ≥10 years ago	19	24	0.8	0.4-1.5
Surgery to tubes, ovarian cystectomies	13	16	0.8	0.4-1.7
Other surgery†	7	10	0.7	0.2-1.8
Unknown	0	2		

* Adjusted for menopausal estrogen use, menopausal hot flashes, and menopausal cramps.

† Surgery to cervix, fibroidectomies, uterine support surgery.

TABLE 5
Estimated ovarian cancer incidence rate ratios, according to menopausal symptoms

Symptoms	Cases (n)	Controls (n)	Estimated rate ratio*	95% confidence interval
Heavy flow	65	91	1.1	0.7-1.8
Irregular periods	88	119	0.7	0.5-1.1
Painful cramps	30	61	0.6	0.3-1.0
Hot flashes	93	84	1.8	1.1-3.1
Night sweats	65	72	0.8	0.5-1.4
Severe depression	27	47	0.7	0.4-1.3
Vaginal dryness	24	26	1.2	0.6-2.3
Any symptoms	162	200	0.7	0.4-1.2

* Adjusted for age, race, menopausal estrogen use, type of menopause, and other symptoms.

pause marked lower risk after adjustment for the effects of other symptoms, age, race, menopausal estrogen use, and type of menopause (estimated RR = 0.6), but the mean duration of cramping was similar in cases and controls with positive history (22 months vs. 21 months). A history of hot flashes marked women with statistically significantly increased risk (estimated RR

= 1.8), but the mean duration of hot flashes was similar among affected cases and controls (22 months vs. 23 months). The apparent lower risk associated with cramps and the higher risk associated with hot flashes were present regardless of type of menopause, parity, or use of menopausal estrogens.

Many of the women who reported men-

strual cramps around the time of their menopause also reported premenstrual cramps and cramps during menstruation in their premenopausal years, but premenstrual cramps and menstrual cramps were not associated with ovarian cancer risk. Many of the women reporting hot flashes also reported night sweats, but 35 per cent of the women who reported hot flashes reported no night sweats, and 19 per cent of those reporting night sweats reported no hot flashes, so the effects of the two symptoms could be distinguished. Night sweats were weakly related to decreased risk.

Cases were less likely than controls to report having used menopausal estrogens (table 6). The rate ratio was estimated as 0.6 and was statistically significant. The estimate was not confounded by the separate effects of type of menopause, oophorectomy, age at menopause, symptoms of

menopause, oral contraceptive use, infertility, parity, race, or age. Women who had taken estrogens for less than one month showed an apparent increase in risk (estimated RR = 2.0). The more recent the last reported episode of use and the earlier the age at first use, the greater was the degree of protection. Among the estrogen users, the effects of age at start of use, recency of use, and duration of use were not confounded by the effects of each other or of the other factors shown in table 6. Perimenopausal and postmenopausal use were equally protective, once the effects of duration and age at start of use were controlled.

With the analysis restricted to estrogen use that was confirmed by physicians, the rate ratio estimate was unchanged. Sixty-eight per cent of users said they had used Premarin. The protective effect of estrogen

TABLE 6
Estimated ovarian cancer incidence rate ratios, according to menopausal estrogen use

Estrogen use	Cases* (n)	Controls* (n)	Estimated rate ratio†	95% confidence interval
No use	143	140	1.0	
Any use	60	104	0.6	0.4-0.8
<1 month	8	4	2.0	0.6-6.9
1-5 months	15	23	0.6	0.3-1.3
6-29 months	15	29	0.5	0.2-0.9
≥30 months	20	48	0.4	0.2-0.7
Last use ≥5 years ago	35	49	0.7	0.4-1.1
Last use 1-4 years ago	11	25	0.4	0.2-0.9
Current use	11	28	0.4	0.2-0.8
Premarin	38	73	0.5	0.3-0.8
Other compound	22	31	0.8	0.4-1.3
Aged <45 at first use	12	43	0.3	0.1-0.6
Aged 45-54	35	49	0.7	0.4-1.1
Aged ≥55	12	10	1.2	0.5-2.8
Perimenopausal‡	37	74	0.5	0.3-0.8
Premenopausal	2	6	0.3	0.1-1.6
Postmenopausal	18	22	0.8	0.4-1.6

* Numbers do not total because of missing data.

† Adjusted for age and race.

‡ Perimenopausal period was defined as age at menopause ± 3 years. Subjects are classified as premenopausal users only if they had no perimenopausal use and as postmenopausal users only if they had neither perimenopausal nor premenopausal use.

use was slightly greater for women who had taken Premarin than for women who had only taken other brands.

The overall protective effect estimated for menopausal estrogen use varied slightly according to whether other risk factors were present, with the protection generally being more marked in the groups at lower risk of ovarian cancer. The protective effect of estrogens was slightly greater among women with hysterectomy, among women without hot flashes at menopause, among women with cramps at menopause, among women of higher parity, and among younger women. On the other hand, the protective effect was greater among women who reported fertility problems, a group at higher risk. None of the differences in degree of protection among these subgroups were statistically significant. The protective effect was absent in blacks. Five cases and three controls who were still menstruating a year before diagnosis reported using menopausal estrogens (estimated RR = 1.6).

We also considered the histologic types separately (table 7). The patterns reported for the total case group were present among subjects with serous and endometrioid tumors. We found no association between risk of developing mucinous tumors and either menopausal estrogen use or early surgical menopause, but the estimates were very unstable because of the small number of such tumors in the postmenopausal women (12 women). We examined the cases who had low malignant potential separately and found their patterns of risk similar to those of the frankly malignant cases. The increased risk associated with hot flashes and the decreased risk associated with

cramps, menopausal estrogen use, and early surgical menopause were similar in the two groups. A more detailed analysis of cancer of low malignant potential is presented elsewhere (9).

DISCUSSION

Many interesting and provocative discussions of the etiology of ovarian cancer have appeared in recent years, yet some of the most basic and critical epidemiologic features of the disease have not been established. Hysterectomy and menopausal symptoms, time, and therapy are among the factors whose effects remain unmeasured or in dispute.

Hysterectomy with preservation of both ovaries appears to convey about 30 per cent protection, according to our data, after adjustment for other risk factors. Although this estimate is not statistically significant in this study, it is entirely compatible with other available estimates. Annegers et al. (1) called attention to the apparent protection in 1979, citing their rate ratio estimate of 0.4 and Wynder's (2) estimate of 0.7. Joly et al. (3) had also noted fewer hysterectomies among cases but could not distinguish which had included oophorectomy. McGowan et al. (4) and Franceschi et al. (5) also reported protective effects. Cramer et al.'s (6) data yielded an estimated rate ratio of 0.7 for "surgical vs. natural menopause." On the other hand, Hildreth et al. (10) and Casagrande et al. (11) reported no effect, and Newhouse et al. (12) reported a slightly elevated rate ratio among women reporting menopause induced by surgery.

Hysterectomy could appear to be protective simply because unilateral or bilateral oophorectomies were performed at the time

TABLE 7

Estimated ovarian cancer incidence rate ratios, specific for histologic type, according to menopausal estrogen use

Estrogen use	Controls	Serous	Mucinous	Endometrioid	Other
Never (<i>n</i>)	140	57	7	43	36
Ever (<i>n</i>)	104	20	5	18	17
Estimated rate ratio*	1.0	0.5	1.1	0.5	0.6
95% confidence interval		0.3-0.8	0.3-3.6	0.3-1.0	0.3-1.2

* Adjusted for age and race.

of the hysterectomy and not remembered. Analyses restricted to data confirmed by operative notes or pathology records in our study and that by Annegers et al. (1) still show hysterectomy to be protective. In addition, if the controls' hysterectomies for which we could not confirm ovarian preservation had included oophorectomies, there would be very little protection conferred by oophorectomy, an unlikely possibility. In our view, women who have had hysterectomies or other gynecologic surgery probably do have a slightly lower risk of ovarian cancer. It may be that visualization of the ovaries permits the surgeon to remove any that look unusual, a disproportionate fraction of which would have subsequently developed malignancies. This is the interpretation offered by Weiss and Harlow (13), whose data show no reduced risk among women whose hysterectomies occurred more than five years before diagnosis. Another possibility is that surgery compromises ovarian function, reducing the chance of malignancy. A recent study of women undergoing tubal ligation showed estrogen deficiency following surgery, possibly as a result of localized hypertension at the ovary (14).

Age at menopause has not been consistently related to ovarian cancer. In our study, cases had a later menopause than controls, but only because they were less likely to have undergone an early surgical menopause. Most previous studies have not used the life table method to combine data from menopausal and premenopausal women, but if late menopause is a risk factor, one would expect both that more cases would be premenopausal and that menopausal cases would have had a later menopause than controls. Franceschi et al. (5) report a marked difference in age at menopause, but no difference in the proportions menopausal. Risch et al. (15) do not report data on age at menopause, but they report later age at end of ovulation (menopause or interview date) among cases, adjusting for other factors affecting ovulation. Hildreth et al. (10) found cases

less likely to be menstruating at diagnosis but older at menopause. McGowan et al. (4) found cases more likely to be menstruating at diagnosis but not different from controls in age at menopause. Annegers et al. (1) found no difference in proportion menstruating or in age at menopause. Cramer et al. (6) found cases less likely to be menstruating at diagnosis but of similar age at menopause. Newhouse et al. (12) found cases more likely to be menstruating at diagnosis but, among those who were postmenopausal, 0.8 years younger at menopause.

In total, these conflicting data suggest that age at menopause is not an important predictor of ovarian cancer risk. If age at menopause is a risk indicator, it is much weaker for ovarian cancer than for breast cancer, for which a twofold difference has been consistently reported for menopause at age 55 or later compared with menopause before age 45 (16).

Menopausal symptoms appeared to be risk indicators in our data, with hot flashes being reported more often and cramps being reported less often by the cases. Symptoms at menopause have not been mentioned previously as risk indicators. It is possible that hot flashes indicate increased risk because they reflect dramatically changing levels of gonadotropins. It is not clear why menstrual cramps near the menopause would indicate decreased risk. In general, the symptom-related relative risks require cautious interpretation, since the symptoms are hard to define or recall precisely.

Menopausal estrogen use has been reported to be weakly related or unrelated to ovarian cancer risk in most studies (5, 9, 17). Cramer et al. (6) and Weiss et al. (18) reported slightly increased risk among users. Smith et al. (19) reported a significant protective effect. Our data show an apparent protective effect, which increases with longer duration of use and decreases with discontinuation. We offer no ready explanation for the absence of an effect reported by other investigators. Our find-

ings on other risk factors are consistent with published estimates, so we doubt that any aspect of study design explains our finding of a protective effect for menopausal estrogens. The finding could be due to chance or to reduced risk, perhaps because of reduced pituitary gonadotropin stimulation.

One striking aspect of our findings and those of other investigators is that the ovarian cancer risks associated with menopausal factors are smaller than the risks associated with family history, parity, or recent oral contraceptive use. This may indicate that events early in life matter most in determining ovarian cancer risk or that the later events that influence risk have not been identified.

REFERENCES

1. Annegers JF, Strom H, Decker DG, et al. Ovarian cancer—incidence and case-control study. *Cancer* 1979;43:723-9.
2. Wynder EL. Epidemiology of cancer of the ovary. *Cancer* 1969;23:352-70.
3. Joly DJ, Lilienfeld AM, Diamond EL, et al. An epidemiologic study of the relationship of reproductive experience to cancer of the ovary. *Am J Epidemiol* 1974;99:190-209.
4. McGowan L, Parent L, Lednar W, et al. The woman at risk for developing ovarian cancer. *Gynecol Oncol* 1979;7:325-44.
5. Franceschi S, La Vecchia C, Helmrich SP, et al. Risk factors for epithelial ovarian cancer in Italy. *Am J Epidemiol* 1982;115:714-19.
6. Cramer DW, Hutchison GB, Welch WR, et al. Determinants of ovarian cancer risk. I. Reproductive experiences and family history. *JNCI* 1983;71:711-16.
7. Gart JJ. Point and interval estimation of the common odds ratio in the combination of 2×2 tables with fixed marginals. *Biometrika* 1970;57:471-5.
8. Breslow NE, Day NE. Statistical methods in cancer research. Vol 1. Lyon, France: International Agency for Research on Cancer, 1980.
9. McGowan L, Norris HJ, Hartge P, et al. Risk factors for ovarian cancer. *Eur J Gynecol Oncol* (in press).
10. Hildreth NG, Kelsey JL, LiVolsi VA, et al. An epidemiologic study of epithelial carcinoma of the ovary. *Am J Epidemiol* 1981;114:398-405.
11. Casagrande JT, Pike MC, Ross RK, et al. "Incessant ovulation" and ovarian cancer. *Lancet* 1979;2:170-3.
12. Newhouse ML, Pearson RM, Fullerton JM, et al. A case-control study of carcinoma of the ovary. *Br J Prev Soc Med* 1977;31:148-53.
13. Weiss NS, Harlow BL. Why does hysterectomy without bilateral oophorectomy influence the subsequent incidence of ovarian cancer? *Am J Epidemiol* 1986;124:856-8.
14. Cattanaach J. Oestrogen deficiency after tubal ligation. *Lancet* 1985;1:847-9.
15. Risch HA, Weiss NS, Lyon JL, et al. Events of reproductive life and the incidence of epithelial ovarian cancer. *Am J Epidemiol* 1983;117:128-39.
16. Trichopoulos D, MacMahon B, Cole P. The menopause and breast cancer risk. *JNCI* 1972;48:605-13.
17. Annegers JF, O'Fallon W, Kurland LT. Exogenous estrogens and ovarian cancer. (Letter). *Lancet* 1977;2:869-70.
18. Weiss NS, Lyon JL, Krishnamurthy S, et al. Non-contraceptive estrogen use and the occurrence of ovarian cancer. *JNCI* 1982;68:95-8.
19. Smith EM, Sowers MF, Burns TL. Effects of smoking on the development of female reproductive cancers. *JNCI* 1984;73:371-6.