



American Journal of EPIDEMIOLOGY

Volume 136

Number 10

November 15, 1992

Copyright © 1992 by The Johns Hopkins University

School of Hygiene and Public Health

Sponsored by the Society for Epidemiologic Research

ORIGINAL CONTRIBUTIONS

Characteristics Relating to Ovarian Cancer Risk: Collaborative Analysis of 12 US Case-Control Studies

I. Methods

Alice S. Whittemore,¹ Robin Harris,¹ Jacqueline Itnyre,¹ Jerry Halpern,² and the Collaborative Ovarian Cancer Group³

Data from 12 US case-control studies of ovarian cancer, conducted during the period 1956–1986 and representing some 3,000 cases and 10,000 controls, were pooled and reanalyzed. Separate analyses were conducted for four subgroups of the pooled data: invasive epithelial ovarian cancers in white women; epithelial ovarian cancers of low malignant potential in white women, epithelial ovarian cancers in black women, and nonepithelial ovarian cancers. This paper gives a brief description of the participating studies and describes the methods used in the collaborative analysis. *Am J Epidemiol* 1992;136:1175–83.

case-control studies; methods; ovarian neoplasms

This is the first in a series of articles describing a collaborative combined analysis

of data from 12 case-control studies of ovarian cancer conducted in the United States

Received for publication August 21, 1991, and in final form July 23, 1992.

¹ Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA.

² Division of Biostatistics, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA.

³ Members of the Collaborative Ovarian Cancer Group: Dr. John T. Casagrande, Department of Preventive Medicine, University of Southern California, Los Angeles, CA; Dr. Daniel Cramer, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, MA; Dr. Patricia Hartge, Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD; Dr. Jennifer L. Kelsey, Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA; Dr. Marion Lee, Department of Epidemiology, University of California, San Francisco, San Francisco, CA; Dr. Nancy C. Lee, Women's Health and Fertility Branch, Division of Reproductive Health, Centers for Dis-

ease Control, Atlanta, GA; Dr. Joseph L. Lyon, Department of Family and Community Medicine, The University of Utah Medical Center, Salt Lake City, UT; Dr. James R. Marshall, Department of Social and Preventive Medicine, State University of New York at Buffalo School of Medicine, Buffalo, New York; Dr. Larry McGowan, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, George Washington University Medical Center, Washington, D. C.; Dr. Philip C. Nasca, New York State Department of Health, Bureau of Cancer Epidemiology, School of Public Health, Department of Epidemiology, Albany NY; Dr. Ralph S. Paffenbarger, Jr., Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA; Dr. Lynn Rosenberg, Slone Epidemiology Unit, School of Public Health, Boston University School of Medicine, Brookline, MA; and Dr. Noel S. Weiss, Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA. *Project Consultant:* Dr. Genrose D. Cooley, Extramural Programs, Division of Cancer Etiology, National Cancer Institute, Bethesda, MD.

during the period 1956–1986 (1–12). The major goals of the analysis were examination of 1) relations between specific types of ovarian cancer and certain reproductive and hormonal characteristics, taken singly and in combination; and 2) variation in these relations with age and race. This paper describes the methods used for the analysis. Part II (13) presents results for invasive epithelial ovarian cancers in white women, and part III (14) gives results for epithelial tumors of low malignant potential in white women. Part IV (15) relates these results to current hypotheses for the pathogenesis of epithelial ovarian cancer. Part V, with results for epithelial ovarian cancer in blacks, and part VI, with results for nonepithelial ovarian cancer, are reported elsewhere (16, 17).

DATA

Studies

Studies included in the analysis satisfied the following criteria: 1) they must have included women newly diagnosed with epithelial ovarian cancer at a US hospital; 2) control women must have resided in the US during the period of case ascertainment and, if they were hospital controls, could not have been hospitalized for gynecological conditions; 3) characteristics of study subjects must have been ascertained through personal interviews using a structured questionnaire; 4) questionnaire data must have been coded and stored electronically, and 5) variable definitions must have been documented.

Table 1 lists the 12 studies that met these criteria. Other published US case-control studies of ovarian cancer either did not involve personal interviews (18–20) or did not store their data in machine-readable form (21). Representatives from each of the 12 eligible studies met initially to describe their

own studies, to determine feasibility of a combined analysis, and, if the analysis was deemed feasible, to determine resources needed to conduct it. This meeting was funded by the Small Grants Program of the Division of Etiology of the US National Cancer Institute. Further National Cancer Institute funding allowed the collaborators to meet annually three more times.

Subjects

The 12 studies differed in their eligibility criteria for subjects. For example, some studies in table 1 excluded nonwhite cases or cases outside a certain age range; some excluded cases with a prior cancer diagnosis; others excluded cases with nonepithelial ovarian cancer or with tumors of low malignant potential. The studies in table 1 also differed in their procedures for control selection. Those studies using hospital controls varied in their eligibility criteria for the controls; most excluded women admitted for obstetric, gynecologic, psychiatric, or malignant conditions. One study (6) excluded women admitted with myocardial infarction, stroke, thromboembolism, osteoporosis, or gallbladder disease; another (1) excluded women admitted with diabetes or gastrointestinal conditions, while yet another (4) excluded women (both cases and controls) with a prior hysterectomy. Most, but not all, studies excluded controls with a prior bilateral oophorectomy. Another source of variation among the studies is the closeness with which controls were matched to cases on characteristics such as age and race. Some used a matched design, some used frequency matching, and others used an unmatched design and instead stratified in the analysis.

Such differences mandate criteria for including subjects in the study and analytic methods that separate or stratify the data by the study from which they arose, as discussed in the statistical section below. We excluded women whose characteristics were reported by a surrogate, women who did not know their total number of pregnancies or total number of term pregnancies (variables deemed essential to all analyses), and control

Reprint requests to Dr. Alice S. Whittemore, Stanford University School of Medicine, Department of Health Research and Policy, HRP Modular no. 2, Stanford, CA 94305-5092.

Supported by National Cancer Institute grants CA 43689, CA 47427, and CA 47448.

The authors are grateful to Drs. Sally Glaser, Esther M. John, Pamela Horn-Ross, and Carolyn Westat for helpful comments on earlier versions of the manuscript.

TABLE 1. Case-control studies of epithelial ovarian cancer among US white women

Authors (reference no.)	Cases				Controls	
	Invasive	Low malignant potential	Year of diagnosis	Place of diagnosis	No.*	Source
Byers et al. (1)	196		1956-1963	Buffalo, NY	795	Case hospitals
Hildreth et al. (2)	59	3	1976-1979	Connecticut	1,068	Case hospitals
McGowan et al. (3)	133	33	1974-1977	Washington, DC	165	Case hospitals
Wu et al. (4)	111		1975-1977	San Francisco Bay Area, CA	482	Case hospitals
Rosenberg et al. (5)	115	8	1976-1980	Eastern US cities†	486	Case hospitals
Hartge et al. (6)	220	41	1978-1981	Washington, DC	288	Case hospitals
Casagrande et al. (7)	133		1973-1976	Los Angeles, CA	134	Case neighborhoods
Cramer et al. (8)	177	41	1978-1981	Boston, MA	229	Town directories
Nasca et al. (9)	314	27	1977-1980	New York State	694	Motor vehicle files
Weiss et al. (10)	269	23	1975-1979	Utah, Washington	700	Household and RDD‡ phone surveys
CASH‡ group (11)	303	107	1980-1982	8 SEER‡ areas§	3,542	RDD phone surveys
Whittemore et al. (12)	167	44	1983-1986	San Francisco Bay Area, CA	310	Group 1: RDD phone surveys Group 2: case hospitals
Total	2,197	327			8,893	

* Number included in the present analysis.

† Including Boston, Massachusetts; New York, New York; Philadelphia, Pennsylvania; and Baltimore, Maryland.

‡ RDD, random digit dialing; CASH, Cancer and Steroid Hormone Study; SEER, Surveillance, Epidemiology, and End Results program.

§ Atlanta, Georgia; Detroit, Michigan; Seattle, Washington; San Francisco Bay Area, California; Iowa; Connecticut; New Mexico; and Utah.

women who had or might have had a bilateral oophorectomy. Table 1 shows the numbers of white women with epithelial ovarian cancer (classified by tumor behavior) and white control women included in the analysis.

ANALYSIS

Analysis involved the following tasks: 1) constructing the basic variables (e.g., race and subtype of disease) needed to organize the data into subsets for separate analysis; 2) choosing the major hypotheses to be tested; 3) defining the variables needed to test these hypotheses; 4) reviewing the individual questionnaires and code books to determine the information available on the variables of interest; 5) using this information to identify a list of "working variables" to be used in all analyses; 6) identifying the positions on each of the data tapes of the information needed to assemble each variable and writing a sep-

arate program to extract this information from each tape; 7) preparing descriptive statistics for each variable and each study in search of outlying observations and outlying studies; 8) merging the extracted data into a composite file containing data for all variables and all studies; 9) extracting subsets of data for separate analyses; 10) assembling a list of regression models for each variable; 11) conducting study-specific and combined regression analyses; 12) documenting and cataloging output; and 13) discussing and interpreting results and planning further follow-up regressions. These steps are discussed below.

Data organization

We first copied to an IBM 3090 mainframe computer (IBM, Poughkeepsie, NY) original data files from the 12 studies. This represented data for some 13,600 subjects and comprised 3,900 variables, ranging from

44 to 1,308 variables per study. Collaborating investigators had stored their original data in many different formats, including seven- and nine-track tapes with fixed and variable-length record formats and formats produced by various types of data processing software. We used versatile tape-reading software on the mainframe computer to create new flat files with fixed record length. We then subdivided these files into manageable subfiles and transferred them to an IBM PS/2 model 70 microcomputer (IBM, Raleigh, NC) containing two megabytes of random access memory and a 120-megabyte hard disk. After displaying and checking the variables of interest on these files, we merged them into a composite file containing records for all eligible subjects and all variables of potential interest. For speed and efficiency, we stored the composite file on a Sun Workstation (Sun Microsystem, Milpitas, California) which was connected to both the mainframe computer and the microcomputer. These network connections allowed electronic data transfer to and from the collaborating investigators at their institutions. We then extracted subsets of this file for the various subgroup-specific analyses.

Hypotheses to be tested

Table 2 lists the major hypotheses evaluated. Other issues, such as the relation of ovarian cancer risk to exposures to talc, tobacco, alcohol, and coffee, were not addressed because too few of the studies had comparable data on the relevant variables.

Original plans for analyses specific for histologic type of ovarian cancer were abandoned in response to the group consensus that possible lack of uniformity of the histological classifications made this approach potentially less fruitful than other subdivisions of the data. Instead, we separated women with epithelial and nonepithelial ovarian cancers and, among those with epithelial cancers, separated white women from black women. White women with epithelial ovarian cancers were further separated by the invasiveness of their tumor (invasive vs. low malignant potential).

TABLE 2. Major hypotheses tested in ovarian cancer analysis

Pregnancies	
Risk among the parous does not depend on the number of term pregnancies.	
Risk among the parous is unrelated to age at first livebirth, after adjustment for number of term pregnancies.	
Risk is unrelated to number of failed pregnancies, after adjustment for the number of term pregnancies.	
Risk among the nulliparous is unrelated to marital status and gravidity.	
Risk among the ever-married is unrelated to history of physician-diagnosed infertility and reported difficulty in conceiving.	
Breast feeding	
Risk among the parous is unrelated to duration of breast feeding.	
Exogenous estrogens	
Risk is unrelated to duration of oral contraceptive use.	
The relation between risk and oral contraceptive use does not vary by parity.	
Risk among women aged 40 years or more is unrelated to duration of estrogen replacement therapy.	
Menstrual events	
Risk is unrelated to age at menarche.	
Risk among naturally menopausal women aged 55 years or more is unrelated to age at menopause.	
Pelvic surgery	
Risk is unrelated to prior tubal ligation.	
Risk is unrelated to prior hysterectomy with ovarian conservation.	
Years of ovulation	
Risk is unrelated to estimated years of ovulation.	
Risk per month of anovulation does not differ by source of anovulation, age at anovulation, or age at risk.	

Variable definition

After selecting the most important hypotheses, we listed the working variables needed for all regressions related to each hypothesis. For example, all regressions required the working variable "reference age," defined as a subject's age at the reference date assigned to her for evaluation of her personal characteristics. The assignment of reference date varied by study and case-control status. Usually, the reference date for a case was the date of her cancer diagnosis, and the reference date for a control was the date of her interview or the date of diagnosis for her matched case. Other ex-

amples of working variables include a woman's total number of term pregnancies, defined as pregnancies of at least 20 weeks gestation and coded as 0, 1, . . . , 5, ≥ 6 , and her total number of failed pregnancies, defined as miscarriages, induced abortions, ectopic pregnancies, and stillbirths, and coded similarly.

Once a working variable was identified, the individual questionnaires and code books were reviewed to determine a common definition and coding scheme. This sometimes involved difficult trade-offs between coding detail and study inclusion in order to obtain data from as many studies in as much detail as possible. For example, we defined failed pregnancies to include stillbirths (which also are term pregnancies) in order to use data from a study that had aggregated stillbirths with the other types of pregnancy failure. When the convention of using the coarsest definition resulted in unacceptable loss of specificity or detail for too many studies, we conducted additional, more detailed analyses using only those studies with appropriate data.

To produce the working variables, separate programs were written to extract the data from the individual study files. For complex variables, such as menopausal status or estimated age at last ovulation, flow charts (e.g., figure 1) helped to ensure that the different studies contributed comparable information. Once created, the working variables were edited for subtle interstudy incompatibilities. Descriptive statistics were used to identify outliers and other problems. Some of these were resolved locally; others required discussion with the collaborating investigators. Some investigators occasionally had to review their original data to confirm or recode questionable values or to provide further detail. More than 90 working variables were constructed.

Data processing and management

Once created and edited, the working variables were used to derive categorical and other variables for regressions. When analyzing a topic, we included only those studies that had data for all variables occurring in

all relevant regressions. Further, women with unknown values of a variable were deleted from all regressions containing that variable. Thus, total case and control numbers vary across regressions, and numbers presented in the following parts vary across tables.

Statistical analysis

Several pitfalls may result from pooling data from separate studies with differing protocols and differing exposure prevalence. The variable "study" could represent both a strong confounding factor and an effect modifier. It is a potential confounder because both the case:control ratio and the prevalence for a particular exposure may vary from study to study. It is a potential effect modifier because odds ratios may vary from one study population to another. Therefore, an analysis that pools data across studies could yield seriously misleading results.

We used several strategies to address these pitfalls. First, we stratified all analyses jointly by study and reference age (<25, 25–29, . . . , 75–79, and ≥ 80 years). Studies 10 and 11 were further stratified by their constituent study centers. We used conditional logistic regression (22), implemented on EGRET software (23), to estimate odds ratios and calculate (two-tailed) significance levels and confidence intervals. This approach has two advantages over an unconditional analysis containing dummy variables for the studies, the age groups, and their interactions: It avoids unwieldy output of regression coefficients for the resulting 200-plus age-study variables which are not of primary interest, and it allows inspection of numbers of subjects who failed to contribute to a given analysis because their age-study stratum lacked cases or controls or discordant exposures. However, either conditional or stratified unconditional regression could be used (22); we found that the two produced nearly identical estimates for odds ratios and their standard errors when performed on the same data. The standard errors and confidence intervals produced by these regressions do not reflect variance because of interstudy

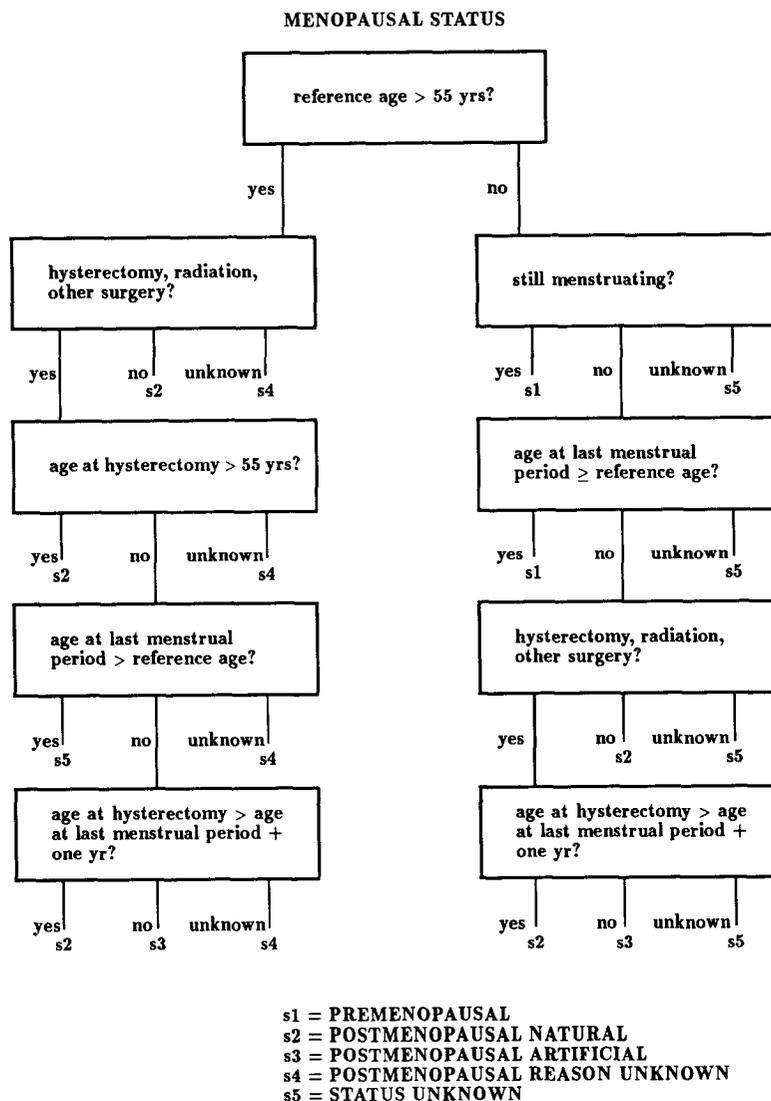


FIGURE 1. Flow chart for creation of the variable "menopausal status" from data obtained in 12 case-control studies of ovarian cancer.

differences in odds ratios. An analysis of variance of the log odds ratios (24) or jack-knife procedure (25), although not performed for the ovarian cancer data, would produce variance estimates that include an interstudy variance component.

Second, we looked for heterogeneity across studies in odds ratio estimates for all major variables associated with risk of invasive epithelial ovarian cancers. To do so, we computed individual study-specific odds ratios for the variables and inspected them

visually. More formally, we also evaluated the log-likelihood of a given regression model versus that of an expanded model. The latter includes product terms obtained by multiplying the major variable of interest by a dummy variable for each of the studies (22). As a simple example, when testing the null hypothesis that odds ratio estimates for parity do not vary across the six hospital-based studies, we fit both a small model and an expanded model. The small model contained only the parity variable PAR (coded

one for parous women and zero for nulliparous women), while the expanded model contained PAR and five additional dummy variables of the form $PAR \times STUDY_j$, $j = 1, \dots, 5$, where $STUDY_j$ is coded one if a woman participated in study j and 0 otherwise. The coefficient for $PAR \times STUDY_j$ gives the proportional amount that the odds ratio for parity in study j differs from that of study 6, an arbitrarily chosen referent study. An overall test of the null hypothesis of no study heterogeneity is provided by the likelihood ratio statistic based on the maximized log-likelihoods of small and expanded models. Under the null hypothesis, this statistic has approximately a chi-squared distribution with degrees of freedom equal to one less than the number of studies being examined (22).

In addition to examining heterogeneity across studies of odds ratios for all major variables associated with risk of invasive epithelial ovarian cancer, we also evaluated such odds ratio heterogeneity with respect to parity, history of oral contraceptive use, and 10-year strata of reference age. Other effect modification was evaluated when motivated by a specific biological mechanism suggested by one or more of the collaborating investigators.

Third, we conducted two sets of combined analyses: one for the six studies that involved hospital controls (studies 1–6 in table 1, hereafter called hospital studies (1–6)) and one for the six studies that involved random digit dial or neighborhood controls (studies 7–12, hereafter called population studies (7–12)). Study 12 used both hospital and population controls; we omitted the hospital control data. Software limitations on the maximum numbers of study subjects and variables in a regression mandated the split into hospital and population studies, which fortuitously allowed us to assess the strength and consistency of an association by comparing two independent sets of odds ratio estimates. The split also provided an opportunity to compare odds ratio estimates and prevalence of characteristics between hospital and population controls. Overall, we

found good agreement between odds ratios obtained by the two types of study; such agreement lends support to both study designs.

Finally, we included year of birth as a continuous variable in all regressions to control more precisely for reference age and to control for any case-control differences in year of interview that might bias comparison of temporal variables such as oral contraceptive use.

Limitations and strengths

Combined analyses such as this share some of the pitfalls of meta-analysis (i.e., the review and synthesis of published findings). Despite the common definitions used to re-code variables and all efforts to ensure inter-study comparability, the data available to a combined analysis nevertheless derive from questions whose wording varied across studies and thus could have elicited different responses. Interpretation of the final results also is hampered by any defects in the original studies, including selection bias in the enrollment of cases and controls and confounding by unmeasured or imprecisely measured variables. Pooling data from several studies that have the same types of bias can produce relative risk estimates that are statistically highly significant but nevertheless unconvincing of an underlying causal relation. (See reference 26 for further discussion of the sources of bias in pooled analyses of epidemiologic data.)

On the other hand, a combined analysis offers several benefits. It provides large sample sizes for examining effects of rare exposures, interactions among established or suspected risk factors, consistency of associations previously suggested by some studies but not confirmed by others, and effects of risk factors by subtype of disease. For example, part IV (15) in this series describes the finding that odds ratios relating epithelial ovarian cancer risk to pregnancy and oral contraceptive use differ between younger and older women, a finding that has not emerged from any individual study and

would not emerge from meta-analysis of published results from individual studies.

In addition, a combined analysis produces variables that have a common coding across studies, thus removing a major obstacle to interpretation of published results from individual studies with differing variable definitions. For example, part II in this series (13) examines invasive epithelial ovarian cancer risk in relation to total duration of unprotected intercourse, an issue that could not be studied by synthesis of published results because this variable had not been defined and coded consistently across studies.

A combined analysis also provides a framework for evaluating the consistency of findings across studies conducted in different populations using different methodologies.

Finally, a collaborative analysis involving detailed substantive oversight by the individual investigators offers the opportunity for experts in the disease under investigation to meet regularly to discuss causal mechanisms. Such discussions may generate new hypotheses and provide a basis for planning further coordinated research to test such hypotheses. The advantages of coordinated research with common design features and common questions are emphasized by the extensive effort needed to reanalyze data from disparate studies.

REFERENCES

1. Byers T, Marshall J, Graham S, et al. A case-control study of dietary and nondietary factors in ovarian cancer. *J Natl Cancer Inst* 1983;71:681-6.
2. Hildreth NG, Kelsey JL, LiVolsi VA, et al. An epidemiologic study of epithelial carcinoma of the ovary. *Am J Epidemiol* 1981;114:398-405.
3. McGowan L, Parent L, Lednar W, et al. The woman at risk for developing ovarian cancer. *Gynecol Oncol* 1979;7:325-44.
4. Wu ML, Whittemore AS, Paffenbarger RS Jr, et al. Personal and environmental characteristics related to epithelial ovarian cancer. I. Reproductive and menstrual events and oral contraceptive usage. *Am J Epidemiol* 1988;128:1216-27.
5. Rosenberg L, Shapiro S, Slone D, et al. Epithelial ovarian cancer and combination oral contraceptives. *JAMA* 1982;247:3210-12.
6. Hartge P, Schiffman MH, Hoover R, et al. A case-control study of epithelial ovarian cancer. *Am J Obstet Gynecol* 1989;161:10-16.
7. Casagrande JT, Louie EW, Pike MC, et al. "Incessant ovulation" and ovarian cancer. *Lancet* 1979; 2:170-3.
8. Cramer DW, Hutchison GB, Welch GR, et al. Determinants of ovarian cancer risk. I. Reproductive experiences and family history. *J Natl Cancer Inst* 1983;71:711-16.
9. Nasca PC, Greenwald P, Chorost S, et al. An epidemiologic case-control study of ovarian cancer and reproductive factors. *Am J Epidemiol* 1984; 119:705-13.
10. Weiss NS, Lyon JL, Liff JM, et al. Incidence of ovarian cancer in relation to the use of oral contraceptives. *Int J Cancer* 1981;28:669-71.
11. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. The reduction in risk of ovarian cancer associated with oral contraceptive use. *N Engl J Med* 1987; 316:650-5.
12. Whittemore AS, Wu ML, Paffenbarger RS Jr, et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol* 1988;128:1228-40.
13. Whittemore AS, Harris R, Itnyre J, et al. 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;136:1184-203.
14. Harris R, Whittemore AS, Itnyre J, et al. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. III. Epithelial tumors of low malignant potential in white women. *Am J Epidemiol* 1992;136: 1204-11.
15. Whittemore AS, Harris R, Itnyre J, et al. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. IV. The pathogenesis of epithelial ovarian cancer. *Am J Epidemiol* 1992;136:1212-20.
16. John EM, Whittemore AS, Harris R, et al. Characteristics relating to ovarian cancer risk: collaborative analysis of twelve US case-control studies. V. Epithelial cancer among black women. *J Natl Cancer Inst* (in press).
17. Horn-Ross PL, Whittemore AS, Harris R, et al. Characteristics relating to ovarian cancer risk: collaborative analysis of twelve US case-control studies. VI. Nonepithelial cancers. *Epidemiology* 1992; 3:490-5.
18. Annegers JF, Strom H, Decker DG, et al. Ovarian cancer: incidence and case-control study. *Cancer* 1979;43:723-9.
19. Demopoulos RI, Seltzer V, Dubin N, et al. The association of parity and marital status with the development of ovarian carcinoma: clinical implications. *Obstet Gynecol* 1979;54:150-5.
20. 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.
21. Wynder EL, Dodo H, Barber HRK. Epidemiology of cancer of the ovary. *Cancer* 1969;23:352-70.
22. Breslow NE, Day NE. Statistical methods in cancer

- research. Vol 1. The analysis of case-control studies. (IARC scientific publication no. 32). Lyon: International Agency for Research on Cancer, 1980.
23. Mauritsen R. EGRET software program. Seattle, WA: Statistics and Epidemiology Research Corporation, 1986.
 24. Der Simonian R, Laird N. Meta-analysis in clinical trials. *J Control Clin Trial* 1986;7:177-88.
 25. Miller R. The jackknife—a review. *Biometrika* 1974;61:1-17.
 26. Clayton D. The EURODEM collaborative re-analysis of case-control studies of Alzheimer's disease: some methodological considerations. *Int J Epidemiol* 1991;20(Suppl. 2):S62-4.