

Association of Parity and Ovarian Cancer Risk by Family History of Breast or Ovarian Cancer in a Population-Based Study of Postmenopausal Women

Celine M. Vachon,¹ Pamela J. Mink,² Carol A. Janney,¹ Thomas A. Sellers,¹ James R. Cerhan,¹ Lynn Hartmann,³ and Aaron R. Folsom⁴

Abstract: Although parity is associated with a decreased risk of ovarian cancer in the general population, this association among women with a family history is less clear. We examined this question in a prospective cohort of 31,377 Iowa women 55–69 years of age at baseline. Relative risks (RRs) and 95% confidence intervals (CIs) were estimated through Cox regression. We identified 181 incident epithelial ovarian cancers through 13 years of follow-up. At baseline, 14% of the women reported breast or ovarian cancer in a first-degree relative, and an additional 12% reported a family history in a second-degree relative. Among women without a family history of breast or ovarian cancer in a first-degree relative, nulliparous women

were at slightly increased risk of ovarian cancer (RR = 1.4, 95% CI = 0.9–2.4) compared with parous women, whereas among women with a family history, nulliparous women were at a much higher risk (RR = 2.7, 95% CI = 1.1–6.6) than parous women. Similar results were seen when family history included first- or second-degree relatives with breast or ovarian cancer or a first- or second-degree relative with ovarian cancer only. Nulliparity may be more strongly associated with an increased risk of ovarian cancer among women with a family history of breast or ovarian cancer, compared with women who do not have a family history of those cancers. (EPIDEMIOLOGY 2002;13:66–71)

Key words: ovarian cancer, parity, family history, risk factors, prospective cohort study.

Most epidemiologic studies of ovarian cancer have observed an inverse association with full-term pregnancy. Ovarian cancer risk decreases with increasing number of livebirths,^{1,2} with a 40% decrease for the first pregnancy and a 14% decrease for each subsequent birth.³ Although the underlying mechanism is unknown, these findings are consistent with hypotheses invoking incessant ovulation⁴ and elevated gonadotropins.⁵

Five case-control studies^{6–10} have examined the modifying effects of family history on the association of parity with ovarian cancer, but the results are inconsistent. Some have reported no difference by family history of ovarian⁶ or breast cancer.^{9,10} Others have observed inverse associations only in the family history-positive group.^{7,8} In contrast, a study of BRCA1 carriers found that parity was associated with increased risk.¹¹ Thus, the question of whether parity is differentially associated with familial and sporadic ovarian cancers remains uncertain.

We examined the association of parity with ovarian cancer by family history of breast and/or ovarian cancer in the prospective Iowa Women's Health Study. We considered family history of ovarian and/or breast cancer in our primary analyses, as BRCA1 and BRCA2 mutations have been related to familial ovarian and breast cancers.^{12–14}

Subjects and Methods

Sample Population

Details of the Iowa Women's Health Study have been published.¹⁵ Briefly, in January 1986, a 16-page question-

From the Departments of Department of ¹Health Sciences Research and ³Oncology, Mayo Clinic and Mayo Clinic Cancer Center, Rochester, MN; ²Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD; and ⁴Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN.

Address correspondence and reprint requests to: Celine M. Vachon, Department of Health Sciences Research, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905; vachon@mayo.edu

This work was supported by National Cancer Institute Grant CA39742.

Submitted February 19, 2001; final version accepted September 7, 2001.

Copyright © 2001 by Lippincott Williams & Wilkins, Inc.

naire was mailed to 98,029 women 55–69 years of age randomly selected from the state driver's license list. The 41,836 respondents form the cohort under study.

Data Collection

The baseline questionnaire assessed anthropometrics, lifestyle characteristics, and reproductive factors. Participants were asked whether they had ever been pregnant and, for each pregnancy (up to ten), their age at pregnancy, duration, and outcome (livebirth, stillbirth, miscarriage, ectopic pregnancy, and induced abortion). To assess infertility, women were asked whether they had ever tried unsuccessfully for a year or more to become pregnant. Menopause was ascertained as natural or surgical.

Participants were also asked whether their mother, sisters, daughters, maternal or paternal aunts, or grandmothers had ever had a diagnosis of cancer. If a participant answered yes for a particular relative, the cancer site was asked: breast, ovary, uterus, cervix, a reproductive organ of unknown site, another site, or unknown.

Exclusion Criteria

Women were excluded if they reported a history of cancer other than skin cancer ($N = 3,830$), a bilateral oophorectomy ($N = 8,064$), both ($N = 1,454$), or a borderline ovarian tumor ($N = 16$). A total of 31,377 women remained for analysis.

Follow-Up

Questionnaires were mailed in 1987, 1989, 1992, and 1997 to establish vital status and change of address. Deaths among nonrespondents were identified through annual linkage to Iowa death certificates, supplemented by linkage to the National Death Index. Cancer incidence was ascertained through the State Health Registry of Iowa, part of the Surveillance, Epidemiology, and End Results (SEER) Program.¹⁶ A computer match was performed annually between cohort members and the Iowa Health Registry using combinations of name, zip code, birth date, and Social Security number.

Statistical Analysis

Person-years were accrued from completion of the baseline questionnaire until the earliest date of the following: ovarian cancer, estimated date of move from Iowa, date of death, or December 31, 1998.

We calculated relative risks and 95% confidence intervals using Cox regression, and modeled survival as a function of age.¹⁷ Both the main effects and the interactions are on a multiplicative scale. Analyses that included the number of livebirths, age at first birth, or age at last birth were restricted to parous women.

We examined whether the associations of parity, number of livebirths, age at first birth, and age at last

birth with ovarian cancer risk were modified by family history of breast or ovarian cancer. Family history of breast or ovarian cancer was defined in two ways: family history in a first-degree relative and family history in a first- or second-degree relative. We also conducted analyses of the joint association of the parity variables and family history of ovarian cancer only in a first- or second-degree relative. The analyses based on family history of ovarian cancer alone should be considered exploratory because of small numbers in some categories.

Analyses were carried out using the SAS (SAS Institute, Cary, NC) and Splus (Mathsoft, Seattle, WA) software systems.

Results

Through December 31, 1998, and 13 years of follow-up, 181 cases of invasive epithelial ovarian cancer were identified among women who were 56–81 years of age at diagnosis. Borderline tumors of low malignant potential were excluded; however, similar results were observed in analyses that included borderline tumors (data not shown). Ovarian cancer cases with a family history of breast or ovarian cancer in a first-degree relative were similar in age (mean age = 69.5 years) to cases without a family history (mean age = 68.8 years). Findings with regard to age were similar for all definitions of family history.

We previously reported risk factors for ovarian cancer after 7 years of follow-up.¹⁸ With 6 additional years of follow-up, results are similar. Risk is positively associated with waist-to-hip ratio (RRs for second, third, and fourth quartiles *vs* lowest: 2.0, 1.2, and 1.7), physical activity (RRs for moderate and high activity *vs* low: 1.2 and 1.5), and nulliparity (RR = 1.5). Risk is inversely associated with history of hysterectomy (RR = 0.9), unilateral oophorectomy (RR = 0.4), or both (RR = 0.5). Table 1 provides the age- and multivariate-adjusted associations with ovarian cancer for the parity variables under investigation and for family history. The distribution of parity variables and other potential risk factors does not differ materially by family history (data not shown).

Regardless of whether family history was based on first-degree or first- and second-degree relatives with breast or ovarian cancer, the elevated risk associated with nulliparity appears to be limited to women with a positive family history (Table 2). Among women without a family history of breast or ovarian cancer in a first-degree relative, nulliparous women are at slightly increased risk of ovarian cancer (RR = 1.4, 95% CI = 0.9–2.4), compared with parous women, whereas among women with a family history, nulliparous women are at a much higher risk (RR = 2.7, 95% CI = 1.1–6.6) than parous women. Defining family history to include a first- or second-degree relative with breast or ovarian cancer,

TABLE 1. Age- and Multivariate-Adjusted Relative Risks of Ovarian Cancer for Parity and Family History Variables, Iowa Women's Health Study, 1986–1998

| Variables | No. of Cases* | N (%) | RR | 95% CI† | Multivariate RR | 95% CI‡ |
|----------------------------------|---------------|---------------|------|-----------|-----------------|-----------|
| Parity | | | | | | |
| Nulliparous | 23 | 2,727 (8.7) | 1.55 | 1.00–2.39 | 1.62 | 1.04–2.52 |
| Parous§ | 157 | 28,455 (91.3) | 1.00 | | 1.00 | |
| Number of livebirths | | | | | | |
| 1–2§ | 55 | 9,793 (34.4) | 1.00 | | 1.00 | |
| 3–4 | 71 | 12,415 (43.6) | 1.02 | 0.72–1.46 | 1.01 | 0.71–1.45 |
| >4 | 31 | 6,247 (22.0) | 0.89 | 0.57–1.38 | 0.87 | 0.55–1.36 |
| Age at first livebirth | | | | | | |
| ≤19§ | 33 | 5,973 (21.1) | 1.00 | | 1.00 | |
| 20–24 | 82 | 14,116 (49.9) | 1.03 | 0.69–1.54 | 1.01 | 0.67–1.54 |
| ≥25 | 41 | 8,181 (28.9) | 0.87 | 0.55–1.38 | 0.87 | 0.55–1.40 |
| Age at last livebirth | | | | | | |
| ≤29 | 66 | 11,429 (40.6) | 1.27 | 0.86–1.88 | 1.32 | 0.89–1.97 |
| 30–34§ | 40 | 8,683 (30.8) | 1.00 | | 1.00 | |
| Ovarian or breast cancer | 48 | 8,070 (28.6) | 1.28 | 0.84–1.95 | 1.28 | 0.83–1.95 |
| First-degree relative | | | | | | |
| No FH§ | 149 | 26,282 (86.5) | 1.00 | | 1.00 | |
| FH | 30 | 4,113 (13.5) | 1.28 | 0.87–1.90 | 1.32 | 0.89–1.96 |
| First- or second-degree relative | | | | | | |
| No FH§ | 124 | 22,426 (74.5) | 1.00 | | 1.00 | |
| FH | 54 | 7,674 (25.5) | 1.27 | 0.93–1.75 | 1.28 | 0.93–1.77 |
| Ovarian cancer | | | | | | |
| First-degree relative | | | | | | |
| No FH§ | 171 | 29,714 (98.0) | 1.00 | | 1.00 | |
| FH | 7 | 597 (2.0) | 2.06 | 0.97–4.38 | 2.13 | 1.00–4.53 |
| First- or second-degree relative | | | | | | |
| No FH§ | 166 | 28,968 (97.2) | 1.00 | | 1.00 | |
| FH | 10 | 836 (2.8) | 2.12 | 1.12–4.02 | 2.19 | 1.15–4.14 |
| Breast cancer | | | | | | |
| First-degree relative | | | | | | |
| No FH§ | 155 | 26,704 (87.9) | 1.00 | | 1.00 | |
| FH | 23 | 3,674 (12.1) | 1.08 | 0.69–1.67 | 1.11 | 0.71–1.71 |
| First- or second-degree relative | | | | | | |
| No FH§ | 130 | 22,906 (76.2) | 1.00 | | 1.00 | |
| FH | 47 | 7,166 (23.8) | 1.15 | 0.83–1.61 | 1.16 | 0.83–1.63 |

Family history. *Total numbers of women do not equal 31,377 because of missing values. Total case counts do not equal 181 because of missing values.

† Cox proportional hazards modeled as a function of age.

‡ All models are adjusted for hysterectomy, physical activity and waist-to-hip ratio. Family history models are also adjusted for parity.

§ Reference category.

|| The questionnaire allowed space for information on ten births. There were 398 women who had more than ten births; age at tenth birth was used in all analyses for these women.

the risk estimates are $RR = 3.0$ and $RR = 1.1$ for nulliparous women with and without a family history, compared with their respective parous groups. The risk associated with nulliparous women is strongest among women with a family history of ovarian cancer only ($RR = 5.8$), but this estimate is based on only three ovarian cancer cases with a family history of ovarian cancer. Results are not materially changed with adjustment for other risk factors (data not shown).

Risks associated with number of livebirths by family history are also shown in Table 2. Overall, there is no evidence for an interaction of family history of breast or ovarian cancer and number of livebirths on ovarian cancer risk. A suggestive positive association with ovarian cancer is observed for more than four births among women with, but not without, a family history. Multivariate adjustment does not alter these results (data not shown).

There is also no evidence for an interaction between age at first birth or age at last birth and family history status on ovarian cancer risk (data not shown).

Discussion

Risk factors for ovarian cancer may differ according to a family history of breast or ovarian cancer. Our findings provide evidence that nulliparity is a stronger risk factor for ovarian cancer among women with a self-reported family history of breast or ovarian cancer than among women without a family history.

It has been hypothesized that ovarian cancer risk is increased with a greater number of lifetime ovulatory cycles, which results in more mitotic events and chances for genetic mutation.⁴ Evidence supporting this hypothesis includes the inverse associations of ovarian cancer risk with bilateral oophorectomy, parity, and oral contraceptive use.¹⁹ Thus, the greater risk to nulliparous women may reflect the greater number of ovulatory cycles than in parous women. Therefore, if family history of breast or ovarian cancer reflects an inherited propensity to genetic mutation with each mitosis, nulliparity could enhance this predisposition.⁸ Our results are also compatible with the inter-

TABLE 2. Association of Parity and Number of Livebirths with Ovarian Cancer Risk by Family History (FH), Iowa Women's Health Study, 1986-1998

| Risk Factor | FH of Breast or Ovarian Cancer in First-Degree Relative | | FH of Breast or Ovarian Cancer in First- or Second-Degree Relative | | FH of Ovarian Cancer in First- or Second-Degree Relative | |
|----------------------|---|------------------|--|------------------|--|-------------------|
| | No FH | FH | No FH | FH | No FH | FH |
| Parity | | | | | | |
| Nulliparous | | | | | | |
| RR (95% CI)* | 1.44 (0.87-2.39) | 2.70 (1.10-6.61) | 1.10 (0.59-2.04) | 2.99 (1.57-5.69) | 1.35 (0.83-2.21) | 5.82 (1.51-22.52) |
| Person-years | 25,336 | 4,032 | 21,533 | 7,757 | 28,031 | 662 |
| Cases† | 17 | 6 | 11 | 12 | 18 | 3 |
| Parous‡ | | | | | | |
| RR (95% CI)* | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Person-years | 285,402 | 44,184 | 243,607 | 82,678 | 314,443 | 9,079 |
| Cases† | 131 | 24 | 112 | 42 | 147 | 7 |
| Number of livebirths | | | | | | |
| 1-2‡ | | | | | | |
| RR* | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Person-years | 97,005 | 14,747 | 82,781 | 28,042 | 106,846 | 2,958 |
| Cases† | 47 | 8 | 41 | 14 | 54 | 1 |
| 3-4 | | | | | | |
| RR (95% CI)* | 1.01 (0.69-1.47) | 0.95 (0.38-2.41) | 1.01 (0.67-1.52) | 0.93 (0.46-1.88) | 0.95 (0.66-1.36) | 2.94 (0.33-26.30) |
| Person-years | 124,981 | 19,626 | 106,013 | 37,207 | 137,840 | 4,125 |
| Cases† | 60 | 10 | 52 | 17 | 65 | 4 |
| >4 | | | | | | |
| RR (95% CI)* | 0.80 (0.49-1.31) | 1.15 (0.40-3.31) | 0.72 (0.41-1.23) | 1.29 (0.59-2.84) | 0.81 (0.51-1.28) | 3.02 (0.27-33.34) |
| Person-years | 63,417 | 9,811 | 54,813 | 17,429 | 69,757 | 1,996 |
| Cases† | 24 | 6 | 19 | 11 | 28 | 2 |

* Cox proportional hazards modeled as a function of age.
 † Total case counts do not equal 181 because of missing values.
 ‡ Reference category.

pretation that family history is a marker of an inherited deficiency in DNA repair.

Consistent with these arguments, we would expect women with a positive family history of breast or ovarian cancer or with a high-risk mutation to have an increased prevalence of preneoplastic changes in ovarian tissue. To date, there appears to be little evidence that high-risk tissue changes increase risk for women with a family history or known mutation.^{20,21} No study, however, has specifically examined tissue from nulliparous women within genetically predisposed subgroups.

Our definitions of family history considered a first-degree relative with breast or ovarian cancer, a first- or second-degree relative with breast or ovarian cancer, and a first- or second-degree relative with ovarian cancer alone. These familial cases presumably included both genetically influenced cases and cases due to environmental clustering or chance. Sporadic breast cancer is common and may cluster with ovarian cancer, regardless of the genetic status of the patient. Thus, absence of data on the BRCA1/2 mutation status of these familial ovarian cases is a notable limitation. We would expect that a small fraction of our family history-positive cases, especially those with multiple breast and ovarian cancers, would be carriers of a BRCA1 or BRCA2 mutation,²² despite the age at onset of ovarian cancer in the women in this study (mean age = 69 years). Risch *et al*²² recently demonstrated in an unselected series that 19% of ovarian cancer cases with a first-degree relative who had breast or ovarian cancer had a mutation in the BRCA1 or BRCA2 gene. And, 26% of those with either a first-degree relative who had ovarian cancer or breast cancer before age 60, or two or more first- or second-degree relatives with breast or ovarian cancer, carried a mutation in one of these genes.²² These authors also showed that even though BRCA1 mutations were associated with age at onset of hereditary ovarian cancer less than 50 years, the majority of hereditary ovarian cancers diagnosed at 60 or more years of age were due to BRCA2 mutations.²² It is also possible that unidentified genes for breast and/or ovarian cancer could also be responsible for the aggregation of cases in the families in the present study.

Family history of breast and ovarian cancer was self-reported in our cohort. Breast cancer in a first-degree relative is reported accurately^{23–26}; however, family history of ovarian cancer^{24,26,27} or breast cancer in a second-degree relative²⁵ is less accurate. Family history was assessed before the onset of cancer, but women with a stronger family history may report their family history of cancer more accurately than other women and may also be more likely to develop ovarian cancer. Data on mutation status, rather than reporting of family history, would alleviate this potential bias.

Several studies have suggested that the reason for nulliparity (such as infertility or subfertility) may be important in ovarian cancer.^{19,28,29} These studies have shown that infertility, measured in a variety of ways, may be associated with an increased risk of ovarian cancer; however, this association may be limited primarily to nulliparous women.^{3,30,31} The questions of whether type of infertility or use of fertility drugs is associated with increased ovarian cancer risk have not yet been adequately addressed.³² In the current study, small numbers prevent us from examining whether the increased risk in the family history-positive, nulliparous women may be limited to infertile women. This is an area for future investigation.

We did not evaluate the interaction of oral contraceptive (OC) use with family history in this report, because the older women forming the cohort under study did not have the opportunity for significant exposure to OCs. When OCs were first marketed in this country, women in our cohort were between the ages of 30 and 44 years. As shown in a previous report from this study, ever-use of OCs was not associated with decreased risk of ovarian cancer (RR for ever-use *vs* never-use = 1.22; 95% CI = 0.7–2.1).¹⁸ The absence of a main effect tempered the motivation to examine effect modification by family history.

To our knowledge, this is the first prospective cohort study to examine the joint association of parity (and related variables) and family history of cancer on ovarian cancer risk. Prospective study designs, unlike case-control studies, are not prone to family recall bias, which may arise when those with cancer discover family history after the diagnosis. The case-control studies by Kerber *et al*⁸ and by Schildkraut *et al*⁷ also found evidence of a significant interaction of parity and family history on ovarian cancer risk, but the direction was opposite of our findings; they found an inverse association of parity and ovarian cancer only among those with no family history. None of the other previous studies^{6,9,11} found an increased risk with nulliparity among the family history-positive women.

A reason for the inconsistency in the literature may be the differences in the ages at diagnosis of ovarian cancer across studies. We studied primarily postmenopausal women, with ovarian cancer cases diagnosed between the ages of 56 and 81 years; most of the other studies involved significantly younger cases^{6,7,9,11} and, most likely, a different proportion of BRCA1 and BRCA2 mutation carriers. This cohort (mean diagnosis age = 69 years) may more appropriately reflect the experience of ovarian cancer in the general population, given that the mean age of ovarian cancer diagnoses nationally is 60–64 years.³³ Inconsistencies could also reflect differences in the definition of family history used. Previous studies defined family history on ovarian

cancer only,^{6,7} breast and/or ovarian cancer,^{9,10} any cancer history,⁸ or BRCA1 mutation carrier status.¹¹ In our study, all three definitions of family history examined yielded similar results. The strongest association for the nulliparous, family history-positive groups was seen among women with a family history of ovarian cancer.

References

- Daly M, Ostram GI. Epidemiology and risk assessment for ovarian cancer. *Semin Oncol* 1998;25:255-264.
- Hankinson SE, Colditz GA, Hunter DJ, et al. A prospective study of reproductive factors and risk of epithelial ovarian cancer. *Cancer* 1995;76:284-290.
- Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 U.S. case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol* 1992;136:1184-1203.
- Fathalla MF. Incessant ovulation: a factor in ovarian neoplasia? *Lancet* 1971;2:163.
- Cramer DW, Welch WR. Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. *J Natl Cancer Inst* 1983;71:717-721.
- Godard B, Foulkes WD, Provencher D, et al. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *Am J Obstet Gynecol* 1998;179:403-410.
- Schildkraut JM, Thompson WD. Familial ovarian cancer: a population-based case-control study. *Am J Epidemiol* 1988;128:456-466.
- Kerber RA, Slattery ML. The impact of family history on ovarian cancer risk. The Utah Population Database. *Arch Intern Med* 1995;155:905-912.
- Tavani A, Ricci E, La Vecchia C, et al. Influence of menstrual and reproductive factors on ovarian cancer risk in women with and without family history of breast or ovarian cancer. *Int J Epidemiol* 2000;29:799-802.
- Chiapparino F, Pelucchi C, Parazzini F, et al. Reproductive and hormonal factors and ovarian cancer. *Ann Oncol* 2001;12:337-341.
- Narod SA, Goldgar DE, Cannon-Albright L, et al. Risk modifiers in carriers of BRCA1 mutations. *Int J Cancer* 1995;64:394-398.
- Ford D, Easton DF, Stratton M, et al. The Breast Cancer Linkage Consortium. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. *Am J Hum Genet* 1998;62:676-689.
- Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate gene for the breast and ovarian cancer susceptibility gene, BRCA1. *Science* 1994;266:66-71.
- Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene BRCA2. *Nature* 1995;378:789-792.
- Bigard KM, Folsom AR, Hong CP, Sellers TA. Mortality and cancer rates in nonrespondents to a prospective study of older women: 5-year follow-up. *Am J Epidemiol* 1994;139:990-1000.
- Ries L, Kosary C, Hankey B, et al. SEER Cancer Statistics Review, 1973-1996. Bethesda, MD: National Cancer Institute, 1999.
- Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol* 1997;145:72-80.
- Mink PJ, Folsom AR, Sellers TA, Kushi LH. Physical activity, waist-to-hip ratio, and other risk factors for ovarian cancer: a follow-up study of older women. *Epidemiology* 1996;7:38-45.
- Riman T, Persson I, Nilsson S. Hormonal aspects of epithelial ovarian cancer: review of epidemiological evidence. *Clin Endocrinol (Oxf)* 1998;49:695-707.
- Stratton JF, Buckley CH, Lowe D, Ponder BA. Comparison of prophylactic oophorectomy specimens from carriers and noncarriers of a BRCA1 or BRCA2 gene mutation. United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Familial Ovarian Cancer Study Group. *J Natl Cancer Inst* 1999;91:626-628.
- Hartge P, Hayes R, Reding D, et al. Complex ovarian cysts in postmenopausal women are not associated with ovarian cancer risk factors: preliminary data from the prostate, lung, colon, and ovarian cancer screening trial. *Am J Obstet Gynecol* 2000;183:1232-1237.
- Risch HA, McLaughlin JR, Cole DE, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *Am J Hum Genet* 2001;68:700-710.
- Eerola H, Blomqvist C, Pukkala E, Pyrhonen S, Nevanlinna H. Familial breast cancer in southern Finland: how prevalent are breast cancer families and can we trust the family history reported by patients? *Eur J Cancer* 2000;36:1143-1148.
- Douglas FS, O'Dair LC, Robinson M, Evans DG, Lynch SA. The accuracy of diagnoses as reported in families with cancer: a retrospective study. *J Med Genet* 1999;36:309-312.
- Love RR, Evans AM, Josten DM. The accuracy of patient reports of a family history of cancer. *J Chron Dis* 1985;38:289-293.
- Kerber RA, Slattery ML. Comparison of self-reported and database linked family history of cancer data in a case-control study. *Am J Epidemiol* 1997;146:244-248.
- Airewele G, Adatto P, Cunningham J, et al. Family history of cancer in patients with glioma: a validation study of accuracy. *J Natl Cancer Inst* 1998;90:543-544.
- Klip H, Burger CW, Kenemans P, van Leeuwen FE. Cancer risk associated with subfertility and ovulation induction: a review. *Cancer Causes Control* 2000;11:319-344.
- Whittemore AS, Wu ML, Paffenbarger RS Jr, et al. Epithelial ovarian cancer and the ability to conceive. *Cancer Res* 1989;49:4047-4052.
- Hartge P, Schiffman MH, Hoover R, McGowan L, Leshner L, Norris HJ. A case-control study of epithelial ovarian cancer. *Am J Obstet Gynecol* 1989;161:10-16.
- Mosgaard BJ, Lidgaard O, Kjaer SK, Schou G, Andersen AN. Infertility, fertility drugs, and invasive ovarian cancer: a case-control study. *Fertil Steril* 1997;67:1005-1012.
- Glud E, Kjaer SK, Troisi R, Brinton LA. Fertility drugs and ovarian cancer. *Epidemiol Rev* 1998;20:237-257.
- Surveillance, Epidemiology and End Results (SEER) Program Public-Use Data (1973-1998), National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch, released April 2001, based on the August 2000 submission.