A Case-Control Study of Analgesic Use and Ovarian Cancer[1]

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Abstract

A recent case-control study raised the hypothesis that acetaminophen use 1 day or more per week for at least 6 months reduces the risk of epithelial ovarian cancer. We assessed analgesic use in relation to epithelial ovarian cancer risk using data from our case-control surveillance study of medication use and cancer. Patients were interviewed in hospitals in Baltimore, Boston, New York, and Philadelphia during 1976–1998. We compared 780 women with epithelial ovarian cancer to 2053 cancer controls and 2570 noncancer controls. For acetaminophen use 1 day or more per week for at least 6 months, the odds ratio estimate was 0.9 (95% confidence interval, 0.6–1.4) derived with cancer controls and 1.0 (0.6–1.5) with noncancer controls. Estimates for more frequent and longer term use were also compatible with 1.0. The odds ratios among patients with metastatic ovarian cancer were reduced but not statistically significant. The odds ratio for use of nonsteroidal anti-inflammatory drugs 4 or more days per week for at least 5 years, 0.5, was statistically significant. The present results provide only weak support for a reduction in the risk of epithelial ovarian cancer among acetaminophen users. They raise the possibility of an inverse association with long-term nonsteroidal anti-inflammatory drug use.

Introduction

In a recent case-control study of epithelial ovarian cancer (1), the risk appeared to be halved among women who had taken acetaminophen 1 day or more per week for at least 6 months; there was no association with the use of NSAIDs.[3] In a subsequent report from a follow-up study (2), the relative risk estimate for death from ovarian cancer among women who had used acetaminophen 30 or more times a month at entry into the study was reduced, 0.55, but not statistically significant. A hospital-based case-control study of ovarian cancer yielded an odds ratio of 0.8, compatible with 1.0, for women who used acetaminophen at least 1 day per week for at least 6 months (3). On the basis of information on prescription and nonprescription drug use collected in our Case-Control Surveillance Study of medication and cancer (4), we report here an assessment of the relation of acetaminophen and NSAID use to the risk of epithelial ovarian cancer.

Materials and Methods

Data Collection. Since 1976, the Case-Control Surveillance Study has collected information from patients admitted for various cancers and nonmalignant conditions to hospitals in several cities on the eastern seaboard (4). Nurse-interviewers administer standard questionnaires to obtain data on personal characteristics, medical and reproductive history, and other potential risk factors for illness. Histories of prescription and nonprescription drug use before hospitalization are obtained by asking about use for 42 indications, which include pain, headache, muscle ache, fever, and other conditions for which acetaminophen and other analgesics are used. For each episode of use, the drug name, date started, and duration and frequency of use (days per week or month) are recorded. Discharge summaries and pathology reports are reviewed, blind to the drug exposures of the patient, for details of the diagnoses. The study was confined to persons <70 years of age until 1997 and to patients up to age 79 after 1997. Of the patients approached for an interview, 95% participated. The present analyses are based on interviews in Baltimore, Boston, New York, and Philadelphia during 1976–1998.

Cases and Controls. The cases were 780 women with primary ovarian cancer diagnosed within the previous year who had no previous cancer. The pathology reports of 748 women indicated that the cancer was epithelial; 32 women for whom the pathology report did not mention the type of ovarian cancer were also included because 81% of ovarian cancers in the Case-Control Surveillance Study for which the type is known are epithelial.

Two control groups were selected. Potential cancer controls were 2573 women admitted for any of several cancers diagnosed within the previous year that we judged were unrelated to analgesic use, who had no previous cancer, and who had at least one ovary. Among cases <40 years of age, the ratio of controls to cases exceeded 10:1, whereas the ratio was 4:1 or less in the older age groups; to reduce the excess of controls

Received 3/8/00; revised 6/21/00; accepted 6/28/00.
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[1] Data collection was supported by Grant R01 CA45762 from the National Cancer Institute and Grant FD-U-000082 from the Food and Drug Administration. The analyses for this report were funded by McNeil Consumer Health Care, Fort Washington, PA 19034.
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[3] The abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; CI, confidence interval.

Table 1 Selected factors among cases of epithelial ovarian cancer, cancer controls, and noncancer controls (%)

	Cases (780)	Cancer controls (2053)	Noncancer controls (2570)
Age (yr)			
<40	19	20	20
40–49	25	25	38
50–59	29	28	21
60–79	27	27	22
Parity			
0	27	19	23
1–2	42	37	35
3+	29	38	39
Oral contraceptive use (yr)			
0	71	65	67
1–4	20	22	21
5+	7	11	10
Hysterectomy	11	17	15
Age at menopause[a]			
<45	24	35	40
45–49	30	29	26
50+	46	36	34
Mother or sister with ovarian cancer	2	<1	<1

[a] Among postmenopausal women.

<40, the cases under 40 were frequency matched up to 4:1 with controls on 5-year age group, interview year, and study center. The final cancer control group comprised 2053 women with lung or other respiratory cancer (719), malignant melanoma (563), lymphoma (266), leukemia (249), bone and connective tissue cancer (188), or thyroid cancer (68). Potential noncancer controls were 4204 women who had been admitted for nonmalignant conditions judged to be unrelated to analgesic use, who had not had cancer, and who had at least one ovary. Cases <40 were frequency matched up to 4:1 with noncancer controls on 5-year age group, interview year, and study center. The final noncancer control group comprised 2570 women, of whom 1368 had been admitted for trauma and 1202 for acute infections.

The prevalence of acetaminophen use 1 day or more per week for at least 6 months that began at least 1 year before admission across five major diagnostic categories in the controls (respiratory cancer, lymphoma or leukemia, other cancer, trauma, and infection) was 5, 4, 3, 4, and 3%, respectively; the overall prevalence was 4% among all cancer controls and also 4% among all noncancer controls. The prevalence of NSAID use 1 day or more per week for at least 6 months beginning at least 1 year before admission was 9, 9, 11, 10, and 10%, respectively, across the five diagnostic categories; the overall rates were 9% among all cancer controls and 10% among all noncancer controls.

Drug Exposure. Most use of analgesics is sporadic. We focused on regular use (at least 1 day per week for at least 6 months) because it is more likely to play an etiological role and to be better remembered. We only considered use that began at least 1 year before admission. We excluded women whose only regular use was initiated in the year before admission because such use would not have played an etiological role. In the analysis of acetaminophen use, 1 case, 14 cancer controls, and 7 noncancer controls who used acetaminophen at least 1 day per week for at least 6 months only during the year before admission were excluded; in the analysis of NSAID use, 2 cases, 16 cancer controls, and 20 noncancer controls were excluded.

Table 2 Acetaminophen use and NSAID use 1 day or more per week for at least 6 months among 780 cases of epithelial ovarian cancer, 2053 cancer controls, and 2570 noncancer controls[a]

Drug and use	Cases	Cancer controls	OR[b] (95% CI)	Noncancer controls	OR[b] (95% CI)
Acetaminophen					
No	750	1955	Ref.	2462	Ref.
Yes	28	81	0.9 (0.6–1.4)	95	1.0 (0.6–1.5)
Duration 5+ yr	18	43	1.0 (0.6–1.8)	50	1.1 (0.6–1.9)
First use 10+ yr ago	7	25	0.6 (0.2–1.4)	27	0.8 (0.3–1.8)
Last use <1 yr ago	26	76	0.9 (0.5–1.4)	88	1.0 (0.6–1.5)
NSAIDs					
No	715	1833	Ref.	2278	Ref.
Yes	58	195	0.8 (0.6–1.1)	256	0.7 (0.5–1.0)
Duration 5+ yr	33	84	0.7 (0.4–1.1)	103	0.7 (0.4–1.2)
First use 10+ yr ago	21	69	0.8 (0.5–1.3)	72	1.0 (0.6–1.6)
Last use <1 yr ago	42	150	0.8 (0.5–1.1)	227	0.6 (0.4–0.9)

[a] Women whose only use began within the year before admission or whose timing of use was unknown are excluded.
[b] OR, odds ratio from logistic regressions with terms for age, geography, and interview year.

These categories of drug use were not associated with the risk of ovarian cancer.

Data Analysis. Odds ratios were estimated for regular analgesic use relative to nonregular use (the combined category of nonregular use and never use) using unconditional multiple logistic regression (5). Analgesic use varied by age, interview year, and study center, and we included terms for these factors in the logistic regressions. Control for other potential risk factors for ovarian cancer, including race, parity, duration of oral contraceptive use, hysterectomy status, age at menopause, and family history of ovarian cancer did not materially alter the estimates. These factors were therefore not included in the logistic regressions.

Results

As shown in Table 1, about half of the cases and controls were <50 years of age. The controls had higher parity, longer duration of oral contraceptive use, earlier age at menopause, and a higher prevalence of hysterectomy than the cases. A positive family history of ovarian cancer (mother or sister) was more common among the cases.

For acetaminophen use 1 day or more per week for at least 6 months that began at least 1 year before admission (Table 2), the overall odds ratio was 0.9 (95% CI, 0.6–1.4) when the cases were compared with cancer controls and 1.0 (95% CI, 0.6–1.5) with noncancer controls. The odds ratios for use of at least 5 years duration, use that began at least 10 years previously, and use that continued into the year before admission ranged from 0.6 to 1.1 and were all compatible with 1.0. The results for acetaminophen use were unchanged when NSAID users were excluded.

For NSAID use 1 day or more per week for at least 6 months that began at least 1 year before admission (Table 2), the overall odds ratio derived with cancer controls was 0.8 (95% CI, 0.6–1.1) and with noncancer controls, 0.7 (95% CI, 0.5–1.0). For use of at least 5 years duration, use that began at least 10 years previously, and use that continued into the year before admission, the odds ratios were in the range 0.6–1.0 and were all compatible with 1.0 with one exception: for use that continued into the year before admission, the odds ratio derived with noncancer controls was 0.6 (95% CI, 0.4–0.9). Results were unchanged when acetaminophen users were excluded.

Table 3 Acetaminophen use and NSAID use 4 days or more per week for at least 6 months among 780 cases of epithelial ovarian cancer, 2053 cancer controls, and 2570 noncancer controls[a]

Drug and use	Cases	Cancer controls	OR[b] (95% CI)	Noncancer controls	OR[b] (95% CI)
Acetaminophen					
No	765	1992	Ref.	2514	Ref.
Yes	14	50	0.7 (0.4–1.3)	52	0.9 (0.5–1.6)
Duration 5+ yr	10	24	0.9 (0.4–1.9)	26	1.2 (0.5–2.6)
First use 10+ yr ago	5	16	0.6 (0.2–1.7)	13	1.1 (0.4–3.2)
Last use <1 yr ago	13	44	0.7 (0.4–1.4)	47	0.9 (0.5–1.7)
NSAIDs					
No	733	1870	Ref.	2338	Ref.
Yes	41	160	0.7 (0.5–1.0)	207	0.7 (0.5–1.0)
Duration 5+ yr	11	63	0.5 (0.2–0.9)	81	0.5 (0.3–0.9)
First use 10+ yr ago	10	56	0.5 (0.2–0.9)	53	0.7 (0.3–1.3)
Last use <1 yr ago	32	117	0.7 (0.5–1.1)	181	0.6 (0.4–0.9)

[a] Women whose only use began within the year before admission or whose timing of use was unknown are excluded.
[b] OR, odds ratio from logistic regressions with terms for age, geography, and interview year.

Table 4 Aspirin use and nonaspirin NSAID use 4 days or more per week for at least 6 months among 780 cases of epithelial ovarian cancer, 2053 cancer controls, and 2570 noncancer controls[a]

Drug and use	Cases	Cancer controls	OR[b] (95% CI)	Noncancer controls	OR[b] (95% CI)
Aspirin					
No	750	1938	Ref.	2430	Ref.
Yes	27	101	0.7 (0.4–1.1)	130	0.8 (0.5–1.2)
Duration 5+ yr	8	51	0.4 (0.2–0.9)	67	0.5 (0.2–1.0)
Nonaspirin NSAIDs					
No	763	1971	Ref.	2465	Ref.
Yes	14	72	0.5 (0.3–0.9)	88	0.5 (0.3–0.9)
Duration 5+ yr	3	12	0.4 (0.2–0.9)	15	0.6 (0.2–2.2)

[a] Women whose only use began within the year before admission or whose timing of use was unknown are excluded.
[b] OR, odds ratio from logistic regressions with terms for age, geography, and interview year.

The analyses were repeated for a more intensive category of regular use, 4 or more days per week for at least 6 months (Table 3). All odds ratios for acetaminophen use were compatible with 1.0. For NSAID use, the odds ratios for 5 or more years of use were statistically significant, 0.5 (95% CI, 0.2–0.9) derived with cancer controls and 0.5 (95% CI, 0.3–0.9) derived with noncancer controls; reduced odds ratios were observed across the four study centers. Also statistically significant were the odds ratio for NSAID use that began at least 10 years previously derived with cancer controls (0.5) and for use that continued into the year before admission derived with noncancer controls (0.6).

The most commonly used NSAID was aspirin. For at least 6 months of aspirin use 4 or more days per week, the odds ratios were reduced but compatible with 1.0 (Table 4). For use of at least 5 years duration, the odds ratio was 0.4 (95% CI, 0.2–0.9) based on cancer controls and 0.5 (95% CI, 0.2–1.0) based on noncancer controls. For use of nonaspirin NSAIDs, the odds ratio for at least 6 months of use 4 or more days per week derived with either cancer or noncancer controls was reduced, 0.5, and statistically significant. Only three cases reported use of nonaspirin NSAIDs for at least 5 years, insufficient for informative analysis.

There were 485 women whose ovarian cancer had spread beyond the ovary to other organs or lymph nodes at the time of diagnosis (metastatic cancer). We repeated the overall analyses of acetaminophen and NSAID use 1 day or more and 4 days or more per week for at least 6 months separately among the cases of metastatic and nonmetastatic cancer (Table 5). For acetaminophen use, the odds ratios for use 4 days or more per week for at least 6 months were nonsignificantly reduced (0.4; 95% CI, 0.2–1.2) derived with cancer controls and 0.7 (95% CI, 0.3–1.6) derived with noncancer controls. For NSAID use, the odds ratio estimates were statistically significantly reduced for NSAID use 1 day or more per week based on noncancer controls (0.6; 95% CI, 0.4–0.9), and for NSAID use 4 days or more per week based on both cancer controls (0.5; 95% CI, 0.3–0.8) and noncancer controls (0.5; 95% CI, 0.3–0.8). For 245 cases of epithelial ovarian cancer without metastases, the odds ratios for acetaminophen use ranged from 0.9 to 1.3 and for NSAID use from 0.9 to 1.0, and all were compatible with 1.0. The estimates were also compatible with the corresponding estimates for metastatic ovarian cancer.

If some cases had taken analgesics for early symptoms of ovarian cancer, this could have resulted in weakened associations between use and ovarian cancer risk. We repeated the overall analyses for use of acetaminophen and NSAIDs 4 or more days per week for at least 6 months and for at least 5 years, this time considering use that began 2 or more years before admission. The results were closely similar to those for use that began 1 or more years before admission. For metastatic cancer, numbers were sufficient only to consider use that lasted 6 months or more. Again, the results were similar to those for use that began 1 or more years before admission.

For completeness, we compared the analgesic use of 176 cases of nonepithelial ovarian cancer to that of the 2053 cancer controls and the 2570 noncancer controls. The use of acetaminophen was too sparse for analysis. The odds ratios for NSAID use 1 day or more per week for at least 6 months and for use 4 days or more per week for at least 6 months ranged from 0.8 to 1.0 and were compatible with 1.0.

Discussion

Cramer *et al.* (1) raised the hypothesis that use of acetaminophen, but not other analgesics, might protect against epithelial ovarian cancer. In their population-based case-control study conducted from 1992–1997, the odds ratio for acetaminophen use 1 day or more per week for at least 6 months was statistically significantly reduced, 0.52, based on 26 users among 563 cases and 46 users among 523 controls identified by random-digit dialing. The reduction was greater for longer duration and more frequent use, but the estimates for these categories were compatible with the overall estimate. For use of aspirin and ibuprofen 1 day or more per week for at least 6 months, the odds ratios were 0.78 and 1.20, respectively, compatible with 1.0. On the basis of experimental results in rodents, Cramer *et al.* (6) suggested that acetaminophen might have an antigonadotropic effect that could result in a reduced incidence of ovarian cancer. In addition, in an observational study gonadotropin and estradiol levels were lower among women who reported having used acetaminophen for menstrual pain then among women who reported having used other analgesics or none at all (7).

In response to the findings of Cramer *et al.* (1), Rodriquez *et al.* (2) assessed data collected from 675,000 women in the Cancer Prevention Study II of the American Cancer Society. The use of one brand of acetaminophen (Tylenol) <30 times a month during the month before entry into the study (238 ex-

Table 5 Acetaminophen use and NSAID use 1 day or more per week and 4 days or more per week for at least 6 months among 485 cases of metastatic epithelial ovarian cancer and 295 cases of nonmetastatic epithelial ovarian cancer[a]

	Use	Cases	OR[b] (95% CI)	
			Cancer controls	Noncancer controls
Metastatic ovarian cancer				
Acetaminophen				
1+ days/week	No	466	Ref.	Ref.
1+ days/week	Yes	18	0.9 (0.5–1.5)	1.0 (0.6–1.7)
4+ days/week	No	477	Ref.	Ref.
4+ days/week	Yes	7	0.4 (0.2–1.2)	0.7 (0.3–1.6)
NSAIDs				
1+ days/week	No	445	Ref.	Ref.
1+ days/week	Yes	34	0.7 (0.5–1.0)	0.6 (0.4–0.9)
4+ days/week	No	458	Ref.	Ref.
4+ days/week	Yes	22	0.5 (0.3–0.8)	0.5 (0.3–0.8)
Nonmetastatic ovarian cancer				
Acetaminophen				
1+ days/week	No	284	Ref.	Ref.
1+ days/week	Yes	10	0.9 (0.4–1.8)	1.0 (0.5–1.9)
4+ days/week	No	288	Ref.	Ref.
4+ days/week	Yes	7	1.0 (0.4–2.3)	1.3 (0.6–3.0)
NSAIDs				
1+ days/week	No	270	Ref.	Ref.
1+ days/week	Yes	24	1.0 (0.6–1.6)	0.9 (0.6–1.4)
4+ days/week	Yes	275	Ref.	Ref.
4+ days/week	Yes	19	0.9 (0.6–1.6)	0.9 (0.6–1.6)

[a] Women whose only use began within the year before admission are excluded.
[b] OR, odds ratio from logistic regressions with terms for age, geography, and interview year.

posed cases) was unrelated to ovarian cancer mortality during 12 years of follow-up. For acetaminophen use 30 or more times a month (eight exposed cases), the relative risk was reduced, 0.55, but compatible with 1.0. There was no association of ovarian cancer mortality with the duration of acetaminophen use. Also in response to the results of Cramer *et al.* (1), Moysich *et al.* (3) published an abstract with results of an assessment of analgesic use in a case-control study of 543 women with ovarian cancer and 1569 controls with nonendocrine-related malignancies. The case group was not confined to epithelial cancers. Neither use of acetaminophen nor use of NSAIDs 1 day or more per week for at least 6 months was significantly related to ovarian cancer risk; the odds ratios were 0.80 and 1.01, respectively. The odds ratios were smaller for use of acetaminophen seven or more times per week (0.63) and for 10 or more years of use (0.69), but the CIs included 1.0.

In the present study, acetaminophen use 1 day or more per week for at least 6 months that began 1 year or more previously was not associated with the risk of ovarian cancer; the odds ratio was 0.9 (95% CI, 0.6–1.4) derived with cancer controls and 1.0 (95% CI, 0.6–1.5) with noncancer controls. Odds ratio estimates for more intensive and longer duration use were also not statistically significant. There was no relation of risk to the timing of first or last use. For NSAID use 1 day or more per week for at least 6 months, the overall odds ratios were slightly reduced but compatible with 1.0. However, the odds ratios for use 4 days or more per week for at least 5 years were statistically significantly reduced, 0.5, based on comparisons to either cancer or noncancer controls, and these results were consistent across the study centers. Results for aspirin and nonaspirin NSAIDs were similar to those for NSAIDs overall. The results were unchanged when the main analyses were repeated for use that began 2 or more years previously, suggesting that the findings were not distorted by analgesic use taken for early symptoms of ovarian cancer.

The present study used cancer and noncancer control groups comprising women admitted for illnesses judged to be unrelated to regular analgesic use. The similarity of the prevalence of acetaminophen use and NSAID use across the diagnostic categories among the controls suggests that the control selection was unbiased. In addition, the odds ratio point estimates obtained separately with each control group for the more prevalent drug exposures were similar. Major potential risk factors for ovarian cancer were found not to confound the analyses.

We considered metastatic ovarian cancer separately because such cases would inevitably have been admitted to hospital and would, therefore, have been less likely to have been affected by selection bias. The point estimates of the odds ratio for acetaminophen use for cases of metastatic ovarian cancer were smaller than those for nonmetastatic cancer, although the estimates were compatible with a uniform estimate. For NSAID, use the odds ratios were also smaller in the metastatic cancer group. The differences may well have been attributable to chance. It could be postulated that the difference in the findings between metastatic and nonmetastatic cases is explained by selective admission of cases with earlier stage ovarian cancer who tended to use analgesics regularly. However, it is unlikely that admission would have been related to use of over-the-counter medications. Moreover, the distribution of physician visits in the previous year was quite similar for the metastatic and nonmetastatic cases. Previous studies did not carry out analyses according to the presence or absence of metastatic disease. In the study of Cramer *et al.* (1), inverse associations with acetaminophen use were seen for both borderline and invasive ovarian cancer.

A major problem in studying analgesic use is inaccuracy in reporting. In the study of Cramer *et al.* (1), participants were asked about the duration of use, age started, and frequency of use of over-the-counter acetaminophen, aspirin, and ibuprofen 1 day or more per week for at least 6 months. Major brand names were mentioned, but hundreds of products have been marketed in the past or are now on the market. In the Cancer Prevention Study II (2), information was collected on the use of aspirin and of one brand of acetaminophen, Tylenol, during the month before entry to the study; the number of times in the month and the duration of use were recorded only for women who used the drugs in that month. No information was collected on use that might have ended before the month before entry, nor were data collected on drug use during the course of follow-up. Details of the methods used to ascertain acetaminophen and NSAID use in the case-control study of Moysich *et al.* (3), published only as an abstract, are not available. The Case-Control Surveillance Study assesses the effects of many drugs (4). Because it is not feasible to ask specifically about the thousands of drugs marketed now and in the past, histories of drug use are elicited by questions about indications for use, such as pain. For every episode of use, the drug name, date started, duration, and frequency of use are recorded. To a greater or lesser extent, all of the studies to date will have underascertained and misclassified the use of acetaminophen and NSAIDs. Misclassification, if random, would have tended to weaken real associations with ovarian cancer.

Using the same methods and the same database as in the present analysis, we found previously a strong statistically significant inverse association between recent regular aspirin use and the risk of large bowel cancer (8), an association that has been confirmed in many subsequent studies (9, 10). How-

ever, the prevalence of regular and long duration aspirin use was appreciably greater than that of acetaminophen use, providing much more statistical power to assess the use of aspirin. Regular acetaminophen use has been uncommon until relatively recently. Studies with much larger numbers of long-term users than in those to date are required for an informative analysis of acetaminophen use in relation to ovarian cancer. Furthermore, future studies need to improve the ascertainment of the many drugs that contain acetaminophen and to improve the characterization of aspects of use.

In conclusion, the analyses conducted since the study of Cramer *et al.* (1), including the present one, provide only weak support for an inverse association between acetaminophen use and epithelial ovarian cancer risk, although they are compatible with such an association. Data providing evidence of a biological mechanism for an inverse association are scanty. Although equivocal in terms of protection, the results to date indicate that there is no adverse effect of acetaminophen use on risk. For NSAID use, the present study raises the possibility of an inverse association with long-term use. This result could be attributable to chance or unidentified bias and requires confirmation. The sparse evidence available from other studies suggests no association of NSAID use with ovarian cancer risk. There are virtually no animal data that bear on the possibility of a protective effect of NSAIDs against ovarian cancer. Clearly, more biological and epidemiological data are needed to clarify the relation of use of acetaminophen and NSAIDs to risk of ovarian cancer.

Acknowledgments

We thank the many physicians who allowed their patients to be interviewed; the nurse-interviewers who collected the data; Marguerite Angeloni, who coordinated data collection; and Leonard Gaetano, who was responsible for data management. The following hospitals participated in this study: in New York, Brookhaven Memorial Hospital, Lenox Hill Hospital, Memorial Sloan-Kettering Cancer Center, and New York Hospital; in Philadelphia, American Oncological Hospital, Crozier Chester Medical Center, Hahnemann University Hospital, Hospital of the Medical College of Pennsylvania, Hospital of the University of Pennsylvania, Lankenau Hospital, Montgomery Hospital, Pennsylvania Hospital, Presbyterian Hospital, and Thomas Jefferson University Hospital; in Massachusetts, Sancta Maria, Beth Israel, Newton Wellesley, Mount Auburn, Massachusetts General, Brigham and Women's, University, and New England Medical Center; in Maryland, Johns Hopkins, University of Maryland, Sinai, Greater Baltimore Medical Center, and Mercy Medical Center.

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Cancer Epidemiol Biomarkers Prev 2000;9:933-937.