

### Short Communication

## Regular Use of Analgesic Drugs and Ovarian Cancer Risk

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### Abstract

Analgesics have been shown to reduce risk for colorectal cancer. Results from three recent reports (D. W. Cramer *et al.*, *Lancet*, 351: 104–107, 1998; C. Rodriguez *et al.*, *Lancet*, 352: 1354–1355, 1998; L. Rosenberg *et al.*, *Cancer Epidemiol. Biomark. Prev.*, 9: 933–937, 2000) suggest that these drugs might be associated with decreased risk for ovarian cancer. In this hospital-based case-control study, we compared 547 patients with ovarian cancer to 1094 age-matched patients with nonneoplastic conditions. All of the participants received treatment at the Roswell Park Cancer Institute between 1982 and 1998 and completed a comprehensive epidemiological questionnaire that included information on demographics, life-style factors, and reproductive characteristics as well as frequency and duration of aspirin and acetaminophen use. Women who reported that they had used one or more of these agents at least once a week for at least 6 months were classified as analgesic users. Logistic regression was used to compute crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Aspirin users were not at reduced risk of ovarian cancer compared with nonusers (adjusted OR, 1.00; CI, 0.73–1.39). There was also no evidence of a decrease in risk as a function of greater frequency of use or prolonged duration of use. Regular acetaminophen use was associated with a reduced risk (adjusted OR, 0.56; 95% CI, 0.34–0.86), and risk reductions were observed for women with the greatest frequency of use (adjusted OR, 0.32; 95% CI, 0.09–1.08) and longest duration of use (adjusted OR, 0.51; 95% CI, 0.27–0.97). These data suggest that regular use of acetaminophen, but not aspirin, may be associated with lower risk of ovarian cancer.

### Introduction

Regular use of aspirin and other nonprescription analgesics has been consistently associated with reduced risk of colorectal

cancer and adenoma (1–4), possibly attributable to analgesic-related inhibition of prostaglandin synthesis, enhancement of cellular immune response, or induction of apoptosis (5–8). A number of epidemiological studies have investigated the potential protective effect of analgesics with respect to other cancer sites. There is some evidence that regular and prolonged analgesic use is associated with reduced risk of cancers of the esophagus (3, 9, 10), stomach (3, 9, 11), lung (12), and female breast (12–14).

The association between analgesic use and ovarian cancer risk was initially addressed in a hospital-based case-control study conducted in Greece (15). Among 189 epithelial ovarian cancer cases and 200 hospital visitor controls, Tzonou *et al.* observed that women classified as frequent analgesic users were at reduced risk for ovarian cancer compared with nonusers. No information on type of analgesic was available. More recently, Cramer *et al.* (16) reported findings from a population-based case-control study of 563 epithelial ovarian cancer and 523 population controls. Their results indicated a slight reduction in risk among aspirin users, but this effect was more pronounced among acetaminophen users. Similarly, Rodriguez *et al.* (17) observed reduced mortality of ovarian cancer in association with daily acetaminophen use in the American Cancer Society Cancer Prevention Study II, which included 676,526 women with 1573 ovarian cancer deaths after 12 years of follow up. In response to the latter two studies, Rosenberg *et al.* (18) compared analgesic use among 780 ovarian cancer patients and 2053 cancer controls, as well as 2570 noncancer controls. Results indicated that there was no strong evidence to suggest that acetaminophen was associated with reduced risk. However, regular use of NSAIDs,<sup>2</sup> including aspirin, was related to lower risk of ovarian cancer. Another recent hospital-based case-control study of 749 cases and 898 controls failed to provide evidence for a reduced risk of ovarian cancer in association with aspirin use (19). The effect of acetaminophen use on risk was not assessed.

In light of the limited and inconsistent body of evidence, we conducted a hospital-based case-control study to further investigate the association between the regular use of analgesics and the risk of epithelial ovarian cancer.

### Materials and Methods

**Study Population.** The study population included women admitted to the RPCI between 1982 and 1998, who agreed to complete a comprehensive epidemiological questionnaire. The case group consisted of 547 women with primary incident epithelial ovarian cancer, identified from the RPCI tumor registry and the diagnostic index. Informed consent was obtained from all participants. Patients in the case group were predominantly Caucasian (98%) and ranged in age from 20 to 87 years.

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<sup>2</sup> The abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; RPCI, Roswell Park Cancer Institute; PEDS, Patient Epidemiology Data System; OR, odds ratio; CI, confidence interval.

Controls included 1094 women who received medical services at RPCI for nonneoplastic conditions, and who were randomly selected from a pool of 5700 eligible women. The most frequently used services for the control patients included the breast clinic (28%), gynecology clinic (17%), surgery (15%), and dermatology clinic (11%). These women came to RPCI with a suspicion of neoplastic disease, but were not diagnosed with either benign or malignant conditions. Similar to cases, women in the control group were predominantly Caucasian and ranged in age between 25 and 90 years. Controls were frequency matched to cases by 5-year age intervals.

**Questionnaire.** All of the participants completed the PEDS questionnaire, which is offered to all new patients as part of the admission process and is returned by approximately 50% of new patients. The 16-page instrument covers information on reproductive and medical histories, family history of cancer, occupational and environmental exposures, tobacco and alcohol consumption, and diet. The instrument also assessed aspirin and acetaminophen use relevant to the period prior to the onset of disease. Specifically, the instrument queried: 'If you are currently ill, indicate how often you took these medications before the illness'. Participants provided information on how many times a week and for how many years they took either aspirin or acetaminophen preparations. Women who reported use of these agents at least once a week for 6 consecutive months were classified as regular analgesic users. Dosage of use was assessed by comparing women who were classified as nonusers to women who reported that they had taken either of the analgesics one to six times per week or seven or more times per week. Duration of use was evaluated by comparing nonusers to women who took analgesics for 6 months to 10 years or >10 years. Reason for analgesic use was unavailable for these analyses.

**Statistical Analyses.** Descriptive analyses included Student *t* tests of means for cases and controls for continuous variables, and  $\chi^2$  tests for categorical variables. Unconditional logistic regression was used to calculate ORs and 95% CIs. ORs were adjusted for potential confounders, including age, age at first birth, history of tubal ligation, parity, presence of irregular menses, and family history of ovarian cancer. Covariates were only included in the final regression model if they were established risk factors in these data or changed the observed risk estimates by at least 15%.

## Results

Descriptive characteristics of ovarian cancer cases and hospital controls are shown in Table 1. Cases were significantly ( $P < 0.05$ ) more likely than controls to be nulliparous (24.3 versus 17.3%), to have an older age at first pregnancy (23.7 versus 22.3 years), and to have a positive family history of ovarian cancer (7.9 versus 3.1%). Cases were significantly less likely than controls to have a personal history of tubal ligation (12.7 versus 18.3%) and to report irregular menses (12.3 versus 16.9%). Cases were more likely to be college educated (47.5 versus 44.4%) and to have never used oral contraceptives (69.2 versus 67.0%), but these differences were not statistically significant.

In this study population, ~12% of cases and controls were classified as regular aspirin users, which is similar to the prevalence of aspirin use reported in the studies conducted by Cramer *et al.* (16) and Rosenberg *et al.* (18). About 5% of cases and 9% of controls were classified as regular acetaminophen users; again, this is consistent with the results reported by Cramer *et al.* (16) but higher than the prevalence of use (~3.5%

Table 1 Descriptive characteristics of ovarian cancer cases and hospital controls—RPCI, Buffalo, NY 1982–1996

	Cases (n = 547)	Controls (n = 1094)	P
Age <sup>a</sup>	54.7 (13.7)	54.5 (13.7)	ns <sup>b</sup>
Education <sup>c</sup>			
Up to high school	286 (52.5)	608 (55.6)	
College	259 (47.5)	486 (44.4)	ns
Tubal ligation <sup>c</sup>			
Yes	69 (12.7)	199 (18.3)	
No	475 (87.3)	887 (81.7)	<0.05
Oral contraceptive use <sup>c</sup>			
Ever	168 (30.8)	358 (33.0)	
Never	377 (69.2)	728 (67.0)	ns
Regularity of menses <sup>c</sup>			
Regular	478 (87.7)	902 (83.1)	<0.05
Irregular	67 (12.3)	183 (16.9)	
Age at menarche <sup>a</sup>	13.7 (9.2)	13.2 (6.7)	ns
Parity			
Nulliparous	131 (24.3)	186 (17.3)	
1–2	191 (35.5)	373 (34.7)	
3–4	175 (32.5)	379 (35.3)	
5+	41 (7.6)	137 (12.7)	<0.01
Age at first pregnancy <sup>a,d</sup>	23.7 (4.5)	22.3 (5.0)	<0.05
Family history of ovarian cancer <sup>c</sup>			
No	504 (92.1)	1060 (96.9)	<0.05
Yes	43 (7.9)	34 (3.1)	

<sup>a</sup> Mean (SD).

<sup>b</sup> ns, not significant.

<sup>c</sup> n (%).

<sup>d</sup> Among parous women.

for cases and controls) in the recent Rosenberg *et al.* (18) study. Risk of ovarian cancer associated with analgesic use is shown in Table 2. Regular aspirin use was not related to ovarian cancer risk (adjusted OR, 1.00; 95% CI, 0.79–1.39), nor was increased dosage (adjusted OR, 0.87; 95% CI, 0.54–1.39 for seven or more tablets per week) or prolonged duration of use (adjusted OR, 0.90; 95% CI, 0.61–1.32 for 11 or more years of use). Regular use of acetaminophen, on the other hand, was associated with a pronounced, statistically significant decrease in risk of ovarian cancer (adjusted OR, 0.56; 95% CI, 0.34–0.86). Compared with women classified as nonusers of acetaminophen, we observed linear relationships with decreased risk as a function of increased dose, with an adjusted OR of 0.62 (95% CI, 0.37–0.98) for the use of one to six tablets per week and an adjusted OR of 0.32 (95% CI, 0.09–1.08) for the use of more than seven tablets per week. It should be pointed out, however, that the latter OR is based on only three cases. Similar inverse associations were observed for duration of use; acetaminophen use, lasting 1–10 years and  $\geq 11$  years, was associated with 40% (95% CI, 0.34–1.07) and nearly 50% (95% CI, 0.27–0.97) reductions in risk, respectively.

## Discussion

In this hospital-based case-control study, we investigated the associations between regular use of aspirin and acetaminophen and epithelial ovarian cancer risk. Our results do not support the notion that regular aspirin use plays a role in the chemoprevention of ovarian neoplasm. In contrast, we observed evidence for a potential protective effect of acetaminophen use on ovarian cancer risk. We demonstrated statistically significant or borderline significant risk reduction for regular use, higher-dose use, and prolonged use of these preparations.

Table 2 Risk of ovarian cancer in association with analgesic use—RPCI, Buffalo, NY 1982–1996

	Cases <i>n</i> (%)	Controls <i>n</i> (%)	Crude OR (95% CI)	Adjusted OR <sup>a</sup> (95% CI)
Aspirin use				
Nonuser	480 (87.8)	959 (87.7)	1.0	1.0
Regular user <sup>b</sup>	67 (12.2)	135 (12.3)	0.99 (0.73–1.36)	1.0 (0.73–1.39)
1–6 tablets/wk	37 (6.8)	70 (6.4)	1.05 (0.70–1.80)	1.14 (0.74–1.74)
7+ tablets/wk	30 (5.5)	65 (5.9)	0.92 (0.59–1.44)	0.87 (0.54–1.39)
0.5–10 yr of use	22 (4.0)	33 (3.0)	1.33 (0.77–2.31)	1.32 (0.75–2.34)
11+ yr of use	45 (8.2)	102 (9.3)	0.88 (0.61–1.27)	0.90 (0.61–1.32)
Acetaminophen use				
Nonuser	518 (94.7)	996 (91.0)	1.0	1.0
Regular user <sup>b</sup>	29 (5.3)	98 (9.0)	0.57 (0.37–0.87)	0.56 (0.34–0.86)
1–6 tablets/wk	26 (4.8)	78 (7.1)	0.64 (0.41–1.01)	0.62 (0.37–0.98)
7+ tablets/wk	3 (0.5)	19 (1.7)	0.30 (0.09–1.03)	0.32 (0.09–1.08)
0.5–10 yr of use	16 (2.9)	51 (4.7)	0.60 (0.34–1.07)	0.60 (0.34–1.07)
11+ yr of use	13 (2.4)	47 (4.3)	0.53 (0.29–0.99)	0.51 (0.27–0.97)

<sup>a</sup> OR adjusted for age, age at first birth, history of tubal ligation, parity, presence of irregular menses, and family history of ovarian cancer.

<sup>b</sup> Regular use defined as self-reported use at least once a week for 6 consecutive months.

Our findings are consistent with two recent investigations. Cramer *et al.* (16) conducted a population-based case-control study in New England and reported significantly reduced risk for women who were regular acetaminophen users, as well as pronounced reductions associated with increased dose, duration, and tablet-years. Similar to our findings, these associations were not apparent for aspirin users. Results from the Cancer Prevention Study II indicated that daily acetaminophen use was associated with a pronounced decrease in ovarian cancer mortality, although no evidence for a dose-response relationship was apparent, nor was prolonged duration of use associated with decreased mortality (17). On the other hand, our results are quite different from those most recently reported by Rosenberg *et al.* (18). Although similar in design compared with our study, the previous study of Rosenberg *et al.* (18) observed risk reductions associated with NSAIDs use, but not with acetaminophen use.

In contrast to the association of aspirin with colon carcinogenesis, there is no clear biological mechanism to explain the role of acetaminophen in preventing ovarian neoplasms. It is improbable that acetaminophen reduces risk via a prostaglandin inhibitor pathway, because of its limited anti-inflammatory and prostaglandin inhibitory properties. Cramer *et al.* (16) proposed that the decrease in risk associated with acetaminophen use might be explained by its antigonadotropic effect. In fact, Cramer *et al.* (20) demonstrated in a separate clinic-based observational study that women who regularly used acetaminophen had significantly lower gonadotropin and estradiol levels than women who used other types of analgesics or no drugs.

Several methodological issues should be considered in interpreting these results. As in all case-control studies, bias could have affected the validity of the current findings. Selection bias is likely to have occurred in this investigation. The ovarian cancer patient group was restricted to women who were treated at RPCI, a large regional cancer treatment center, and are not likely to represent the general population of ovarian cancer patients in the western New York region. However, it is unlikely that self-reported analgesic use would be different for RPCI patients than for women treated in different facilities.

Furthermore, in this study, the control group consisted of female patients who received medical services at RPCI for a large variety of nonneoplastic conditions. The use of hospital controls might introduce bias, because of the possibility that some controls were suffering from conditions that would make them more likely to use analgesic drugs. Thus, it is feasible that we failed to observe modest risk reductions in association with aspirin because of the greater prevalence of analgesic among some controls. On the other hand, we consistently observed risk reductions in association with acetaminophen use and consistently failed to see these relationships for aspirin use, which suggests that it is improbable that greater prevalence of analgesic use among controls would be restricted to acetaminophen only. In addition, hospital controls were selected from a large pool of eligible participants with a wide variety of diagnostic groups, minimizing bias arising from potential overrepresentation of patients with characteristics that might be associated with the exposures. However, no significant differences with respect to analgesic use were observed for the most common diagnostic categories among controls. Selection bias may have also been introduced because of the low participation rate in this study. Only about 50% of eligible cases and controls agreed to complete the PEDS questionnaire. We have no way of ascertaining whether or not those women who refused to complete the instrument differed from participants with respect to the exposures of interest. Nevertheless, previous studies that used the PEDS database and faced the same methodological issue, consistently replicated established epidemiological associations for a variety of cancer sites, including ovary (21), colon (22), breast (23), prostate (24), and lung (25).

Recall bias is always a problem in case-control studies of cancer. However, in this investigation, it may have been less of an issue, because of our use of hospital controls. Furthermore, the questionnaire used in this investigation places no particular emphasis on any specific item. Thus, there is little reason to believe that cases were more motivated than controls to recall analgesic use. Exposure misclassification may also have affected our results, because we based our analyses on self-reported analgesic use and were not able to independently

verify this information. Also, the questionnaire did not assess the specific doses of analgesic preparations, such as regular or extra-strength tablets. Yet, it is unlikely that this potential misclassification was differential in nature; again, we consistently observed risk reduction for acetaminophen but not for aspirin, and there is no reason to believe that participants would be biased to over-report one analgesic over the other.

Another limitation relates to the fact that no information on history of migraines, headaches, and menstrual or arthritic pain was available, nor did the questionnaire assess reasons for analgesic use. Thus, it is possible that our findings are biased because of a greater prevalence of conditions associated with analgesic use among controls.

In summary, in this hospital-based case-control study of ovarian cancer, we did not observe an association between aspirin use and risk, but found some suggestive evidence for a potential role of acetaminophen in the prevention of ovarian cancer. Clearly, future research is needed to further explore this association. Laboratory investigations should be conducted to further define the biological mechanism by which acetaminophen might influence risk. Future epidemiological investigations should use larger sample sizes to ensure that a sufficiently large proportion of women are regular and long-term acetaminophen users.

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