Regular Analgesic Use and Risk of Endometrial Cancer

Kirsten B. Moysich,[1] Julie A. Baker,[1] Kerry J. Rodabaugh,[2] and Jeannine A. Villella[2]

Departments of [1]Epidemiology and [2]Surgery, Division of Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, New York

Abstract

Background: **Analgesic use has been implicated in the chemoprevention of a number of solid tumors, but thus far, no previous research has focused on the role of aspirin in endometrial cancer etiology.**

Methods: **We conducted a hospital-based case-control study of 427 women with primary, incident endometrial cancer, and 427 age- and residence-matched controls without benign or malignant neoplasms. All participants received medical services at Roswell Park Cancer Institute in Buffalo, NY, and completed a comprehensive epidemiologic questionnaire. Women who reported analgesic use at least once a week for at least 6 months were classified as regular users and served as the reference group throughout the analyses. We used unconditional logistic regression analyses to compute crude and adjusted odds ratios (OR) with corresponding 95% confidence intervals (CI).**

Results: **Compared with nonusers, regular aspirin users were not at reduced risk of endometrial cancer (adjusted OR, 0.91; 95% CI, 0.66-1.26), nor were women with the highest frequency, duration, or cumulative lifetime aspirin use. When the sample was divided by body mass index status, regular aspirin use was not associated with risk among women classified as normal weight or overweight, but a significant risk reduction was seen for obese women (adjusted OR, 0.50; 95% CI, 0.27-0.92). Significant decreases in risk were also observed for obese women with the greatest frequency, duration, and cumulative aspirin use. No significant associations in the overall sample or among obese women were noted for acetaminophen use.**

Conclusion: **We observed no evidence of an overall chemoprotective effect of aspirin on endometrial cancer risk, but the significant risk reductions among obese women warrant further investigation.** (Cancer Epidemiol Biomarkers Prev 2005;14(12):2923–8)

Introduction

Endometrial cancer is the most common gynecologic malignancy in North America and the fourth most common female cancer, accounting for 6% of all cancers in women (1). The American Cancer Society estimates that 40,880 women will be diagnosed with endometrial cancer and 7,310 women will die of this disease in 2005 (1). Primarily a disease of postmenopausal women, affected women typically present with postmenopausal vaginal bleeding, resulting in earlier diagnosis than for most other gynecologic malignancies (2). Seventy-five percent of patients present with tumors that are confined to the uterine corpus at the time of diagnosis (3). Established risk factors for endometrial cancer include age, Caucasian race, history of complex atypical hyperplasia, unopposed estrogen use, Tamoxifen use, history of diabetes mellitus, history of hypertension, obesity, and nulliparity (2). Although family history of endometrial cancer is not a risk factor, the presence of the hereditary nonpolyposis colorectal cancer syndrome is strongly related to increased risk, as endometrial cancer is the most common noncolonic malignancy in hereditary nonpolyposis colorectal cancer (3).

Nonsteroidal anti-inflammatory drugs (NSAID), such as aspirin, have gained attention as potential chemopreventive agents for several cancers, including colorectal cancer and adenoma (4-7), esophageal (6, 8, 9), stomach (6, 8, 10), ovarian (11-13), and breast cancer (14-16). Decreased cancer risk may be attributable to NSAID-related inhibition of cyclooxygenase-2 (COX-2) expression and subsequent prostaglandin synthesis, enhancement of cellular immune response, or induction of apoptosis (17-20). There have been few studies that address the role of analgesics in the chemoprevention of endometrial cancer. Clinical studies have shown that COX-2 is expressed in both normal endometrial tissue (21) and endometrial tumor tissue (21, 22). In cell culture experiments, aspirin has been shown to reduce the cellular proliferation of endometrial cancer cells in a dose-dependent manner and to induce apoptosis (23, 24). Thus, it is biologically plausible that aspirin might influence endometrial cancer risk by inhibiting COX-2 expression in the endometrial tissue. We are unaware of any previous epidemiologic investigation that has focused on the association between aspirin use and risk of endometrial cancer. We conducted a hospital-based case-control study at Roswell Park Cancer Institute to address this gap in the literature. We also conducted analyses on the association between acetaminophen use and risk of this disease. The purpose of including acetaminophen, which does not have COX-2-inhibitory properties, is to rule out the possibility that our results might reflect the effect of factors associated with greater use of pain medication in general, rather than the use of aspirin in particular. Thus, we hypothesized that aspirin use, but not acetaminophen use, would be associated with reduced risk of endometrial cancer.

Materials and Methods

Study population. The study population included women who received medical services at Roswell Park Cancer Institute (RPCI) in Buffalo, NY, between 1982 and 1998, and who agreed to complete a comprehensive epidemiologic questionnaire. These data collection efforts were approved by the RPCI Institutional Review board. Participants with missing medication data were excluded. Informed consent was obtained from all participants. The case group consisted of 427 individuals with primary, incident endometrial cancer, identified from the RPCI tumor registry. Controls included 427 individuals, randomly selected from a pool of 4,291 eligible women who received medical services at RPCI for nonneoplastic conditions. These participants came to RPCI with a suspicion of

Received 6/20/05; revised 9/22/05; accepted 10/10/05.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Kirsten B. Moysich, A-316 Carlton House, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263. Phone: 716-845-8004; Fax: 716-845-1126; E-mail: kirsten.moysich@roswellpark.org

doi:10.1158/1055-9965.EPI-05-0457

neoplastic disease, but were not diagnosed with either benign or malignant tumors. Controls were most commonly treated for genitourinary disorders (33%), gastrointestinal disorders (14%), circulatory disorders (8%), breast disorders (7%), and infectious disorders (5%). Conditions that were prevalent in <5% of controls included skin disorders, ill-defined symptoms, musculoskeletal disorders, metabolic disorders, injuries, and neurologic disorders. For 54 controls (12%), the underlying diagnosis was not available; it is likely these individuals came to RPCI for specialized testing or procedures, but received their medical care elsewhere. Controls were frequency-matched to cases on 5-year age and residence inside or outside western New York.

Questionnaire. All participants completed the Patient Epidemiology Data System (PEDS) questionnaire, which was offered to all new patients as part of the admission process, and was returned by ~50% of new patients. The 16-page instrument covered information on tobacco and alcohol consumption, family history of cancer, occupational and environmental exposures, reproductive and medical histories, 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 aspirin or acetaminophen. Participants who reported use of these medications at least once a week for 6 months were classified as regular users. Frequency of use was assessed by comparing participants who were classified as nonusers to participants who reported that they had taken aspirin either one to six times per week or seven or more times per week. Duration of use was evaluated by comparing nonusers to participants who took aspirin for 6 months to 10 years or >10 years. We also evaluated a combined measure of frequency and duration by computing tablet years (tablets per day × years of use). Reason for aspirin use was unavailable for these analyses.

Statistical analyses. Descriptive analyses included Student's *t* tests of means for cases and controls for continuous variables, and χ^2 tests for categorical variables. Unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI). ORs were adjusted for potential confounders, including age, education, body mass index (BMI), parity, age at menarche, and age at menopause. Covariates were only included in the final regression model if they were established risk factors in these data, changed the observed risk estimates by at least 15%, or significantly contributed to explaining the variance in the statistical models. Variables that were evaluated but not included in the final multivariate model included year of participation, smoking status, menopausal status, prior vaginal infection, and oral contraceptive use. The PEDS instrument included questions regarding hormone replacement therapy (HRT) use. Unfortunately, the instrument did not distinguish between unopposed estrogen and combined estrogen/progesterone preparations. In light of the fact that unopposed estrogen, but not combined HRT, is a strong risk factor for endometrial cancer, we were concerned that our HRT variable was unable to distinguish this important difference. As such, we did not include this variable in our statistical model. However, we conducted descriptive analyses and detected no notable differences in the prevalence of regular aspirin use or use patterns between women who reported that they used HRT and those who did not report such use. Furthermore, whereas the instrument included a question regarding the prevalence of diabetes mellitus, such data was missing for a large proportion of women and therefore this variable was not considered in the statistical analyses. Participants classified as nonusers (i.e., those who did not report having used aspirin or acetaminophen at least once a week for at least 6 months) served as the referent category throughout the logistic regression analyses.

Results

The characteristics of the 427 patients with endometrial cancer and the 427 hospital control participants are displayed in Table 1. Both groups were predominately Caucasian and did not differ by educational attainment or family history of endometrial cancer. Although very similar with respect to age, cases were more likely to be postmenopausal than controls, which is likely due to the fact that the most common symptom of endometrial cancer (vaginal bleeding) is more likely to lead to medical intervention in postmenopausal women. Cases were less likely than controls to have ever smoked cigarettes regularly or to have used oral contraceptives. As expected, endometrial cancer patients had a higher BMI, earlier onset of menarche, later onset of menopause, and fewer children than hospital controls. No differences between the groups were noted for age at first pregnancy or birth, but cases tended to breast-feed for slightly shorter durations compared with controls.

Crude and adjusted associations between analgesic use and risk of endometrial cancer are displayed in Table 2. Women classified as regular aspirin users were not at lower risk of endometrial cancer than nonusers in this study population (adjusted OR, 0.91; 95% CI, 0.66-1.26). We also observed no significant risk reductions when nonusers were compared with women who took seven or more aspirin tablets per week (adjusted OR, 0.77; 95% CI, 0.49-1.22); women who took aspirin regularly for >10 years (adjusted OR, 1.05; 95% CI, 0.71-1.56); or women who were classified as having >10 tablet years of cumulative use (adjusted OR, 1.20; 95% CI, 0.75-1.92). Similarly, no significant associations were apparent for regular (adjusted OR, 0.96; 95% CI, 0.60-1.54), more frequent use (adjusted OR, 1.12; 95% CI, 0.42-2.98), prolonged duration of use (adjusted OR, 0.69; 95% CI, 0.33-1.46), and greater cumulative use of acetaminophen (adjusted OR, 0.49; 95% CI, 0.15-1.60). It should be pointed out that the prevalence of regular acetaminophen use was low (11% among controls), resulting in the small number of participants in these subgroups, which likely accounts for these inconsistent findings.

We further examined if the association between analgesic use and risk of endometrial cancer was modified by level of BMI. Participants were classified as ''ideal weight'' (BMI, 18.5-24.9 kg/m^2), overweight (BMI, 25-30 kg/m^2), or obese (BMI, >30 kg/m^2). Twelve and 15 participants were excluded from these analyses due to missing BMI data or being classified as underweight (BMI, <18.5 kg/m^2), respectively. Results from these analyses are presented in Table 3. Associations between regular aspirin use and endometrial cancer did not differ markedly from those observed in the total sample among ideal weight (adjusted OR, 1.16; 95% CI, 0.71-1.90) or overweight women (adjusted OR, 1.21; 95% CI, 0.65-2.23). In contrast, a statistically significant risk reduction was observed for obese women who were regular aspirin users (adjusted OR, 0.50; 95% CI, 0.27-0.92). Nonsignificant risk elevations were observed for women who were regular acetaminophen users with ideal weight (adjusted OR, 1.49; 95% CI, 0.82-2.12) and overweight (adjusted OR, 2.00; 95% CI, 0.76-4.52). However, these estimates were based on very small numbers as indicated by the width of the corresponding CIs. No association between regular acetaminophen use and risk was apparent for obese women (adjusted OR, 0.89; 95% CI, 0.40-1.82). To further investigate the interesting risk reduction associated with aspirin use among obese women, we investigated the effects

Table 1. Characteristics of 427 endometrial cancer patients and 427 hospital controls—Roswell Park Cancer Institute (1982-1998)

Characteristic	Cases, *n* (%)	Controls, *n* (%)	*P**
Non-Hispanic Caucasian	418 (97.9)	422 (98.8)	not significant
College graduate	73 (17.1)	86 (20.2)	not significant
First-degree relative with endometrial cancer	1 (0.2)	1 (0.2)	not significant
Ever smoked cigarettes regularly	158 (37.1)	184 (43.5)	0.057
Postmenopausal	402 (95.7)	369 (88.7)	<0.001
Ever used oral contraceptives	62 (14.8)	82 (19.5)	0.07
	Mean (SD)	Mean (SD)	*P*†
Age (y)	62.2 (11.7)	62.1 (11.8)	not significant
Year completed questionnaire	1988 (4.4)	1987 (4.1)	<0.001
Usual BMI (kg/m^2)	29.9 (8.4)	25.8 (5.7)	<0.001
Age at onset of menses (y)	12.7 (1.6)	13.0 (1.6)	0.007
Age at first pregnancy (y)	23.3 (4.8)	23.3 (4.7)	not significant
Age at first birth (y)	23.9 (4.7)	23.9 (4.6)	not significant
Lifetime duration of breast-feeding (mo)	3.8 (8.8)	4.7 (10.7)	not significant
Number of liveborn children	2.3 (1.7)	2.6 (1.9)	0.04
Age at menopause‡ (y)	48.8 (5.9)	46.2 (7.1)	<0.001

*Significance tested using χ^2 or Fisher's exact test, as appropriate.
†Significance tested using two-tailed Student's *t* test.
‡Among postmenopausal women.

of frequency, duration, and cumulative use in this subgroup (Table 4). We were not able to conduct such detailed analyses for acetaminophen use, due to the low prevalence of regular use of acetaminophen, which does not allow for further subclassification. As can be seen in Table 4, among obese women, we observed significant dose-response risk reduction for greater frequency (adjusted OR, 0.40; 95% CI, 0.18-0.92), prolonged duration (adjusted OR, 0.46; 95% CI, 0.22-0.96), and greater cumulative use of aspirin (adjusted OR, 0.49; 95% CI, 0.24-0.99).

Finally, we conducted some sensitivity analyses by examining whether or not prevalence of aspirin use was driven by a specific subgroup of controls, but we found no evidence of such potential bias. The prevalence of regular aspirin use in the disease site subgroups of controls was as follows: genitourinary disorders (45%), gastrointestinal disorders (33%), circulatory disorders (44%), breast disorders (36%), and infectious disorders (44%). Thus, all subgroups of controls were relatively close to 41% prevalence of aspirin use in the combined control group. We further compared cases to the groups of controls defined by the major diagnostic classifications and did not observe substantially different risk estimates for any particular subgroup of controls (data not shown).

Discussion

Results from this hospital-based case-control study do not lend support to the hypothesis that regular use of aspirin might be

Table 2. Association between regular aspirin and acetaminophen use and endometrial cancer—Roswell Park Cancer Institute (1982-1998)

	Cases, *n* (%)	Controls, *n* (%)	OR (95% CI)	Adjusted OR (95% CI)*
Regular aspirin user				
No†	249 (58.3)	252 (59.0)	Ref.	Ref.
Yes	178 (41.7)	175 (41.0)	1.03 (0.78-1.35)	0.91 (0.66-1.26)
Frequency of aspirin use				
Used one to six times per week	118 (27.6)	111 (26.0)	1.08 (0.79-1.47)	1.00 (0.69-1.46)
Used more than seven times per week	60 (14.1)	64 (15.0)	0.95 (0.64-1.41)	0.77 (0.49-1.22)
Duration of aspirin use				
Used for 1 to 10 years	82 (19.2)	83 (19.4)	1.00 (0.70-1.42)	0.77 (0.51-1.17)
Used for >10 years	96 (22.5)	92 (21.5)	1.06 (0.76-1.48)	1.05 (0.71-1.56)
Cumulative aspirin use				
Moderate use (≤10 tablet-yrs)‡	116 (27.2)	122 (28.6)	0.96 (0.71-1.31)	0.79 (0.55-1.14)
High use (>10 tablet-yrs)	62 (14.5)	53 (12.4)	1.18 (0.79-1.78)	1.20 (0.75-1.92)
Regular acetaminophen user				
No†	361 (84.5)	378 (88.5)	Ref.	Ref.
Yes	66 (15.5)	49 (11.5)	1.41 (0.95-2.10)	0.96 (0.60-1.54)
Frequency of acetaminophen use				
Used one to six times per week	53 (12.4)	39 (9.1)	1.42 (0.92-2.21)	0.92 (00.55-1.56)
Used more than seven times per week	13 (3.0)	10 (2.3)	1.36 (0.59-3.14)	1.12 (0.42-2.98)
Duration of acetaminophen use				
Used for 1 to 10 years	45 (10.5)	29 (6.8)	1.63 (0.997-2.65)	1.55 (0.65-2.05)
Used for >10 years	21 (4.9)	20 (4.7)	1.10 (0.59-2.06)	0.69 (0.33-1.46)
Cumulative acetaminophen use				
Moderate use (≤ 10 tablet-yrs)	59 (13.8)	38 (8.9)	1.63 (1.06-2.51)	1.08 (0.65-1.77)
High use (>10 tablet-yrs)	7 (1.6)	11 (2.6)	0.67 (0.26-1.74)	0.49 (0.15-1.60)

*Adjusted for age, education, BMI, parity, age at menarche, age at menopause and parity.
†Nonuser group served as reference group for all regression analyses. User defined as use of at least one tablet a week for at least 6 months.
‡Tablet-years defined as average number of tablets per day × years of use.

Table 3. Adjusted risk of endometrial cancer in association with regular aspirin and acetaminophen use, by BMI—Roswell Park Cancer Institute (1982-1998)

	All endometrial cancers, OR* (95% CI) [cases/controls]†	Ideal (BMI, 18.5-24.9 kg/m^2), OR‡ (95% CI) [cases/controls]†	Overweight (BMI, 25-30 kg/m^2), OR‡ (95% CI) [cases/controls]†	Obese (BMI, >30 kg/m^2), OR‡ (95% CI) [cases/controls]†
Regular aspirin user§				
No	249 (58)/252 (59)	65 (52)/138 (59)	72 (62)/71 (67)	100 (60)/34 (45)
Yes	178 (42)/175 (41)	60 (48)/96 (41)	45 (38)/35 (33)	70 (41)/41 (55)
Adjusted OR (95% CI)	0.91 (0.66-1.26)	1.61 (0.71-1.90)	1.21 (0.65-2.23)	0.50 (0.27-0.92)
Regular acetaminophen user§				
No§	361 (85)/378 (89)	107 (86)/211 (90)	96 (82)/96 (91)	146 (86)/63 (84)
Yes	66 (15)/49 (11)	18 (14)/23 (10)	21 (18)/10 (9)	24 (14)/12 (16)
Adjusted OR (95% CI)	0.96 (0.60-1.54)	1.49 (0.83-2.12)	2.00 (0.76-4.52)	0.89 (0.40-1.82)

*Adjusted for age, education, BMI, parity, age at menarche, age at menopause and parity.
†Cases/controls classified as regular user; *n* (%).
‡Adjusted for age, education and age at menopause.
§Defined as use of at least one tablet a week for at least 6 months.

effective in the chemoprevention of endometrial cancer. Compared with women who were classified as nonaspirin users, we did not observe significant risk reductions for women who regularly used aspirin or for prolonged aspirin use. Although we did not observe consistent patterns linking aspirin use to decreased risk of endometrial cancer, we found a nonsignificant 33% risk reduction for women who used aspirin daily or more often. Acetaminophen use was not associated with risk of endometrial cancer. However, when we stratified the sample according to BMI, we observed consistent statistically significant risk reductions among obese women for regular, more frequent, prolonged and cumulative use.

Potential mechanisms by which aspirin might influence cancer risk are subject to active investigations. Numerous investigations *in vitro* and in animal models have shown that aspirin, NSAIDs, and COX inhibitors possess anticancer effects in sites such as the colorectum, esophagus, stomach, breast, lung, and ovary (18, 23, 25). Biochemical methods have been postulated, and not fully determined, but include inhibition of COX activity and a resultant reduction in prostaglandins (23, 25). COX-2-selective inhibitors have been shown to produce chemopreventive effects by reducing cellular proliferation, inducing apoptosis, and modulating angiogenesis via inhibition of COX-2 activity (26). It is plausible that these mechanisms might also be relevant to endometrial cancer, in light of the observations that COX-2 is expressed in both normal endometrial tissue (21) and endometrial tumor tissue (21, 22), as well as *in vitro* evidence demonstrating that aspirin treatment reduces the cellular proliferation of endometrial cancer cells and induces apoptosis (23, 24).

Interestingly, we saw a significant 50% risk reduction for obese women who were classified as regular users, compared with obese women who did not use aspirin regularly. This finding is further strengthened by our subsequent observations of similar risk reductions associated with greater frequency, duration, and cumulative use of this drug among obese women. These preliminary findings seem to suggest that aspirin exerts a subtle chemoprotective effect in endometrial cancer. There is good evidence linking obesity to insulin resistance and subsequently to higher levels of inflammatory cytokines (27). Thus, the protective effect of regular aspirin use might be most relevant for women in a chronic proinflammatory state, but might be too subtle to detect in a study of this size among women without obesity-related chronic inflammation. Another potential mechanism by which aspirin use may confer protection for endometrial cancer among obese women relates to the observation that COX-2 levels are correlated with aromatase expression (28). Thus, it is plausible that obese women who do not use aspirin regularly have higher COX-2-induced aromatase levels and subsequently have greater aromatase-mediated local conversion of estradiol precursors to estradiol in adipose tissue.

Several methodologic issues should be considered in interpreting these results. As in all case-control studies, bias could have affected the validity of the current findings. The use of hospital controls might introduce bias, due to the possibility that some controls were suffering from conditions that could make them more likely to use aspirin. Thus, the potential greater likelihood of aspirin use in the control group might have exaggerated the decreased risk observed for obese

Table 4. Association between regular aspirin use and endometrial cancer in obese women (BMI, >30)—Roswell Park Cancer Institute (1982-1998)

	Cases, *n* (%)	Controls, *n* (%)	OR (95% CI)	Adjusted OR (95% CI)*
Aspirin use				
No†	100 (59)	34 (45)	Ref.	Ref.
Frequency of aspirin use				
Used one to six times per week	47 (28)	25 (33)	0.64 (0.34-1.19)	0.56 (0.28-1.13)
Used more than seven times per week	23 (13)	16 (21)	0.49 (0.23-1.03)	0.40 (0.18-0.92)
Duration of aspirin use				
Used for 1 to 10 years	36 (21)	18 (24)	0.68 (0.34-1.35)	0.53 (0.25-1.15)
Used for >10 years	34 (20)	23 (31)	0.50 (0.26-0.97)	0.46 (0.22-0.96)
Cumulative aspirin use				
Moderate use (≤10 tablet-yrs)‡	48 (28)	26 (35)	0.63 (0.34-1.16)	0.50 (0.22-1.13)
High use (>10 tablet-yrs)	22 (13)	15 (20)	0.50 (0.23-1.07)	0.49 (0.24-0.99)

*Adjusted for age, education, and age at menopause.
†Nonuser group served as reference group for all regression analyses. User defined as use of at least one tablet a week for at least 6 months.
‡Tablet-years defined as average number of tablets per day × years of use.

women. However, hospital controls were selected from a large pool of eligible participants with a wide variety of noncancer diagnostic groups, minimizing bias arising from potential overrepresentation of patients with characteristics that may be associated with the exposures. In fact, no significant differences with respect to aspirin use were observed for the most common diagnostic categories among controls. Furthermore, we conducted sensitivity analyses in which we compared cases to the groups of controls defined by the major diagnostic classifications of their conditions. Results from these analyses were very similar to our overall findings. Selection bias may have been introduced due to 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 individuals who refused to complete the instrument differed from participants with respect to aspirin use. Nevertheless, previous studies that used the PEDS database and faced the same methodologic issue, consistently replicated established epidemiologic associations for a variety of cancer sites, including the ovary (11, 29), colon (30), breast (31), prostate (32), and lung (33). Recall bias is a common problem in case-control studies of cancer. However, in this investigation, it may have been less of an issue, due to our use of hospital controls. Furthermore, the questionnaire used in this investigation places no particular emphasis on any specific item, which makes it unlikely that cases were more motivated than controls to recall aspirin use. Thus, although we cannot completely rule out the influence of bias, we do not believe that the observed risk reductions associated with aspirin use are the direct result of the potential sources of bias outlined above.

Exposure misclassification might have also affected our results, as we based our analyses on self-reported aspirin use and were not able to independently verify this information. Also, the questionnaire did not assess the specific doses of aspirin preparations, such as regular or low-dose tablets. It is possible that some women who took daily low-dose aspirin tablets (81 mg) were classified as heavier users than women who took regular aspirin tablets (325 mg) twice a week. Furthermore, we did not have detailed information on other NSAIDs that participants may have taken and cannot rule out the possibility that cases or controls may have been more likely to have taken preparations such as ibuprofen or prescription NSAIDs, which might have resulted in overestimated, underestimated, or entirely spurious results. However, it is unlikely that any of these potential sources of misclassification were differential in nature. Another limitation relates to the fact that we were unable to account for the potential confounding effect of unopposed estrogen replacement therapy. Although the PEDS questionnaire did include a question about use of HRT, the instrument did not distinguish between unopposed estrogen and combined estrogen and progesterone preparations. Whereas unopposed HRT use is clearly linked to risk of endometrial cancer, we observed no significant differences in aspirin use patterns among women who were HRT users and those who were not. Similarly, we were not able to evaluate the prevalence of diabetes mellitus as a potential confounder, as this information was missing for >85% of participants. It is possible that diabetic women are more likely to use aspirin, due to obesity-related joint pain.

Despite these limitations, there are several strengths associated with this study. First, this is the only study thus far that has attempted to establish a highly biologically plausible link between aspirin use and risk of endometrial cancer. Laboratory evidence has shown COX-2 expression in normal and tumor endometrial tissue (21, 22), as well as an antiproliferative effect of aspirin administration in endometrial cancer cell lines (23, 24). Thus, it is possible that aspirin might influence risk by inhibiting COX-2 expression in endometrial tissue. COX-2 inhibition may also lead to reduced aromatase induction and subsequent estradiol synthesis. Second, the study sample in this investigation was relatively large, allowing for a careful evaluation of aspirin use, including frequency of use effects, duration, and tablet years. Finally, our findings are strengthened by the observations that acetaminophen use was not associated with reduced risk of endometrial cancer in obese women. Thus, we can rule out the possibility that the risk reduction among obese women is associated with factors related to pain medication use in general, rather than aspirin use in particular.

In summary, in this first study of the role of aspirin use in the chemoprevention of endometrial cancer, we observed no strong evidence that aspirin use was associated with overall reduced risk of this disease. Significant decreases in risk were seen among obese women who were regular aspirin users, used aspirin more frequently, and used aspirin for prolonged durations. The latter findings warrant further investigation.

References

1. American Cancer Society. Cancer facts and figures, 2005. Atlanta: American Cancer Society; 2005.
2. DeVita VT, Hellman S, Rosenberg SA, editors. Cancer principles & practice of oncology. Philadelphia: Lippincott Williams & Wilkins; 2005.
3. Hoskins WJ, Perez CA, Young RC, Barakat RR, Markman M, Randall ME, editors. Principles and practice of gyncelogic oncology. Philadelphia: Lippincott Williams & Wilkins; 2005.
4. Collet JP, Sharpe C, Belzile E, Boivin JF, Hanley J, Abenhaim L. Colorectal cancer prevention by non-steroidal anti-inflammatory drugs: effects of dosage and timing. Br J Cancer 1999;81:62–8.
5. Rosenberg L, Louik C, Shapiro S. Nonsteroidal antiinflammatory drug use and reduced risk of large bowel carcinoma. Cancer 1998;82:2326–33.
6. Thun MJ. Aspirin and gastrointestinal cancer. Adv Exp Med Biol 1997;400A: 395–402.
7. Marnett LJ. Aspirin and related nonsteroidal anti-inflammatory drugs as chemopreventive agents against colon cancer. Prev Med 1995;24:103–6.
8. Farrow DC, Vaughan TL, Hansten PD, et al. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiol Biomarkers Prev 1998;7:97–102.
9. Funkhouser EM, Sharp GB. Aspirin and reduced risk of esophageal carcinoma. Cancer 1995;76:1116–9.
10. Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Aspirin protects against gastric cancer: results of a case-control study from Moscow, Russia. Int J Cancer 1999;82:473–6.
11. Moysich KB, Mettlin C, Piver MS, Natarajan N, Menezes RJ, Swede H. Regular use of analgesic drugs and ovarian cancer risk. Cancer Epidemiol Biomarkers Prev 2001;10:903–6.
12. Rosenberg L, Palmer JR, Rao RS, et al. A case-control study of analgesic use and ovarian cancer. Cancer Epidemiol Biomarkers Prev 2000;9:933–7.
13. Akhmedkhanov A, Toniolo P, Zeleniuch-Jacquotte A, Kato I, Koenig KL, Shore RE. Aspirin and epithelial ovarian cancer. Prev Med 2001;33: 682–7.
14. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology 1994;5:138–46.
15. Coogan PF, Rao SR, Rosenberg L, et al. The relationship of nonsteroidal anti-inflammatory drug use to the risk of breast cancer. Prev Med 1999; 29:72–6.
16. Harris RE, Namboodiri KK, Farrar WB. Nonsteroidal antiinflammatory drugs and breast cancer. Epidemiology 1996;7:203–5.
17. Subongkot S, Frame D, Leslie W, Drajer D. Selective cyclooxygenase-2 inhibition: a target in cancer prevention and treatment. Pharmacotherapy 2003;23:9–28.
18. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. J Natl Cancer Inst 2002;94:252–66.
19. Gupta RA, DuBois RN. Aspirin NSAIDs, colon cancer prevention: mechanisms? Gastroenterology 1998;114:1095–8.
20. Shiff SJ, Rigas B. The role of cyclooxygenase inhibition in the antineoplastic effects of nonsteroidal antiinflammatory drugs (NSAIDs). J Exp Med 1999;190:445–50.
21. Uotila PJ, Erkkola RU, Klemi PJ. The expression of cyclooxygenase-1 and -2 in proliferative endometrium and endometrial adenocarcinoma. Ann Medicine 2002;34:428–33.
22. Cao QJ, Einstein MH, Anderson PS, Runowicz CD, Balan R, Jones JG. Expression of COX-2, Ki-67, cyclin D1, and P21 in endometrial endometrioid carcinomas. Int J Gynecol Pathol 2002;21:147–54.
23. Gao J, Niwa K, Sun W, et al. Non-steroidal anti-inflammatory drugs inhibit cellular proliferation and upregulate cyclooxygenase-2 protein expression in endometrial cancer cells. Cancer Sci 2004;95:901–7.
24. Arango HA, Icely S, Roberts WS, Cavanagh D, Becker JL. Aspirin effects on endometrial cancer cell growth. Obstet Gynecol 2001;97:423–7.

25. Huls G, Koornstra JJ, Kleibeuker JH. Non-steroidal anti-inflammatory drugs and molecular carcinogenesis of colorectal carcinomas. Lancet 2003;362:230–2.
26. Stack E, DuBois RN. Role of cyclooxygenase inhibitors for the prevention of colorectal cancer. Gastroenterol Clin North Am 2001;30:1001–10.
27. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation 2005;111:1448–54.
28. Fowler JM, Ramirez N, Cohn DE, et al. Correlation of cyclooxygenase-2 (COX-2) and aromatase expression in human endometrial cancer: tissue microarray analysis. Am J Obstet Gynecol 2005;192:1262–71; discussion 1271–3.
29. Cornelison TL, Natarajan N, Piver MS, Mettlin CJ. Tubal ligation and the risk of ovarian carcinoma. Cancer Detect Prev 1997;21:1–6.
30. Suh O, Mettlin C, Petrelli NJ. Aspirin use, cancer, and polyps of the large bowel. Cancer 1993;72:1171–7.
31. Mettlin C, Croghan I, Natarajan N, Lane W. The association of age and familial risk in a case-control study of breast cancer. Am J Epidemiol 1990;131:973–83.
32. Mettlin C, Natarajan N, Huben R. Vasectomy and prostate cancer risk. Am J Epidemiol 1990;132:1056–61; discussion 1062–5.
33. Mettlin C. Milk drinking, other beverage habits, and lung cancer risk. Int J Cancer 1989;43:608–12.

Regular Analgesic Use and Risk of Endometrial Cancer

Kirsten B. Moysich, Julie A. Baker, Kerry J. Rodabaugh, et al.

Cancer Epidemiol Biomarkers Prev 2005;14:2923-2928.