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Aspirin and Acetaminophen Use and the Risk of Cervical Cancer

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Abstract

Objective—In this study, we investigated whether regular use of aspirin or acetaminophen was associated with risk of cervical cancer in women treated at an American cancer hospital.

Methods—This case-control study included 328 patients with cervical cancer and 1,312 controls matched on age and decade enrolled. Controls were women suspected of having but not ultimately diagnosed with a neoplasm. Analgesic use was defined as regular (at least once per week for 6 months), frequent (7 tablets/week), very long term (11 years), or frequent, long term (7 tablets per week for 5 years).

Results—Compared to nonusers, frequent aspirin use was associated with decreased odds of cervical cancer (odds ratio, 0.53; 95% confidence interval, 0.29–0.97). A slightly larger association was observed with frequent, long-term use of aspirin (odds ratio, 0.46; 95% confidence interval, 0.22–0.95). Acetaminophen use was not associated with the risk of cervical cancer.

Conclusions—Our findings suggest that frequent and frequent, long-term use of aspirin is associated with decreased odds of cervical cancer. To our knowledge, this is the first US-based study examining these associations. Given the widespread use of nonsteroidal anti-inflammatory drugs and acetaminophen worldwide, further investigations of the possible role of analgesics in cervical cancer, using a larger sample size with better-defined dosing regimens, are warranted.

Keywords

aspirin; acetaminophen; NSAID; cervical cancer; COX-2

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²In SEER data from 2003 to 2009, cases were 47% local, 36% regional, 12% distant, and 4% unknown. Data from SEER from 1973 to 2002 report that 67% had SCC, 13% had adenocarcinomas, and 20% had other histological types (see also Table 3).

Inflammation as a cofactor in human papillomavirus (HPV) and cervical carcinogenesis is an active area of research.¹ Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen reportedly affect the risk of certain cancers, mainly as cyclooxygenase (COX) inhibitors. Although some findings were mixed, evidence points to the chemoprotective effect of aspirin in colorectal² and other cancers.^{3,4} Studies on acetaminophen and cancer show no association,^{5,6} reduced risk,⁷ and increased risk.^{8,9} There have been promising in vitro results on the antitumor role of aspirin alone in cervical carcinogenesis and in combination with other treatments.^{10,11} Furthermore, a recent review of 150 abstracts of in vivo and in vitro studies of cervical intraepithelial neoplasia (CIN), a possible precursor stage to cervical cancer, concluded that cyclooxygenase-2 (COX-2) inhibitors could serve as an alternative to surgical treatment.¹²

Aspirin is an irreversible inhibitor of COX-1 and COX-2 proteins, preferring COX-1 inhibition.¹³ Not considered an NSAID because of weak anti-inflammatory effects, acetaminophen reversibly inhibits COX-1 and COX-2, with recent evidence confirming selectivity for COX-2.¹⁴ In vitro studies demonstrate overexpression of COX-1 and COX-2 in cervical carcinogenesis.¹⁵ The mechanisms of action of aspirin and acetaminophen in cervical oncogenesis proposed by other studies include inhibition of inflammation and angiogenesis related to COX-1 and COX-2,^{12,16} induction of apoptosis,^{10,17} and reduction of estradiol,¹⁸ which has been shown to stimulate HPV oncogene expression¹⁹ and cervical carcinogenesis.²⁰

Algra and Rothwell⁴ urgently call for more methodologically rigorous observational studies assessing aspirin as a potentially effective chemopreventive strategy based on their conclusion that well-designed, case-control studies report associations consistent with the effect of aspirin on colorectal cancer in randomized controlled trials. We are aware of only 2 investigations focusing on associations between NSAIDs and cervical cancer risk in humans (Appendix, available at <http://links.lww.com/LGT/A15>). In a large Danish record linkage study, there was no evidence of an association with low-dose aspirin use and cervical cancer risk. Whereas significant risk reductions were observed with at least one NSAID prescription (standardized incidence ratio [SIR], 0.60; 95% CI, 0.50–0.80), there was no evidence of a dose-response relationship with decreasing risk as a function of increasing number of prescriptions ($p = .24$).^{21,22} In a British study that linked data from a clinical practice database to prescription data, there was no evidence for an association between aspirin or nonaspirin use and cervical cancer risk.²³ Neither study addressed acetaminophen in cervical cancer. Based on our current knowledge of aspirin, acetaminophen, and carcinogenesis, we aimed to examine the association between aspirin and acetaminophen use with cervical cancer risk. We hypothesized that regular usage of these analgesics would be associated with reduced risk of cervical cancer.

MATERIALS AND METHODS

We conducted a hospital-based case-control study drawn from 26,831 patients who received treatment at Roswell Park Cancer Institute (RPCI) in Buffalo, NY, and completed the Patient Epidemiology Data System (PEDS) questionnaire between 1982 and 1998. Written informed consent was obtained from all participants upon recruitment. The PEDS study was

approved by the RPCI institutional review board, and this case-control study falls under its ongoing institutional review board–approved protocol.

The PEDS questionnaire was offered to all patients upon admission to RPCI, and approximately 50% of patients returned a completed questionnaire. The study enrolled 16,189 patients with pathologically confirmed cancer, of whom 328 women had primary, incident cervical cancer (an additional 68 women were coded as having cervical cancer, but their stage was unknown; since they could have been the precursor stage CIN, they were dropped from the analysis). Eligible controls were 7,049 women enrolled who were admitted for suspected neoplastic conditions but ultimately did not have diagnosis of benign or malignant conditions and who were not missing age nor year enrolled in study. From this eligible pool of controls, a stratified random selection based on 5-year age categories and decade of enrollment, at a 4:1 ratio to cases, yielded 1,312 controls for this analysis.

In the questionnaire, the participants reported on their use of tobacco, alcohol, medications, and vitamins; diet; reproductive histories; personal medical histories; and family medical histories. Regarding analgesics, they were asked to complete answers for each medication and directed “If you are currently ill, indicate how often you took these medications before the illness.” The participants provided information on frequency and duration of aspirin or acetaminophen use. The participants were categorized as regular analgesic users (at least once a week for 6 months), frequent users (7 or more tablets a week), long-term users (11 or more years of use), or frequent, long-term users (7 or more tablets a week for 5 or more years).

Bivariate statistics were calculated to describe the sample and test for differences between cases and controls. The Pearson χ^2 test was applied to categorical data and the Student *t* tests to continuous data. The unconditional generalized logit model was used to compute crude and adjusted odds ratios (ORs), with corresponding 95% confidence intervals (CIs). Potential confounders were considered based on a priori consideration of association to exposure variables, known risk factors for cervical cancer, and proxies for sexual activity. Multivariable logistic regression analyses were conducted using forward, backward, and stepwise selection of potential confounders as covariates. Only those covariates that resulted in a change in the odds ratio (OR) by more than 15% were retained in the final adjusted model. The final adjusted model (Table 1) included age; the year the survey was completed; education; age at first pregnancy; cigarette smoking status; menopausal status; genital tract disease; circulatory system disease; blood and blood-forming organs disease; and oral, barrier, and spermicide contraceptive use. Statistical analysis of the data was conducted using SAS 9.3.²⁴

RESULTS

The descriptive characteristics reported in Table 2 demonstrate a few commonalities but mostly significant differences between cases and controls. Cases were more likely than controls to be white, obese (body mass index, >30), and lack a high school diploma. Despite similar age distributions, cases were more likely to be menopausal. Overall, cases were more likely to report other diseases at admission, however, controls were more likely to report

diseases of the breast and oral cavity, salivary glands, and jaw. Comparison of established risk factors for cervical cancer between cases and controls showed that cases were more likely to be current smokers, smoke more cigarettes per day, smoke for more years, first become pregnant before 21 years old, have more than 5 children, and report long-term use of oral contraceptives.

Table 3 shows that the cervical cancer cases in our sample were 71.7% squamous cell carcinoma (SCC), 20.1% adenocarcinomas, and 8.2% other histology types.¹ Most patients had localized cancer (50.6%), 37.8% had regional metastasis, and 11.6% had distant metastasis. Most patients had International Federation of Gynecology and Obstetrics stage I cancer (58.8%), 21.3% had stage II cancer, 16.2% had stage III cancer, and 3.7% had stage IV cancer.

Aspirin use was associated with a 47% reduced risk of cervical cancer (adjusted OR, 0.53; 95% CI, 0.29–0.97) among frequent users (used aspirin 7 or more times a week) and 54% reduced risk among frequent users with 5 or more years of use (adjusted OR, 0.46; 95% CI, 0.22–0.95). Regular use of aspirin was not significantly associated with risk of cervical cancer (adjusted OR, 0.76; 95% CI, 0.54–1.06), nor was prolonged use of 11 or more years (adjusted OR, 0.82; 95% CI, 0.54–1.23) (Table 1). Acetaminophen use of any frequency or duration was not significantly associated with the risk of cervical cancer

DISCUSSION

In our analysis of self-reported analgesic usage, aspirin use was associated in a frequency- and duration-dependent manner with a reduced risk of cervical cancer in 2 groups of users. Using aspirin 7 or more times a week regardless of duration was associated with a 47% reduced risk of cervical cancer (adjusted OR, 0.53; 95% CI, 0.29–0.97). Using aspirin 7 or more times a week for 5 or more years as associated with 54% reduced risk of cervical cancer (adjusted OR, 0.46; 95% CI, 0.22–0.95). Neither less frequent use of aspirin regardless of duration nor prolonged use regardless of frequency was significantly associated with cervical cancer risk. No usage patterns for acetaminophen were associated with cervical cancer risk.

Whereas the body of research into the role of anti-inflammatory agents in carcinogenesis includes multiple agents and cancer sites and is replete with numerous definitions of dose, regimen, duration, and latency periods, our findings are in agreement with some observational studies and randomized clinical trials of other cancers that found daily aspirin use for at least 5 years translates into observable risk reductions.^{3,4,25}

Compared to the findings of other research on anti-inflammatory agents and cervical cancer risk, our study offers more precise definitions of drug use. The most recent study by Wilson et al.²⁶ used a record-linkage design with the United Kingdom Clinical Practice Research Datalink. Drug exposure was defined as oral NSAID prescriptions filled during the study period for cases and controls having at least 5 years of medical history. Wilson et al. found

¹Carcinoma NOS (n = 1); carcinoma undifferentiated type, NOS (n = 3); mucinous adenocarcinoma (n = 6); and adenosquamous carcinoma (n = 17).

no associations with cervical cancer and ever-use of NSAIDs (OR, 0.92; 95% CI, 0.77–1.09), nonaspirin NSAIDs (OR, 0.95; 95% CI, 0.80–1.13), or low-dose aspirin (OR, 1.07; 95% CI, 0.80–1.44). They also found no association with duration of use as measured by a defined daily dose based on the prescription strength and number of pills for the highest users compared to nonusers of NSAIDs (OR, 0.98; 95% CI, 0.69–1.39) or nonaspirin NSAIDs (OR, 1.00; 95% CI, 0.70–1.43) or low-dose aspirin (OR, 1.04; 95% CI, 0.59–1.81). Although this study was large, it does not accurately capture what seems in other research to be the 2 most important elements of aspirin use in reducing cancer risk: daily use and duration of use. Additionally, smoking status for one third of the sample and the length of oral contraceptive use, 2 widely accepted risk factors, were unknown.

Danish researchers also used a record linkage design to compare a county prescription drug database with the national cancer registry to evaluate the relationship between low-dose aspirin and nonaspirin NSAID prescriptions and several cancers including cervical cancer.^{21,22} Looking at prescription data from 1989 to 1995, they found no association between low-dose aspirin use ($n = 15$) and cervical cancer (SIR, 0.90; 95% CI, 0.50–1.6); but among nonaspirin NSAID users ($n = 72$), this study reported a 40% reduction in risk (SIR, 0.60; 95% CI, 0.50–0.80). This reduction was primarily among those with 1 to 4 prescriptions across the 6-year study period; 5 or more prescriptions were not significant. In this study, duration and frequency of analgesic use were not measured; and the study did not control for other accepted risk factors such as smoking, parity, and oral contraceptive use.

Our findings should be viewed with caution given the limitations of our study. Since our study enrolled patients from 1982 to 1998, use of aspirin and NSAIDs has increased significantly²⁷; and thus, our results may not apply to current patient populations. There are inherent methodological challenges associated with hospital-based study designs in general, including the potential for selection bias, recall bias, and exposure misclassification. Selection bias is the greatest concern for our study. We had only a 50% response rate and are unable to ascertain how those who declined participation may differ from those who enrolled. All patients were similarly recruited simply upon admission to the hospital, regardless of NSAID usage or status of suspected neoplasm. Despite these limitations, our cases had a similar distribution of cancer stages as reported in the Surveillance, Epidemiology and End Results (SEER) data; we also have a similar number of SCC cases but more cases with adenocarcinomas.^{2,28} Moreover, previous studies using the PEDS database faced the same methodological issues and consistently replicated established epidemiological associations for a variety of cancer sites.^{29,30} Whereas randomized trials are valued over case-control studies like ours, a recent systematic evaluation of long-term, regular aspirin usage showed in the case of colorectal cancer that the results of the 2 study designs are in close agreement; moreover, our findings are similar to those of randomized trials.^{3,4} Whereas we have more precise definitions of drug use than other studies to date on NSAIDs and cervical cancer, we were unable to assess the dose of the regimens, although a dose-dependent exponential decline in cancer risk with the use of higher doses of aspirin has been reported in colon, lung, breast, and prostate cancers.³¹ Potential confounders for which we could not account include the status of HPV, screening with the Papanicolaou test, human immunodeficiency virus, and sexually transmitted diseases.

CONCLUSIONS

In summary, we report the first study on the role of self-reported use of aspirin and acetaminophen in cervical cancer in a US population of women (Appendix, available at <http://links.lww.com/LGT/A15>). Our results suggest that aspirin use 7 or more times a week as well as aspirin use 7 or more times a week for 5 or more years may be associated with a lower risk of cervical cancer. These findings warrant further investigation in a larger sample size to characterize better the subset of frequent, long-term users, with better-defined dosing regimens, and information on HPV status, screening practices, and cervical cancer histology. Based on our findings related to aspirin, coupled with its low cost and wide availability globally, we encourage future research on the role of daily, long-term use of aspirin and acetaminophen as both cervical cancer chemopreventive agents and enhancement to standard treatment strategies after diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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This study was approved by the Roswell Park Cancer Institute institutional review board and included written informed consent from all participants.

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Use of Aspirin or Acetaminophen and Risk of Cervical Cancer, Roswell Park Cancer Institute, Buffalo, NY (1982–1998)

TABLE 1

	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted OR ^a (95% CI)	p
Aspirin Use					
Nonuser	182 (66.9)	660 (61.6)	1.0	1.0	.10
Regular user	90 (33.1)	412 (38.4)	0.79 (0.60–1.05)	0.76 (0.54–1.06)	
1–6 tablets/wk	72 (26.5)	292 (27.2)	0.89 (0.66–1.21)	0.85 (0.59–1.24)	.40
7+ tablets/wk	18 (6.6)	120 (11.2)	0.54 (0.32–0.92)	0.53 (0.29–0.97)	.04
0.5–10 yrs of use	36 (13.2)	182 (17.0)	0.71 (0.48–1.06)	0.68 (0.43–1.09)	.11
11+ yrs of use	54 (19.9)	230 (21.5)	0.85 (0.61–1.20)	0.82 (0.54–1.23)	.34
Less than 7+ tablets/wk and 5+ yrs of use	78 (28.7)	338 (31.5)	0.84 (0.62–1.13)	0.84 (0.59–1.20)	.33
7+ tablets/wk and 5+ yrs of use	12 (4.4)	75 (6.9)	0.59 (0.31–1.11)	0.46 (0.22–0.95)	.04
Acetaminophen Use					
Nonuser	227 (82.0)	926 (82.5)	1.0	1.0	.58
Regular user	50 (18.1)	196 (17.5)	1.04 (0.74–1.47)	1.13 (0.73–1.75)	
1–6 tablets/wk	43 (15.5)	150 (13.4)	1.17 (0.81–1.69)	1.23 (0.77–1.97)	.38
7+ tablets/wk	7 (2.5)	46 (4.1)	0.62 (0.28–1.39)	0.76 (0.29–2.00)	.58
0.5–10 yrs of use	35 (12.6)	111 (9.9)	1.29 (0.86–1.93)	1.40 (0.85–2.31)	.18
11+ yrs of use	15 (5.4)	85 (7.6)	0.72 (0.41–1.27)	0.71 (0.34–1.48)	.36
Less than 7+ tablets/wk and 5+ yrs of use	44 (17.3)	168 (15.0)	1.17 (0.82–1.66)	1.22 (0.78–1.91)	.39
7+ tablets/wk and 5+ yrs of use	2 (0.7)	28 (2.5)	0.29 (0.07–1.23)	0.42 (0.08–2.12)	.29

^a Aspirin and acetaminophen ORs adjusted for age; year survey completed; education; age at first pregnancy; cigarette smoking status; menopausal status; genital tract disease; circulatory system disease; blood and blood-forming organs disease; and oral, barrier, and spermicide contraceptive use.

TABLE 2

Sample Characteristics, Roswell Park Cancer Institute, Buffalo, NY (1982–1998)

Characteristic	Cases (n = 328)		Controls (n = 1312)		p
	N (%) ^a	Nmiss ^b	N (%) ^a	Nmiss ^b	
Year questionnaire was completed ^a	1988	0	1988	0	.3
Age ^a , yrs	50.9 (15.1)	0	51.0 (15.1)	0	.9
Nonwhite	12 (4.1)	37	90 (7.9)	178	.02
High school graduate	220 (67.8)	2	1,072 (82.0)	5	<.001
Body mass index, kg/m ²		7		20	<.001
<18.5	14 (4.4)		37 (2.9)		
18.5–24.9	153 (47.7)		752 (58.2)		
25–29.9	81 (25.2)		312 (24.2)		
30	73 (22.7)		191 (14.8)		
Smoking status		1		3	.004
Nonsmoker	138 (42.2)		644 (49.2)		
Former smoker	90 (27.5)		382 (29.2)		
Current smoker	99 (30.3)		283 (21.6)		
Number of cigarettes per day, current smokers ^a	7.3 (12.3)	1	4.6 (10.4)	4	<.001
Number of years of smoking ^a	14.7 (16.6)	3	11.2 (14.5)	15	.002
Barrier and spermicide use ^c		13		53	<.001
None	192 (61.2)		574 (45.6)		
Only barrier	85 (27.1)		393 (31.2)		
Only spermicide	11 (3.5)		64 (5.1)		
Both barrier and spermicide	26 (8.3)		228 (18.1)		
Oral contraceptive use		13		31	<.001
Never	181 (57.5)		803 (62.7)		
<10 yrs	93 (29.5)		394 (30.8)		
10+ yrs	41 (13.0)		84 (6.6)		
Spouses		8		32	<.001
None	21 (6.6)		132 (10.3)		

Characteristic	Cases (n = 328)		Controls (n = 1312)		p
	N (%) ^a	Nmiss ^b	N (%) ^a	Nmiss ^b	
One	227 (70.9)		967 (75.6)		
More than one	72 (22.5)		181 (14.1)		
Age at first pregnancy		4		19	<.001
Never pregnant	43 (13.3)		223 (17.3)		
<18	45 (13.9)		116 (9.0)		
18 to <21	106 (32.7)		309 (23.9)		
21 to <25	84 (25.9)		328 (25.4)		
25+	46 (14.2)		317 (24.5)		
Parity (stillborn + live births)		5		29	.1
Nulliparous	55 (17.0)		247 (19.3)		
1–4	214 (66.3)		875 (68.2)		
5+	54 (16.7)		161 (12.6)		
Menopausal status ^d					
Menopausal before diagnosis (cases) or survey completion (controls)	126 (39.3)	7	388 (31.6)	83	.009
Family history of cervical cancer	16 (8.5)	140	19 (2.1)	422	<.001
Other diseases reported					
Blood and blood-forming organs	68 (21.6)	0	44 (3.4)	13	<.001
Circulatory system	153 (48.6)	0	263 (20.1)	13	<.001
Esophagus, stomach, duodenum	12 (3.8)	0	15 (1.1)	13	<.001
Female genital tract	135 (42.9)	0	245 (18.7)	13	<.001
Musculoskeletal system	28 (8.9)	0	26 (2.0)	13	<.001
Nervous system	41 (13.0)	0	31 (2.4)	13	<.001
Breast	9 (2.9)	0	253 (19.3)	13	<.001
Oral cavity, salivary glands, jaw	5 (1.6)	0	28 (2.1)	13	0.5

^aFor continuous variables, the mean and standard deviation are reported.

^bNumber missing.

^cBarrier use includes condom and diaphragm use; spermicide use includes cream, foam, jelly.

^dNatural or hysterectomy.

TABLE 3

Cancer Characteristics of Cervical Cancer Cases, Roswell Park Cancer Institute, Buffalo, NY (1982–1998)

Characteristic	n (%)
Cases	328 (100)
Histology	
Squamous	235 (71.7)
Adenocarcinomas	66 (20.1)
Other	27 (8.2)
Stage	
Localized (confined to primary site)	166 (50.6)
Regional (spread to regional lymph nodes)	124 (37.8)
Distant (metastasized)	38 (11.6)
Unknown	
FIGO stage	
I	193 (58.8)
II	70 (21.3)
III	53 (16.2)
IV	12 (3.7)

FIGO, International Federation of Gynecology and Obstetrics.