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Regular aspirin use and lung cancer risk

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Abstract

Background: Although a large number of epidemiological studies have examined the role of aspirin in the chemoprevention of colon cancer and other solid tumors, there is a limited body of research focusing on the association between aspirin and lung cancer risk.

Methods: We conducted a hospital-based case-control study to evaluate the role of regular aspirin use in lung cancer etiology. Study participants included 868 cases with primary, incident lung cancer and 935 hospital controls with non-neoplastic conditions who completed a comprehensive epidemiological questionnaire. Participants were classified as regular aspirin users if they had taken the drug at least once a week for at least one year.

Results: Results indicated that lung cancer risk was significantly lower for aspirin users compared to non-users (adjusted OR = 0.57; 95% CI 0.41–0.78). Although there was no clear evidence of a dose-response relationship, we observed risk reductions associated with greater frequency of use. Similarly, prolonged duration of use and increasing tablet years (tablets per day × years of use) was associated with reduced lung cancer risk. Risk reductions were observed in both sexes, but significant dose response relationships were only seen among male participants. When the analyses were restricted to former and current smokers, participants with the lowest cigarette exposure tended to benefit most from the potential chemopreventive effect of aspirin. After stratification by histology, regular aspirin use was significantly associated with reduced risk of small cell lung cancer and non-small cell lung cancer.

Conclusions: Overall, results from this hospital-based case-control study suggest that regular aspirin use may be associated with reduced risk of lung cancer.

Background

Regular use of aspirin and other non-steroidal anti-inflammatory dugs (NSAIDs) has been consistently associated with reduced risk of colorectal cancer and adenoma [1–4], possibly due to NSAID-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 NSAIDs with respect to other cancer sites. There is some evidence that regular and prolonged NSAID use is associated with reduced risk of cancers of the esophagus [3,9,10] stomach [3,9,11], ovary [12,13], and female breast [14–16].

Although there is a growing body of epidemiological evidence on the role of aspirin and other NSAIDs in the chemoprevention of lung cancer (Table 1.; [14,17–23]), about half of these studies published to date were not specifically designed to investigate this association [17–19,21]. In a randomized trial aimed at examining the effect of aspirin in the prevention of cardiovascular disease in male physicians, Peto et al [17] first noted lower lung cancer mortality rates in the aspirin intervention group compared to the placebo group. Two subsequent cohort studies demonstrated associations with regular [18] or frequent aspirin use [19] among women, but not men. In contrast, in a prospective analysis of the NHANES I follow-up study, Schreinemachers & Everson [14] reported lower incidence of lung cancer only among men classified as recent aspirin users. Rosenberg [20] observed no strong evidence for a chemopreventive role of aspirin in a hospital-based case-control study; whereas Langman et al. [21], in a record-based case-control study, reported a borderline significant risk reduction associated with frequent prescriptions of NSAIDs. Most recently, results from a case-control study, nested within the NYU Women's Health Study [22], indicated that women classified as regular aspirin users were at a marked, and statistically significant, reduced risk of non-small cell lung cancer (NSCLC) compared to women classified as non-users; however, no significant associations were observed for all histological types combined. Another recent case-control study investigated the effect of aspirin on lung cancer risk in a sample of heavy smokers [23]. Results indicated that daily aspirin use was strongly associated with reduced risk; this effect was apparent for both men and women. We conducted a hospital-based case-control study to further investigate the overall association between aspirin use and lung cancer risk, and to add to the limited body of evidence on the potential effect modifying roles of tumor histology and cigarette smoking on the chemopreventive role of aspirin in lung tumorigenesis.

Statistical analyses

Results

Methods

Study population

The study population included individuals who received medical services at the Roswell Park Cancer Institute (RPCI) between 1982 and 1998, and who agreed to complete a comprehensive epidemiological questionnaire. Informed consent was obtained from all participants. The case group consisted of 868 individuals with primary, incident lung cancer, identified from the RPCI tumor registry and Diagnostic Index. Controls included 935 individuals, randomly selected from a pool of 7957 eligible individuals, who received medical services at RPCI for non-neoplastic conditions. These participants came to RPCI with a suspicion of neoplastic disease, but were not diagnosed with either benign or malignant conditions. The most frequently utilized services among the controls were carried out in the breast clinic (13%), dermatology clinic (12%), gastrointestinal clinic (15%), and sarcoma/melanoma clinic (15%). The remaining controls were seen in a variety of clinics at our institute, including gynecological oncology, hematology, head and neck, radiotherapy, and urology; however the proportion of controls seen at these clinics was less than five percent of all control participants. Controls were frequency matched to cases on sex and five-year age intervals.

Questionnaire

All participants completed the Patient Epidemiology Data System (PEDS) questionnaire, which is offered to all new patients as part of the admission process, and is returned by approximately 50 percent of new patients. The 16-page instrument covers information on tobacco and alcohol consumption, family history of cancer, occupational and environmental exposures, reproductive and medical histories, and diet. The instrument also assesses aspirin 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. Participants who reported aspirin use at least once a week for one year were classified as regular aspirin users. Dosage of use was assessed by comparing participants who were classified as non-users 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 non-users to participants who took aspirin for six months to ten years or more than ten years. We also evaluated a combined measure of dosage and duration by computing tablet years (tablets per day × years of use). Reason for analgesic use was unavailable for these analyses.

Descriptive characteristics of the study population are shown in Table 2. Due to the matching procedures, there

Table 1: Aspirin use and lung cancer risk – summary of published studies.

Study (reference)	Year (place)	Design	Study sample	Key results
Peto et al.[17]	1988 (UK)	Randomized Trial	5139 British physicians: aspirin intervention group (n = 3429) vs. placebo group (n = 1710)	Lung cancer death rates lower in aspirin group (7.4/10.000 person years) vs. placebo group (11.6/10.000 person years)
Paganini-Hill et al.[18]	1989 (US)	Cohort study	13 987 retirement community residents; 111 lung cancer cases after 6.5 years of follow-up	No evidence of lower incidence of lung cancer among male daily aspirin users (RR = 1.35); Lower incidence of lung cancer among female daily aspirin users (RR = 0.29)
Thun et al.[19]	1993 (US)	Cohort study	Cancer Prevention Study II: 635,031 US residents; 6 year follow-up	No evidence of lower mortality from respiratory cancers in association with aspirin use among men; Lower respiratory cancer mortality among women using aspirin 1–15 times/month (RR = 0.73; 95 % CI 0.56–0.97)
Schreinemachers & Everson [14]	1994 (US)	Cohort study	NHANES I follow-up: 12,668 US residents; 189 respiratory cancers after 12.4 years (mean) of follow-up	Significantly lower incidence of lung cancer among men using aspirin in past 30 days (RR = 0.55; 95% CI 0.38–0.81); No evidence of lower lung cancer incidence among women using aspirin (RR = 1.40; 95% CI 0.74–2.66)
Rosenberg[20]	1995 (US)	Hospital-based case-control study	1110 lung cancer cases; 1181 cancer controls and 4906 non-cancer controls	Non-significant risk reduction associated with aspirin use when case group compared to cancer controls (RR = 0.80; 95% CI 0.60–1.20), but not apparent when compared to non-cancer controls (RR = 1.00; 95% CI 0.70–1.40)
Langman[21]	2000 (UK)	Record-linkage case control study	2560 lung cancer patients and 7643 controls identified from general practice research data base	Non-significant risk reduction associated with 7+ prescriptions of NSAIDs 1–3 years prior to diagnosis (OR = 0.84; 95% CI 0.69–1.02)
Akhmedkhanov et al.[22]	2002 (US)	Nested case-control study	81 female lung cancer patients and 808 controls selected from the NYU Women's Health Study	Non significant risk reduction between regular aspirin use and overall lung cancer (OR = 0.66; 95% CI 0.34–1.28); Significant risk reduction between regular use and non-small cell carcinoma of the lung (OR = 0.39; 95% CI 0.16–0.96)
Harris et al [23]	2002 (US)	Case-control study	489 lung cancer patients and 978 screening clinic controls (heavy smokers)	Significant risk reduction among daily aspirin users (OR = 0.32; 95% CI 0.23–0.44); effect seen among men and women
Current study	2002 (US)	Hospital-based case-control study	868 lung cancer cases and 935 hospital controls with non-neoplastic conditions	Significant risk reduction among regular aspirin users (OR = 0.57; 95% CI 0.41–0.78); effect seen among men and women

were no differences between cases and controls with respect to age and sex. Cases were significantly less likely than controls to have obtained a college education ($p < 0.001$). As expected, cases were more likely than controls to be former and current smokers ($p < 0.001$), and to have had more packyears of cigarettes ($p < 0.001$).

Table 3 displays the association between aspirin use and lung cancer risk in the total sample, as well as among females and males separately. Compared to nonusers, regular aspirin use was associated with a significant reduction in risk of lung cancer in the total study sample (adjusted OR = 0.57; 95% CI 0.41–0.78), as well as among female (adjusted OR = 0.52; 95% CI 0.29–0.95) and male (adjusted OR = 0.62; 95% CI 0.43–0.90) participants. Higher dosage of aspirin (seven or more tablets per week) was significantly associated with risk in the total sample (adjusted OR = 0.58; 95% CI 0.41–0.82) and among male participants (adjusted OR = 0.56; 95% CI 0.37–0.83). Prolonged duration of use (11 or more years) was not associated with a significant reduction in risk in either the total sample, nor among the subgroups defined by sex. However, self-reported aspirin use of one to 10 years was associated with a significantly lower risk of lung cancer in all groups. Among male participants, there was evidence of a dose response relationship with lower risk as a function of longer duration of use ($p < 0.01$). Risk of lung cancer was significantly reduced in relation to increasing tablet years in the total sample ($p < 0.001$) and in males ($p < 0.01$). We further explored these associations by restricting the sample to current and former smokers, who were divided into tertiles of packyears of cigarettes smoked. As can be seen in Table 4, risk estimates for the exposure categories described above were generally below the null among all smoking groups. However, statistically significant risk reductions and dose-response relationships were only observed for participants in the lower tertile of packyear distribution (1–34 packyears). Table 5 displays the association between regular aspirin use and risk of histology-specific lung cancer. Significant risk re-

Table 2: Characteristics of 868 lung cancer patients and 935 hospital-based controls – Roswell Park Cancer Institute, 1982–1998.

	Cases (n = 868)	Controls (935)	p value
Age (years)[1]	62.10 (8.76)	61.59 (9.11)	ns
Sex[2]			
Female	335 (38.6%)	358 (38.3%)	
Male	533 (61.4%)	577 (61.7%)	ns
Education[2]			
Up to high school	629 (72.5%)	498 (53.3%)	
College	231 (26.6%)	431 (46.1%)	
Unknown	8 (0.9%)	6 (0.6%)	p < 0.001
Smoking Status[2]			
Current	212 (24.4%)	137 (14.7%)	
Former	611 (70.4%)	425 (45.5%)	
Never	45 (5.2%)	373 (39.8%)	p < 0.001
Packyears[1,3]	58.74 (37.55)	21.35 (27.23)	p < 0.001

[1] Mean (SD); differences in means detected using independent t-tests [2] n (%); differences in proportions detected using chi-square tests [3] Packs per day × years of smoking

ductions were observed for both NSCLC (adjusted OR= 0.62; 95% CI 0.45–0.86) and small cell lung cancer (SCLC) (adjusted OR = 0.32; 95% CI 0.16–0.63).

Conclusions

Results from this hospital-based case control study are largely consistent with the existing body of evidence on the association between regular aspirin use and lung cancer risk. All previous studies reported some evidence of reduced risk of lung cancer in relation to use aspirin or other NSAIDs [14,17–23] . We observed a significant risk reduction among participants defined as regular users in the total sample, as well as among men and women separately. Our data also demonstrated significant risk reductions associated with higher aspirin doses, prolonged duration, and greater tablet years of aspirin use, although significant trends were largely restricted to male participants. We further observed that, after restricting the analyses to current and former smokers, the chemoprotective effect of aspirin was most apparent among individuals in the lower tertile of the packyear distribution. Finally, when we explored this risk association among histological subtypes, significant risk reductions were apparent in when controls were compared to patients with both NSCLC and SCLC.

Table 3: Risk of lung cancer in association with aspirin use – Roswell Park Cancer Institute, 1982–1998.

	Total Sample			Females			Males		
	Cases (n = 868)	Controls (n = 935)	Adjusted OR[1] (95% CI)	Cases (n = 335)	Controls (n = 358)	Adjusted OR[1] (95% CI)	Cases (n = 533)	Controls (n = 577)	Adjusted OR[1] (95% CI)
Non-User	747	768	1.0	299	306	1.0	448	462	1.0
Regular User[2]	121	167	0.57 (0.41–0.78)	36	52	0.52 (0.29–0.95)	85	115	0.62 (0.43–0.90)
1–6 tablets/week	26	41	0.53 (0.28–0.99)	9	26	0.17 (0.05–0.50)	17	15	1.01 (0.46–2.59)
7+ tablets/week	95	126	0.58 (0.41–0.82) p = 0.04	27	26	0.88 (0.43–1.79) p = 0.19	68	100	0.56 (0.37–0.83) p = 0.006
1–10 years of use	90	126	0.56 (0.39–0.79)	23	38	0.42 (0.21–0.86)	67	88	0.65 (0.43–0.98)
11+ years of use	31	41	0.61 (0.34–1.09) p = 0.06	13	14	0.88 (0.30–2.55) p = 0.11	18	27	0.53 (0.26–1.10) p = 0.01
1–10 tablet years[3]	84	106	0.63 (0.44–0.92)	20	30	0.47 (0.22–0.99)	64	76	0.73 (0.48–1.12)
11+ tablet years	37	61	0.45 (0.27–0.77) p < 0.001	16	22	0.61 (0.24–1.54) p = 0.07	21	39	0.40 (0.21–0.78) p = 0.004

[1] Odds ratio adjusted for age, education, and packyears of cigarettes [2] Regular use was defined as self-reported use at least once a week for at least one year [3] Tablets per day × years of use

Although our findings follow the general trend that has been demonstrated in previous investigations, some differences exist. Two cohort studies reported reduced risk among aspirin users among females, but not males [18,19], while we observed strongest associations for male participants. Another study did not demonstrate a risk reduction among females [20], whereas we consistently found non-significant risk estimates below unity for female participants. In a recent report based on the NYU Women's Health Study, Akhmedkhanov et al. [22] reported a significant risk reduction for NSCLC and a more modest, non-significant decease in risk for all histological types of lung cancer. Our data are partly in contrast to these results, in that we observed the most marked reduction for SCLC, but also a significant decrease in risk for all NSCLC subtypes combined.

These discrepancies in results may be partly explained by differences in study designs across studies (i.e., randomized trial [17], cohort study [14,18,19,22] case-control study [20,23], or by the vast differences in exposure assessment, ranging from assignment of participants to aspirin intervention group vs. placebo group [17] over ever use of aspirin in the last 30 days [14] to having had an NSAID prescription in the past three years [21].

One of the proposed mechanisms for the chemopreventive properties of aspirin and other NSAIDs points to the observation that NSAIDs inhibit prostaglandin (PG)-endoperoxide synthase (cyclooxygenase) enzymes [24], of which two forms of similar enzymatic activity exist, COX-1 and COX-2. COX-1 is constitutively expressed and involved in homeostasis [24]; COX-2 is induced and involved in inflammation [24,25]. There is evidence from laboratory studies to suggest that the COX-2 pathway may be involved in lung tumorigenesis. Bauer et al. [26] reported significantly higher levels of COX-2 enzymes in mouse lung tumor tissue compared to normal tissue. It has also been shown that aspirin inhibited nitrosamine induced lung carcinogenesis [27], and it reduced COX-2 enzyme levels in lung cancer cell lines [28]. Further support for a potential role of the COX-2 pathway in lung cancer development comes from several investigations that demonstrated COX-2 overexpression in human lung tumors, specifically NSCLC [29–32] and precursor lesions [33]. While COX-2 expression was generally shown to be increased in NSCLC and to a much lesser extent in SCLC, the role of COX-2 expression in latter tumor type is difficult to determine, due to the fact that the numbers of SCLC tumors examined in these studies was very small.

Table 4: Risk of lung cancer in association with aspirin use among current and former smokers – Effect of packyears of cigarettes smoked – Roswell Park Cancer Institute, 1982–1998.

	Lower tertile of packyear distribution (1 – 34 packyears)			Middle tertile of packyear distribution (34.1 – 60 packyears)			Upper tertile of packyear distribution (60.1 – 260 packyears)		
	Cases (n = 162)	Controls (n = 288)	Adjusted OR[1] (95% CI)	Cases (n = 307)	Controls (n = 157)	Adjusted OR[1] (95% CI)	Cases (n = 336)	Controls (n = 90)	Adjusted OR[1] (95% CI)
Non-User	149	238	1.0	264	127	1.0	278	68	1.0
Regular User[2]	13	50	0.43 (0.22–0.83)	43	30	0.70 (0.41–1.18)	58	22	0.66 (0.37–1.16)
1–6 tablets/week	2	10	0.32 (0.07–1.53)	7	5	0.62 (0.19–2.05)	16	2	2.02 (0.45–9.04)
7+ tablets/week	11	40	0.45 (0.22–0.92) p = 0.02	36	25	0.71 (0.40–1.26) p = 0.20	42	20	0.52 (0.28–0.95) p = 0.06
1–10 years of use	10	35	0.47 (0.22–0.99)	33	23	0.66 (0.37–1.19)	44	16	0.68 (0.36–1.29)
11+ years of use	3	15	0.32 (0.09–1.16) p = 0.01	10	7	0.83 (0.30–2.29) p = 0.26	14	6	0.59 (0.22–1.61) p = 0.15
1–10 tablet years[3]	10	27	0.60 (0.28–1.30)	33	22	0.70 (0.38–1.26)	38	12	0.78 (0.38–1.58)
11+ tablet years	3	23	0.22 (0.06–0.75) p = 0.006	10	8	0.70 (0.26–1.86) p = 0.21	20	10	0.51 (0.22–1.15) p = 0.09

[1] Odds ratio adjusted for age and education [2] Regular use was defined as self-reported use at least once a week for at least one year [3] Tablets per day × years of use

Table 5: Risk of lung cancer in association with regular aspirin use – Effect of histology – Roswell Park Cancer Institute, 1982–1998.

	Controls (n = 935)	Adeno-carcinoma (n = 293)	Adjusted OR[1] (95% CI)	Squamous Cell (n = 307)	Adjusted OR[1] (95% CI)	Large Cell (n = 122)	Adjusted OR[1] (95% CI)	Small Cell (n = 157)	Adjusted OR[1] (95% CI)	Controls (n = 935)	Non-Small Cell Lung Cancer[3] (n = 711)	Adjusted OR[1] (95% CI)
Non-User	768	247	1.0	264	1.0	108	1.0	142	1.0	768	602	1.0
Regular User[2]	167	46	0.70 (0.46–1.06)	43	0.70 (0.41–1.18)	14	0.52 (0.27–1.00)	12	0.32 (0.16–0.63)	167	109	0.62 (0.45–0.86)

[1] Odds ratio adjusted for age, education, and packyears of cigarettes [2] Regular use was defined as self-reported use at least once a week for at least one year [3] Includes patients with adenocarcinoma, squamous cell carcinoma, and large cell carcinoma

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 lung cancer patient group was restricted to individuals who were treated at RPCI, a large regional cancer treatment center, and are not likely to represent the general population of lung cancer patients in the western New York region. However, it is unlikely that self-reported aspirin use would be different for RPCI patients than from patients treated in different facilities. The use of hospital controls might introduce bias, due to the possibility that some controls were suffering from conditions that would make them more likely to use aspirin . However, greater likelihood of aspirin use in the control group would only have attenuated the true risk estimate, rather than produced spurious associations. In addition, hospital controls were selected from a large pool of eligible participants with a wide variety of non-cancer 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. Selection bias may have also been introduced due to the low participation rate in this study. Only about 50 percent 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 utilized the PEDS data base and faced the same methodological issue, consistently replicated established epidemiological associations for a variety of cancer sites, including ovary [34,35], colon [36], breast [37], prostate [38], and lung [39]. Recall bias is always a 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. Further, 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 aspirin use. Exposure misclassification may also have affected our results, as 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. Further, we did not have detailed information on other NSAIDs that participants may have taken and cannot rule out the possibility that cases may have been more likely to have taken preparations such as ibuprofen or prescription NSAIDs, which would have resulted in an overestimated or entirely spurious results. However, we have no reason to believe that any of these potential sources of misclassification were differential in nature.

In summary, in this hospital-based case-control study of lung cancer, we observed consistent associations between aspirin use and risk, particularly among men. Although a number of epidemiological studies have produced fairly consistent results, none of these investigations has been specifically designed to address this research question. These suggestive findings need to be replicated by a well-designed pharmacoepidemiological study that incorporates the newly introduced NSAID preparations.

Competing interests

None declared.

Authors' contributions

AR and HS participated in the statistical analysis and drafting the manuscript. RJM participated in study design, statistical analysis and manuscript preparation. MER, KMC, KLF, and GML participated in study design and manuscript preparation. KBM and GB conceived of the study and participated in its design and manuscript preparation.

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