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Aspirin Use and Mortality from Cancer in a Prospective Cohort Study

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Abstract. *There is evidence that use of aspirin offers several potential health benefits including cancer prevention and cardiovascular disease prevention. The purpose of this study was to assess the association between aspirin use and death from cancer and cardiovascular diseases with a special emphasis on cancer mortality. Materials and Methods: The baseline data for this prospective cohort study were collected in 1971-1975 for the first National Health and Nutrition Examination Study (NHANES I) and 1976-1980 as part of the second NHANES (NHANES II) with mortality follow-up using the National Death Index (NDI) through December 31, 1992. The main analyses were the relative risks of total mortality and cause-specific mortality for persons who used aspirin compared to persons who did not use aspirin adjusted for confounding using Cox proportional hazards. Results: The proportion of aspirin users was lower among cancer cases than non-cases (58% versus 66%) and use of aspirin decreased with age. Consequently, age was a negative confounder attenuating the protective association between aspirin use and cancer and cardiovascular mortality. After adjusting for age, BMI, sex, race, poverty index, education and smoking, we observed a significant association of reduced all cause mortality among all aspirin users (relative risk [RR] = 0.88; 95% confidence interval [CI] 0.85 - 0.99) and lung cancer mortality among male aspirin users (RR = 0.69; CI 0.49-0.96). However, for women we observed adverse associations between aspirin use and bladder (RR=12.31; CI 2.98-50.80) and brain cancer mortality (RR=3.13; CI 1.09-9.00), although case numbers were small. Conclusion: Aspirin use appears to offer protection from all causes of mortality and lung cancer among men. In women aspirin use is associated with increased risk of bladder and brain cancer. Because of the small number of female bladder (n=15) and brain (n=20) cancer cases in this cohort the findings require confirmation.*

Abbreviations: Cyclooxygenase-2, Cox-2; nonsteroidal anti-inflammatory drugs: NSAIDs, NHANES: National Health and Nutrition Examination Study.

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Key Words: Aspirin, NSAIDs, cancer, cardiovascular disease, NHANES, cohort study.

Aspirin is one of the best-documented and most frequently used drugs with an intolerance rate of around 5 percent. In addition to its role as an analgesic, aspirin is potentially important in the prophylaxis against cardiovascular disease (1,2) and gastrointestinal cancer (3). The basis for prophylaxis against cardiovascular disease is that aspirin significantly lowers platelet cycloxygenase (COX) activity, thromboxane synthesis and, thus, platelet activation. COX is the rate-limiting enzyme in the conversion of arachidonic acid to prostaglandin PGH2, which is then converted to bioactive prostaglandins and thromboxanes. Two cyclooxygenase genes (COX-1 and COX-2) have been identified. COX-1 is a housekeeping gene and COX-2 is an inducible early response gene. It is well established that COX-2-derived prostaglandins signal many biologic processes including vasoconstriction, platelet aggregation, angiogenesis, apoptosis and cell proliferation. Indeed, many human neoplasias over express COX-2.

Nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin have been shown to inhibit carcinogenesis in many experimental models (4). Epidemiological studies indicate that aspirin use may reduce the risk of many cancers (3). These studies indicate a 40-50% reduction in risk of colorectal neoplasia among regular aspirin users (5).

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Case reports and randomized controlled trials are also consistent in showing a reduction in colorectal adenomas following administration of the NSAID sulindac to patients with familial adenomatous polyposis (6). There is evidence that aspirin might also be of value in preventing esophageal cancer (7-10). An inverse association between the use of NSAIDs and the incidence of breast and lung cancer has been observed, but these associations have not been statistically significant in all studies.

To provide further observational data in humans, we examine here the association between aspirin use and mortality from cancer, heart disease and stroke among participants of the Epidemiologic Follow-up Study (NHEFS) of the first National Health and Nutrition Examination Survey (NHANES I) and of the mortality follow-up to the second National Health and Nutrition Examination Survey (NHANES II) referred to as the NHANES II Mortality Study (NHMS).

Materials and Methods

The Cohort. The cohort is composed of participants from both the NHEFS and the NHMS. The NHEFS is a prospective cohort study of participants 25-74 years old in the NHANES I (n=14,407), a nationally representative cross-sectional probability sample conducted with face-to-face interviews of the civilian, non-institutionalized population in the United States, between 1971 and 1975 by the National Center for Health Statistics (NCHS) (11). Groups at high risk for malnutrition (the elderly, children, women of childbearing age and the poor) were sampled more frequently than the general population. Participants in the NHEFS were re-interviewed in 1982-84, 1986, 1987 and 1992 (12). By the end of the 1992 follow-up, 96 percent of the cohort was successfully traced.

The NHMS is a prospective cohort study of participants 25-74 years old in the NHANES II (n=9252), a nationally representative cross-sectional probability sample conducted with face-to-face interviews of the civilian, non-institutionalized population in the United States, between 1976 and 1980 by NCHS (13). Individuals 64 years and older and living in poverty areas were sampled more frequently than the general population. No follow-up interviews were conducted for the NHMS. Vital status for NHEFS and NHMS participants was assessed by searching the National Death Index and the Social Security Administration Death Master File for deaths occurring in the United States between the baseline surveys and December 31, 1992. Causes of death were obtained from the National Center for Health Statistics Multiple Cause of Death file or death certificates.

The analytical cohort for the current study is based on the NHEFS and NHMS study participants who completed the interviews at baseline and provided data on aspirin use. In the NHEFS, 131 individuals were missing aspirin usage and 645 were either determined to have died but were missing a death certificate or a determination of vital status could not be made, which leaves an analytic sample of 13,631. In the NHMS, 4 were missing aspirin usage and 45 were missing a death certificate or a determination of vital status could not be made, which leaves an analytic sample of 9203. A total of 22,834 individuals were used in the current analysis.

Aspirin use and other covariate data. Aspirin use data for NHEFS at baseline (1971-1975) were comprised of a question about whether there was aspirin use during the previous 30 days and, if so, how many days prior to the interview was aspirin last taken. For NHMS the aspirin use data was derived from a question "during the past 6 months did you use any aspirin or aspirin type pills", if so, "on average do you use these pills one or more times per week"? For the current analysis the baseline information about aspirin use data were combined to generate a dichotomous variable of aspirin use based simply on whether or not the participants used aspirin. Of the 22,834 in the current study, 14,943 (65%) were classified as aspirin users.

Data regarding potential confounders of gender, age, race, education, smoking, socioeconomic status and body mass index (BMI) were imputed from baseline interviews. Poverty index, the measure of socioeconomic status, was derived by the income necessary for nutritional adequacy of a household. BMI was defined as weight divided by height squared (kg/m^2).

Statistical analyses. Cox proportional hazard regressions were used to estimate relative risks (RR) of aspirin use in relation to all-cause and cause-specific mortality. RRs were estimated unadjusted, adjusted for only age and adjusted for potential confounders. In the unadjusted analysis, the response variable was follow-up time in the study to death. Study participants, who were still alive at the end of follow-up, were censored at the last follow-up date, December 31, 1992. For the cause-specific mortality analyses, participants who died from causes other than the specific cause of interest were censored at their time of death. In the adjusted analyses, the response variable in these analyses was age at death (thus, automatically adjusting for age). The age-adjusted models (with follow-up time as the response variable) yielded very similar results to the unadjusted models with age as the time metric. The baseline hazard in the proportional hazard regressions was stratified by year of birth and by baseline survey NHANES I or II to adjust for potential cohort effects and differences between the baseline surveys. Initially, analyses were conducted separately for each of the NHEFS and the NHMS cohorts to determine differences in results, which were determined to be similar. We present the combined analysis. All analyses were weighted by the sample weights and take into account complex stratified multistage cluster sample designs in the NHEFS and NHMS in the computation of standard error, confidence intervals and hypotheses testing. The PC-SAS callable versions of SUDAAN v.7.5 and a prerelease v.8.0, a statistical software package for analyzing data from weighted complex survey sampling designs, were used to perform the computations for the analyses.

Results

The analytic cohort for this study consisted of 22,843 individuals for whom there was aspirin use data. During follow-up there were 28.7% (N=6554) cumulative deaths in the analytical cohort, with cumulative deaths of 36% among those that reported no aspirin use and 25% among those that reported using aspirin. The proportion of aspirin users was lower among cancer cases than non-cases (58% *versus* 66%).

Table I presents the weighted percentage of aspirin use for a number of potential chronic disease-associated risk

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factors. Aspirin use appeared to be higher among participants of the NHANES II study than NHANES I. Women were more frequent aspirin users than men and aspirin use decreased with increasing age. Whites reported more common use of aspirin than non-whites. People with higher levels of education and higher socioeconomic status also seemed to use aspirin more commonly.

Table II presents the unadjusted, age-adjusted only, and multivariate adjusted associations for aspirin use and cause-specific mortality for both sexes combined. The unadjusted analysis shows that for most causes of mortality aspirin use seemed to reduce the risk of death except for melanoma and urinary cancers. However, after adjusting for potential confounders, especially age, the significant reductions in mortality were attenuated. There was a significant increase in the risk of urinary cancers among aspirin users (RR: 2.68; 95% CI: 1.29-5.55). The only significant protective association with aspirin use after adjusting for confounders was for all cause mortality with an 8% reduction in risk.

Table III presents data on the association between aspirin use and mortality among males. As before, age was a strong confounder of the association between aspirin use and mortality. In the multivariate adjusted analysis, aspirin use was associated with reduced mortality from all causes (RR: 0.88; 95% CI: 0.80-0.98) and lung cancer (RR: 0.69; 95% CI: 0.49-0.96) in men.

Table IV presents data on the association between aspirin use and mortality in females. After adjusting for age, BMI, sex, race, poverty index, education and smoking, there were no reductions in risk of cancer mortality at any site. However, we observed a significant reduction in risk of cerebral artery occlusion (RR: 0.34; 95% CI: 0.16-0.71). Although numbers were small, we also observed significant increases in death from bladder, brain and "other" cancers among those that reported aspirin use. For bladder cancer there was an over 12-fold increase in risk of mortality among those reporting aspirin use compared to women that reported no aspirin use (RR: 12.31; 95% CI: 2.98-50.80). For brain cancer there was an over 3-fold increase in risk of mortality among those reporting aspirin use (RR: 3.13; 95% CI: 1.09-9.00).

Table I. *Weighted percentages of aspirin use in cohort.*

	Aspirin users (%)	Aspirin non-users (%)
All	68.31	31.69
NHANES I	59.21	40.79
NHANES II	77.70	22.30
Gender		
Male	64.12	35.88
Female	72.09	27.91
Age		
<40	72.98	27.02
40-49	70.49	29.51
50-59	67.68	32.32
60-69	61.10	38.90
≥70	57.86	42.12
Race		
White	69.0	31.0
Non-White	62.87	37.13
Education		
<12	62.60	37.40
≥12	69.01	30.99
Missing	60.38	39.62
Smokers		
Never	67.34	32.66
Former	70.02	29.98
Current	69.45	30.55
Missing	54.28	45.72
Poverty index		
≤1.00	65.15	34.85
>1.00	69.89	30.11
Missing	71.06	28.94
Body mass index		
<20	69.64	30.36
20-24.9	69.87	30.13
25-29.9	66.23	33.77
30-34.9	67.10	32.90
≥35.0	70.49	29.51
Missing	87.46	12.54

Discussion

Cyclooxygenase (COX) - particularly the COX-2 isoform - is an attractive target for chemopreventive drug development because it is over-expressed in many tumor types. Nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin inhibit COX and thereby provide a model for mechanistically based cancer chemoprevention and perhaps treatment. Two major trials in which either low-dose aspirin (160 mg) or one aspirin administered every other day, have demonstrated significant reduction in fatal and non-fatal cardiovascular events (14). Discovering whether or not aspirin and other NSAIDs are beneficial in persons at risk for common chronic diseases is an endeavor that may have great public health benefits.

In our current study, the percentages of aspirin use were consistently lower among those that suffered from cancer and cardiovascular diseases. The cardiovascular disease findings are not surprising given that aspirin is routinely recommended for those at elevated risk for adverse cardiovascular events. However, after adjusting for potential confounders, especially age, the significant reductions in

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Table II. *Association between aspirin use and mortality for both sexes combined in NHANES I and II.*

Mortality Cause	ICD9	Aspirin non-users: Cases/ non-cases	Aspirin users: Case/ non-cases	Unajusted[1]		Age-adjusted[2]		Multivariate[3]	
				RR	95% CI	RR	95% CI	RR	95% CI
All cause mortality	All causes	2869/5136	3685/11153	**0.68**	**0.63-0.72**	**0.87**	**0.82-0.92**	**0.92**	**0.85-0.99**
All cancer	140-208 (excluding 173)	667/7329	921/13917	**0.73**	**0.63-0.84**	0.89	0.77-1.03	0.98	0.84-1.14
Digestive	150-159	185/7811	225/14613	**0.66**	**0.51-0.85**	0.82	0.63-1.07	0.96	0.72-1.28
Esophagus	150	21/7975	16/14822	**0.36**	**0.15-0.91**	0.48	0.20-1.20	0.48	0.18-1.29
Stomach	151	25/7971	23/14815	0.63	0.29-1.38	0.84	0.39-1.79	0.82	0.38-1.81
Colorectal	153-154	80/7916	113/14725	0.72	0.52-1.01	0.88	0.62-1.25	1.07	0.71-1.60
Pancreas	157	35/7961	43/14795	0.67	0.34-1.30	0.81	0.42-1.59	0.87	0.42-1.77
Respiratory	160-165	184/7812	242/14596	**0.67**	**0.51-0.87**	0.81	0.63-1.06	0.84	0.64-1.11
Trachea, bronchus and lung	162	178/7818	232/14606	**0.65**	**0.50-0.85**	0.79	0.61-1.04	0.81	0.62-1.07
Urinary	188-189	27/7969	50/14788	1.15	0.62-2.13	1.48	0.81-2.68	**2.68**	**1.29-5.55**
Bladder	188	13/7983	27/14811	1.24	0.46-3.32	1.58	0.61-4.08	**3.36**	**1.03-10.97**
Kidney	189	14/7982	23/14815	1.07	0.49-2.35	1.38	0.63-2.98	2.27	0.93-5.54
Brain	191	10/7986	21/14817	0.75	0.27-2.05	0.89	0.33-2.45	0.76	0.27-2.18
Lymphoma	200-203	43/7953	51/14787	0.68	0.39-1.18	0.82	0.47-1.45	0.97	0.52-1.81
Leukemia	204-208	32/7964	31/14807	**0.50**	**0.28-0.89**	0.64	0.36-1.13	1.08	0.58-2.01
Other	140-9, 170-2, 190, 191-9	68/7928	127/14711	0.85	0.60-1.19	1.03	0.73-1.45	1.05	0.68-1.62
Melanoma	172	4/7992	10/14828	1.46	0.30-7.20	1.76	0.37-8.35	1.81	0.30-10.93
All ischemic heart disease	410-2, 414	823/7173	1018/13820	**0.68**	**0.59-0.79**	0.91	0.79-1.04	0.95	0.81-1.13
Acute Myocardial Infarction	410-2	483/7513	591/14247	**0.69**	**0.58-0.82**	0.91	0.76-1.08	0.97	0.80-1.19
Other ischemic heart disease	414	340/7656	427/14411	**0.67**	**0.55-0.82**	0.90	0.74-1.10	0.92	0.72-1.18
Heart failure	428	41/7955	60/14778	0.92	0.53-1.59	1.28	0.73-2.26	1.44	0.77-2.72
Complications of heart disease	429	103/7893	116/14722	**0.54**	**0.36-0.81**	0.69	0.46-1.03	0.90	0.55-1.50
Intracranial hemorrhage/stroke	430-432	36/7960	58/14780	0.98	0.51-1.87	1.10	0.61-2.00	1.16	0.60-2.24
Cerebral artery occlusion	434	41/7955	55/14783	**0.44**	**0.25-0.76**	0.62	0.36-1.07	0.56	0.29-1.09
Stroke	436	131/7865	157/14681	**0.61**	**0.43-0.87**	0.86	0.60-1.22	0.91	0.62-1.33
Cerebral arteriosclerosis	437	18/7978	21/14817	0.58	0.25-1.38	0.82	0.32-2.11	0.77	0.23-2.61

[1]Person-years in the study used as follow-up time
[2]Age used as the time-metric for follow-up in study weighted models
[3]Adjusted for: BMI, sex, race, poverty index, education and smoking in study with age as time metric for follow-up

mortality, including that for cardiovascular diseases, were attenuated. Age was a very strong negative confounder with proportion aspirin users declining steadily among older cohort participants (Table I). The only significant protective association after adjusting for confounders was for all cause mortality and lung cancer among men.

Risk of brain cancer death appears elevated in female aspirin users compared to non-users (RR: 3.13; 95% CI: 1.09-9.00). The primary limitation of this finding is that there were few women (n=20) with brain cancer in the analytical cohort. We also observed increased risk of death from bladder cancer among women aspirin users (RR:

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Table III. *Association between aspirin use and mortality for males in NHANES I and II.*

Mortality Cause	ICD9	Aspirin non-users: Cases/ non-cases	Aspirin users: Case/ non-cases	Unajusted[1]		Age-adjusted[2]		Multivariate[3]	
				RR	95% CI	RR	95% CI	RR	95% CI
All cause mortality	All causes	1733/2201	1900/4035	**0.68**	**0.62-0.75**	**0.89**	**0.82-0.98**	**0.88**	**0.80-0.98**
All cancer	140-208 (excluding 173)	417/3517	473/5462	**0.68**	**0.56-0.82**	0.86	0.71-1.05	0.90	0.73-1.13
Digestive	150-159	106/3828	104/5831	**0.64**	**0.46-0.90**	0.81	0.58-1.13	0.87	0.60-1.25
Esophagus	150	16/3918	15/5920	0.65	0.28-1.47	0.85	0.39-1.87	0.66	0.34-1.33
Stomach	151	15/3919	14/5921	0.73	0.26-2.01	0.96	0.37-2.47	0.90	0.33-2.46
Colorectal	153-154	44/3890	42/5893	**0.52**	**0.30-0.89**	0.62	0.36-1.06	0.68	0.37-1.26
Pancreas	157	20/3914	24/5911	0.88	0.41-1.89	1.01	0.55-2.22	1.03	0.52-2.07
Respiratory	160-165	145/3789	163/5772	**0.66**	**0.49-0.90**	0.81	0.58-1.13	0.73	0.52-1.02
Trachea, bronchus and lung	162	140/3794	155/5780	**0.63**	**0.46-0.86**	0.77	0.55-1.07	**0.69**	**0.49-0.96**
Prostate	185	59/3875	62/5873	0.63	0.37-1.07	0.89	0.53-1.50	1.11	0.60-2.05
Urinary	188-189	19/3915	33/5902	1.02	0.50-2.12	1.34	0.66-2.73	2.13	0.92-4.92
Bladder	188	8/3926	17/5918	0.99	0.32-3.11	1.29	0.44-3.83	2.20	0.54-8.93
Kidney	189	11/3923	16/5919	1.05	0.42-2.65	1.39	0.55-3.50	2.14	0.75-6.10
Brain	191	6/3928	5/5930	0.37	0.09-1.52	0.36	0.09-1.49	0.29	0.07-1.13
Lymphoma	200-203	22/3912	23/5912	0.69	0.33-1.43	0.84	0.39-1.80	1.23	0.61-2.46
Leukemia	204-208	21/3913	20/5915	0.60	0.30-1.19	0.82	0.43-1.59	1.13	0.56-2.26
Other	140-9, 170-2, 190, 191-9	45/3889	67/5868	**0.62**	**0.39-0.98**	0.77	0.47-1.26	0.80	0.43-1.50
Melanoma	172	3/3931	6/5929	1.76	0.25-12.56	2.61	0.36-19.11	2.67	0.21-34.04
All ischemic heart disease	410-2, 414	520/3414	562/5373	**0.73**	**0.61-0.88**	0.99	0.82-1.19	0.94	0.75-1.16
Acute Myocardial Infarction	410-2	311/3623	343/5592	**0.74**	**0.58-0.94**	0.99	0.77-1.28	0.96	0.72-1.29
Other ischemic heart disease	414	209/3725	219/5716	**0.72**	**0.56-0.92**	0.97	0.76-1.25	0.89	0.68-1.16
Heart failure	428	20/3914	27/5908	0.87	0.42-1.80	1.20	0.52-2.73	1.39	0.51-3.76
Complications of heart disease	429	64/3870	63/5872	0.70	0.45-1.10	0.91	0.58-1.44	0.86	0.48-1.53
Intracranial hemorrhage/stroke	430-432	23/3911	15/5920	0.63	0.26-1.50	0.68	0.30-1.56	0.80	0.31-2.08
Cerebral artery occlusion	434	17/3917	29/5906	0.71	0.29-1.72	1.01	0.41-2.54	0.98	0.38-2.69
Stroke	436	60/3874	54/5881	**0.57**	**0.35-0.94**	0.88	0.53-1.48	1.18	0.69-2.01
Cerebral arteriosclerosis	437	8/3926	8/5927	0.55	0.18-1.72	0.64	0.14-2.91	0.48	0.11-2.03

[1]Person-years in the study used as follow-up time
[2]Age used as time-metric for follow-up in study
[3]Adjusted for: BMI, sex, race, poverty index, education and smoking in study with age as time metric for follow-up

12.31; 95% CI: 2.98-50.80). The limitation here is also small samples size (n=15). The main excretory products of aspirin in urine are aspirin itself (acetyl salicyclic acid), salicyclic acid, salicyluric acid and gentisic acid, none of which are considered to be carcinogenic. There is one report of a protective association between NSAIDs use and bladder cancer risk in a case-control study conducted in Los-Angeles, California (15). However, Hultengren and

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Table IV. *Association between aspirin use and mortality for females in NHANES I and II.*

Mortality Cause	ICD9	Aspirin non-users: Cases/ non-cases	Aspirin users: Case/ non-cases	Unajusted[1]		Age-adjusted[2]		Multivariate[3]	
				RR	95% CI	RR	95% CI	RR	95% CI
All cause mortality	All causes	1127/2935	1785/7118	**0.73**	**0.66-0.81**	0.95	0.86-1.04	0.96	0.86-1.07
All cancer	140-208 (excluding 173)	250/3812	448/8455	0.86	0.70-1.06	1.02	0.84-1.25	1.07	0.84-1.35
Digestive	150-159	79/3983	121/8782	0.71	0.48-1.05	0.89	0.61-1.31	1.03	0.67-1.61
Esophagus	150	5/4057	1/8902	0.07	0.00-1.69	0.08	0.004-1.63	0.07	0.0006-9.64
Stomach	151	10/4052	9/8894	0.59	0.18-1.95	0.75	0.24-2.39	0.51	0.12-2.12
Colorectal	153-154	36/4026	71/8832	1.02	0.63-1.64	1.30	0.81-2.08	1.61	0.91-2.85
Pancreas	157	15/4047	19/8884	0.50	0.15-1.72	0.60	0.17-2.07	0.67	0.17-2.73
Respiratory	160-165	39/4023	79/8824	0.93	0.58-1.50	1.13	0.71-1.80	1.08	0.66-1.78
Trachea, bronchus and lung	162	38/4024	77/8826	0.94	0.58-1.53	1.14	0.71-1.83	1.10	0.67-1.81
Breast	174	47/4015	84/8819	0.70	0.47-1.05	0.89	0.58-1.36	0.82	0.49-1.36
Genital	179-184	22/4040	48/8855	1.09	0.58-2.04	1.43	0.75-2.71	1.26	0.62-2.56
Cervix	180	3/4059	11/8892	3.26	0.65-16.43	4.07	0.81-20.49	3.48	0.78-15.59
Uterus	182	3/4059	5/8898	0.85	0.13-5.78	1.36	0.19-9.54	1.15	0.15-8.49
Urinary	188-189	8/4054	17/8886	**2.99**	**1.17-7.63**	**3.70**	**1.51-9.08**	**4.97**	**1.47-16.79**
Bladder	188	5/4057	10/8893	**4.84**	**1.43-16.41**	**5.83**	**1.72-19.75**	**12.31**	**2.98-50.80**
Kidney	189	3/4059	7/8896	1.91	0.45-8.15	2.45	0.62-9.62	2.58	0.52-12.78
Brain	191	4/4058	16/8887	2.25	0.75-6.77	**3.23**	**1.11-9.36**	**3.13**	**1.09-9.00**
Lymphoma	200-203	21/4041	28/8875	0.68	0.30-1.55	0.85	0.37-1.95	0.81	0.36-1.85
Leukemia	204-208	11/4051	11/8892	0.42	0.15-1.20	0.48	0.18-1.27	0.82	0.31-2.19
Other	140-9, 170-2, 190, 191-9	23/4039	60/8843	1.76	0.97-3.21	**2.23**	**1.26-3.96**	**2.02**	**1.15-3.56**
Melanoma	172	1/4061	4/8899	1.20	0.08-17.44	1.36	0.16-11.83	0.86	0.11-6.69
All ischemic heart disease	410-2, 414	303/3759	456/8447	**0.70**	**0.56-0.87**	0.96	0.78-1.17	0.96	0.77-1.20
Acute Myocardial Infarction	410-2	172/3890	248/8655	**0.72**	**0.58-0.89**	0.97	0.79-1.18	0.96	0.76-1.23
Other ischemic heart disease	414	131/3931	208/8695	0.67	0.45-1.01	0.94	0.64-1.38	0.95	0.63-1.44
Heart failure	428	21/4041	33/8870	0.93	0.46-1.90	1.32	0.65-2.67	1.38	0.65-2.97
Complications of heart disease	429	39/4023	53/8850	**0.42**	**0.22-0.79**	0.59	0.33-1.06	0.97	0.50-1.89
Intracranial hemorrhage/stroke	430-432	13/4049	43/8860	1.75	0.78-3.93	2.04	0.98-4.28	1.91	0.82-4.48
Cerebral artery occlusion	434	24/4038	26/8877	**0.28**	**0.14-0.56**	**0.41**	**0.21-0.80**	**0.34**	**0.16-0.71**
Stroke	436	71/3991	103/8800	**0.61**	**0.38-0.98**	0.87	0.55-1.37	0.85	0.52-1.39
Cerebral arteriosclerosis	437	10/4052	13/8890	0.57	0.18-1.86	0.79	0.21-2.96	0.76	0.13-4.47

[1]Person-years in the study used as follow-up time

[2]Age used as time-metric for follow-up in study weighted models

[3]Adjusted for: BMI, sex, race, poverty index, education and smoking in study with age as time metric for follow-up

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colleagues described an association between analgesic abuse and urinary tract carcinoma incidence in 1965 in Sweden (16). Similarly, other reports have shown an increase in incidence of cancer of the bladder among excessive users of analgesics (17-19) and among individuals with analgesic nephropathy (23). Phenacetin abuse is considered to be the main cause of the increased incidence of carcinoma of the bladder and renal pelvis (21). In the current study, the bladder cancer cases identified could be excessive users of analgesics. Our finding of a possible adverse effect of aspirin use could also be spurious, resulting from the relatively small number of bladder and brain cancer cases and also due to the many comparisons made in our study.

The authors Schreinemachers and Everson (3) conducted a study similar to ours evaluating the incidence of cancer in the NHANES I cohort. In that very important study they showed an association between aspirin use and reduced incidence of lung and breast cancer. One difference between our study and that of Schreinemachers and Everson is that we evaluated the association between aspirin use and mortality, while they evaluated incidence. We felt that a mortality endpoint would be subject to less bias. In addition, our results include 5 years of additional follow-up and the follow-up of people in the NHANES II cohort.

In addition to our study and that of Schreinemachers and Everson, there are many studies examining NSAIDs, COX and risk of chronic diseases. An early population-based cohort study of site-specific cancer risk involving nearly 12,000 Swedish men and women with rheumatoid arthritis (presumed chronic NSAID users), reported decreased stomach and colorectal cancer risks (22). More than 25 subsequent retrospective and prospective epidemiological studies report that regular aspirin or NSAID use reduces the risk of colorectal adenoma, carcinoma, and/or carcinoma-related mortality by approximately 40-50% (5). Only two studies have shown no risk reduction for colorectal cancer in persons using aspirin (23, 24). Though the data are neither equally consistent nor compelling for all sites, in aggregate, studies show associations between NSAIDs and reductions in site-specific cancer risks in bladder (15), breast (3, 25-28), esophagus (8-10, 29), stomach (22, 29, 30), colorectum (6) and lung (3). In clinical trials, in persons with familial adenomatous polyposis (FAP), there have been more than 15 case series or reports describing the chemopreventive effects of sulindac or other NSAIDs on prevalent adenomas (31-36).

COX inhibitors may play a significant role in cancer treatment as well. Preclinical studies dating back 15 years demonstrate the efficacy of NSAIDs, and more recently NSAID derivatives and COX-2 inhibitors, in reducing the growth of tumor xenografts including melanoma (37) and cancers of the stomach (38), colorectum (39-41) and prostate (42). Despite these promising findings, only one clinical trial has been reported to date. Lundholm *et al.* conducted a randomized, placebo-controlled trial of indomethacin or prednisolone in 135 patients with malnutrition and various advanced malignancies (43). At the conclusion of the trial, they reported that patients taking indomethacin had significantly less pain and increased mean survival (510 *versus* 250 days). There is also some recent data suggesting that COX inhibitors and may disrupt the multidrug resistance cancer phenotype (44).

In aggregate, the literature and our study suggest that use of aspirin may have many potential health benefits. To our knowledge the possible adverse association between aspirin use and increased bladder and brain cancer risk in women has not been previously reported. These findings clearly need to be confirmed. However, for many cancers and cardiovascular diseases, our data suggests that aspirin use may be beneficial, although most of our findings were attenuated after adjusting for potential confounders.

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