Research Article

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Nonsteroidal Anti-inflammatory Drug and Acetaminophen Use and Risk of Adult Myeloid Leukemia

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Abstract

Background: Little is known about the causes of adult leukemia. A few small studies have reported a reduced risk associated with regular use of nonsteroidal anti-inflammatory drugs (NSAID).

Methods: In a population-based case–control study, we evaluated analgesic use among 670 newly diagnosed myeloid leukemia cases [including 420 acute myeloid leukemias (AML) and 186 chronic myeloid leukemias (CML)] and 701 controls aged 20 to 79 years. Prior use of aspirin, ibuprofen, acetaminophen, other NSAIDs, and COX-2 inhibitors was assessed and included frequency, duration, and quantity. ORs and 95% CIs were calculated using unconditional logistic regression adjusting for potential confounders.

Results: Regular/extra strength aspirin use was inversely associated with myeloid leukemia in women (OR = 0.59, 95% CI = 0.37–0.93) but not in men (OR = 0.85, 95% CI = 0.58–1.24). In contrast, acetaminophen use was associated with an increased risk of myeloid leukemia in women only (OR = 1.60, 95% CI = 1.04–2.47). These relationships were stronger with increasing dose and duration. When stratified by leukemia type, aspirin use was inversely associated with AML and CML in women. No significant overall associations were found with ibuprofen or COX-2 inhibitors for either sex; however, a decreased risk was observed with other anti-inflammatory analgesic use for women with AML or CML (OR = 0.47, 95% CI = 0.22–0.99; OR = 0.31, 95% CI = 0.10–0.92, respectively).

Conclusions: Our results provide additional support for the chemopreventive benefits of NSAIDs, at least in women. Because leukemia ranks fifth in person-years of life lost due to malignancy, further investigation is warranted.

Impact: NSAIDs may reduce, whereas acetaminophen may increase, myeloid leukemia risk in women. *Cancer Epidemiol Biomarkers Prev; 20(8); 1741–50. ©2011 AACR.*

Introduction

Each year in the United States, approximately 43,000 individuals will have a new diagnosis of leukemia and 22,000 will die from the disease (1). In adults, the most common types of leukemia are chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML); acute lymphoid leukemia (ALL) is very rare. In contrast to CLL, where 5-year survival rates approach 80%, only 24% of patients with AML and 55% of patients with CML are alive 5 years after diagnosis (2). Because of the overall poor survival, leukemia ranks fifth (following lung, breast, colorectal, and pancreas) in person-years of life lost due to cancer.

Despite the poor survival, few epidemiologic studies have been conducted that have specifically focused on the adult myeloid leukemias. There is some evidence that benzene, ionizing radiation, chemotherapeutic drugs, cigarette smoking, and certain genetic syndromes may play a role; however, taken together, these factors account for only a small proportion of adult cases (3).

Frequent use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) has been consistently associated with a reduced risk of colon cancer in observational studies and clinical trials (4). There is also evidence that regular NSAID use may decrease the risk of breast, prostate, lung, stomach, and esophageal cancer, although these data are less consistent (5–9). A few small studies have reported that regular use of nonprescription NSAIDs, especially aspirin, may decrease the risk of adult leukemia (10, 11), whereas one study found no association (12). In a population-based case–control study conducted without proxy interviews, we explored whether

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prior use of aspirin and other analgesics is associated with a reduced risk of adult myeloid leukemia.

Materials and Methods

Study population

Cases. Incident cases diagnosed during the period June 1, 2005, through November 30, 2009, with AML (ICD-O-3 codes: 9840, 9861, 9866–9867, 9871–9874, 9891–9897, 9910, 9920), CML (9863, 9875–9876), chronic myelomonocytic leukemia (CMML; 9945), or other myeloid leukemias (9860, 9865, 9869, 9870, 9911) were identified through the Minnesota Cancer Surveillance System (MCSS), which is an active population-based system that collects information on all malignancies diagnosed in Minnesota residents. MCSS reviews all pathology reports in the state and in border state medical facilities to ensure completeness in reporting.

Given the poor survival for leukemia, MCSS initiated a rapid case ascertainment system. For most hospitals and clinics, MCSS staff typically received and reviewed pathology logs within a month or two of diagnosis. In addition, the study was opened at 19 hospitals that treat the majority of AML cases to facilitate rapid enrollment. Patient eligibility included (a) Minnesota residency, (b) diagnosis between the ages of 20 and 79 years (inclusive), and (c) ability to understand English or Spanish. No proxy interviews were conducted. A total of 1,178 pathologically confirmed incident myeloid leukemia cases were identified through the MCSS. Of these, 230 died soon after diagnosis and thus were never forwarded to study staff and 41 were not referred because of physician and/or patient refusal. From a total of 907 patients referred to the study, we were unable to confirm contact for 52 patients and 22 patients died before contact. Of the 833 patients contacted (contact rate = 71%), 16% refused participation, 3% were ineligible, and 81% enrolled in the study, resulting in a cooperation rate of 83% and an overall response rate of 58% (13). The median time from date of diagnosis to enrollment was 70 days.

Controls. Controls were identified through the Minnesota State driver's license/identification card list. This list contains virtually all Minnesotans between 16 to 85 years of age and is available to qualified researchers. Control eligibility included (a) alive at the time of contact; (b) reside in the state of Minnesota; (c) be between 20 and 79 years of age (inclusive at time of selection); (d) understand English or Spanish; and (e) not have had a prior diagnosis of myeloid leukemia. Controls (as well as cases) with other malignancies were included, as they represented the at-risk population for myeloid leukemia. Controls were frequency matched to cases on age in deciles (20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years). Approximately 1 week before an introductory letter was sent to a potential control, the Social Security Death Index (SSDI) was used to screen out those who were deceased. Telephone numbers were traced using standard publically available tracing tools. Of a total of 1,200 population controls identified, 1,020 were contacted (contact rate = 85%), 213 refused participation, 106 were ineligible, and 701 were enrolled (cooperation rate = 77%), for an overall response rate of 64% (13).

Data collection

Following physician consent, study materials including an introductory letter and Health Insurance Portability and Accountability Act (HIPAA) covering permission for medical record acquisition, questionnaire, and return envelope were mailed to each case (or, if inpatient, provided by hospital staff). Cases were then contacted by study staff who summarized study goals and answered questions. For controls, an introductory letter was first mailed, followed 1 week later by the questionnaire and return envelope. For both cases and controls, if the questionnaire was not received in 3 weeks, telephone calls were placed by study staff to verify receipt and answer questions.

The self-administered questionnaire took approximately 30 minutes to complete. The questionnaire focused on demographics, lifestyle habits, physical activity, NSAID use, medical history, reproductive history, family health history, farm/rural living, pesticide exposure, occupation exposures, and types of chemical exposure around the home.

In addition to the University of Minnesota Institutional Review Board (IRB), IRBs at Mayo Clinic, the Minnesota Department of Health, and the participating area hospitals approved this study.

Pathology/cytogenetic review

Pathology reports, including all available cytochemical and flow cytometric immunophenotypic data, were reviewed by the study pathologist P.L. Nguyen. Results of cytogenetic analysis including both G-banded and FISH analyses were reviewed by B.A. Hirsch. For 91 cases, the actual blood and/or bone marrow slides were also reviewed microscopically for confirmation of the diagnosis and/or subclassification. Central review by Drs. Hirsch and Nguyen was conducted at study midpoint and end to finalize pathologic-genetic classification of all cases. Final classification resulted in 420 AML (3 additional AML cases were enrolled but died before completion of the questionnaire), 186 CML, and 64 CMML/other myeloid leukemia [including not otherwise specified (NOS)]. AML cases were further subclassified by World Health Organization (WHO) and French-American-British (FAB) subtypes (14–16). Of note, as a result of central review, the leukemia diagnosis (AML, CML, and other myeloid) changed for 4% of cases. In addition, 21% of cases were initially classified as AML, NOS; after central review, only 4% of AML cases remained NOS. Furthermore, the AML FAB subtype (not including NOS) changed for 16% of the cases. Results are presented for myeloid leukemia overall, AML, and CML.

Study variables (NSAID)

For the current analysis, we evaluated number of tablets taken per week, duration of use, and primary reason for use for each of the following analgesics: regular or extra strength aspirin, baby or low-dose aspirin, ibuprofen, acetaminophen, other anti-inflammatory (e.g., naproxen, indomethacin), and COX-2 inhibitors. Questions focused on regular use at least 2 years prior to the current date and did not include occasional use of less than once per month. Examples of each type of analgesic were provided. For each analgesic, a user was defined as someone who reported use at least once per week for at least 1 year; a nonuser was defined as no use or infrequent use (less than once per week). In addition to separate measures of aspirin dose (low/baby dose vs. regular/extra strength), we created a composite measure, which assumed 81 mg for low-dose aspirin and 325 mg for regular strength aspirin; thus, the reported use of 1 low-dose aspirin was equivalent to 0.25 regular strength aspirin. We estimated the average number of tablets per week by multiplying the usual number of days per month that tablets were taken by the number of tablets taken on days used and then dividing by 4. We categorized the average number of tablets per week as nonuser, less than 7, and 7 tablets or more. If the number of tablets taken on days used was missing, 1 tablet was assumed ($N = 8$). Duration of analgesic use was categorized as nonuser versus 1 to 5 years, 6 to 10 years, or more than 10 years for the more commonly used analgesics, and nonuser versus either 1 to 5 or more than 5 years and 1 to 2 or more than 2 years for analgesics used for a shorter duration.

Statistical analysis

Unconditional logistic regression (SAS 9.2; SAS Institute, Inc.) was used to evaluate the association between NSAID use and AML. On the basis of evidence of interaction of some analgesics with sex, we present data stratified by sex among combined cases and by AML and CML, separately. ORs and 95% CIs were produced, and the frequency matching variable (age) was included in all regression models as a continuous variable. Variables that were distributed differently among cases and controls and that were associated with one or more of the more commonly used analgesics (regular/extra strength aspirin, ibuprofen, and acetaminophen) were evaluated as potential confounders. Potential confounders that changed the natural logarithm of the OR by 10% or more for any of the commonly used analgesics were included in all multivariate models. We also explored the broad categories reported for taking analgesics among cases and controls including (i) cardiovascular disease health, (ii) musculoskeletal conditions, (iii) headache, general symptoms, and (iv) other reasons but found little evidence that these symptoms/conditions differed by case/control status.

Tests for linear trend were calculated by using the median value of each exposure category. Stratified analyses were carried out to evaluate differences in the effect of analgesic use on myeloid leukemia by sex, older age (<60 vs. ≥60 years), and on AML by WHO and FAB subtypes. The presence of effect modification was determined by a Wald test of the significance for the interaction term.

Results

Overall, cases and controls were similar with respect to age (frequency matching variable), education, and income (Table 1). More than 90% of cases and controls were non-Hispanic white. Men were more likely to develop AML and CML than women. Furthermore, AML cases were significantly more likely to be smokers at some point in their lifetime and to be overweight or obese at least 2 years prior to diagnosis.

Results for analgesic type and risk of myeloid leukemia stratified by sex are shown in Table 2. Female users of regular/extra strength aspirin were at a decreased risk of myeloid leukemia (OR = 0.59, 95% CI = 0.37–0.93), whereas the association was much weaker and not statistically significant in males (OR = 0.85, 95% CI = 0.58–1.24; $P_{interaction} = 0.11$). For females, there was no difference observed in the risk estimates for less than daily versus at least daily use but there was evidence for a significantly decreasing risk with increasing duration of use; no such patterns were observed among men. Low-dose aspirin, ibuprofen, and COX-2 inhibitor use seemed to have little effect on myeloid leukemia risk for either sex, whereas the use of other anti-inflammatory analgesics was significantly associated with a reduced risk, but again, only in females (OR = 0.45, 95% CI = 0.24–0.83; $P_{interaction} = 0.03$). In contrast, female acetaminophen users were at an increased risk of myeloid leukemia (OR = 1.60, 95% CI = 1.04–2.47), which was stronger with increasing tablet usage and duration of use. There was no association with acetaminophen use in males ($P_{interaction} = 0.55$). For the composite aspirin variable, which took into account dosage (low, regular/extra strength) and frequency, results were similar to those observed for regular/extra strength aspirin; the composite aspirin variable was used in subsequent analysis.

We further explored associations by leukemia type (Table 3). Aspirin was associated with a decreased risk of AML in women (OR = 0.61, 95% CI = 0.39–0.96) but not in men (OR = 1.00; 95% CI = 0.69–1.44); a similar pattern was observed for CML. A further decrease in AML risk was observed for increased aspirin frequency in women ($OR_{<7\ tablets/wk} = 0.68$; $OR_{\geq 7\ tablets} = 0.51$, $P_{trend} = 0.05$). No statistically significant associations were observed with ibuprofen or COX-2 inhibitors for either sex or leukemia subtype, although there was a suggestion of an increased risk of CML amongst women who reported frequent use of COX-2 inhibitors (OR = 2.17, 95% CI = 0.88–5.33). There was a decreased risk observed with the use of other anti-inflammatory

Table 1. Selected characteristics of adult myeloid leukemia cases ($N = 670$) and population-based controls ($N = 701$), 2005–2009

	Women			Men			AML ($N = 421$)			CML ($N = 186$)	
	Controls, *n* (%)	Cases, *n* (%)	OR (95% CI)[a]	Controls, *n* (%)	Cases, *n* (%)	OR (95% CI)[a]	Controls, *n* (%)	Cases, *n* (%)	OR (95% CI)[a]	Cases, *n* (%)	OR (95% CI)[a]
Age											
20–29	24 (7)	17 (6)	Matching	21 (6)	25 (6)	Matching	45 (6)	26 (6)	Matching	12 (6)	Matching
30–39	29 (8)	27 (10)	variable	24 (7)	21 (5)	variable	53 (8)	32 (8)	variable	15 (8)	variable
40–49	55 (15)	50 (18)		47 (14)	52 (13)		102 (15)	64 (15)		33 (18)	
50–59	80 (22)	63 (23)		77 (22)	80 (20)		157 (22)	90 (21)		48 (26)	
60–69	100 (28)	77 (28)		105 (31)	118 (30)		205 (29)	129 (31)		48 (26)	
70–79	70 (20)	44 (16)		69 (20)	96 (24)		139 (20)	79 (19)		30 (16)	
Sex											
Female	358	278		–	–		358 (51)	171 (41)	reference	79 (42)	reference
Male	–	–		343	392		343 (49)	249 (59)	1.53 (1.20–1.96)	107 (58)	1.43 (1.03–1.98)
Race/ethnicity											
White, non-Hispanic	339 (95)	262 (94)	reference	332 (97)	367 (94)	reference	671 (96)	394 (94)	reference	172 (92)	reference
Other	19 (5)	16 (6)	1.11 (0.55–2.23)	11 (3)	25 (6)	2.22 (1.07–4.63)	30 (4)	26 (6)	1.51 (0.87–2.61)	14 (8)	1.81 (0.93–3.50)
Education											
≤High school graduate	121 (34)	86 (31)	reference	110 (32)	126 (32)	reference	231 (33)	122 (29)	reference	67 (36)	reference
Some post–high school	115 (32)	101 (36)	1.18 (0.80–1.76)	125 (36)	135 (34)	0.98 (0.68–1.39)	240 (34)	161 (38)	1.28 (0.94–1.72)	55 (30)	0.72 (0.48–1.09)
College graduate	122 (34)	91 (33)	0.99 (0.66–1.49)	108 (31)	131 (33)	1.10 (0.76–1.58)	230 (33)	137 (33)	1.14 (0.84–1.57)	64 (34)	0.87 (0.58–1.30)
Income[b]											
≤$40,000	152 (43)	118 (43)	reference	103 (30)	142 (37)	reference	255 (37)	149 (36)	reference	80 (44)	reference
$40,000–$80,000	137 (39)	100 (37)	0.89 (0.62–1.28)	144 (42)	146 (38)	0.75 (0.53–1.07)	281 (41)	165 (40)	1.01 (0.76–1.34)	64 (35)	0.66 (0.45–0.97)
>$80,000	62 (18)	54 (20)	1.05 (0.67–1.66)	93 (27)	95 (25)	0.77 (0.52–1.14)	155 (22)	95 (23)	1.06 (0.76–1.49)	39 (21)	0.69 (0.44–1.08)
Smoking status											
Never	202 (57)	136 (49)	reference	156 (46)	152 (39)	reference	358 (52)	179 (43)	reference	81 (44)	reference
Ever	152 (43)	141 (51)	1.39 (1.01–1.91)	182 (54)	234 (61)	1.30 (0.96–1.75)	334 (48)	235 (57)	1.42 (1.11–1.81)	104 (56)	1.43 (1.03–1.99)
BMI[c]											
Underweight	7 (2)	3 (1)	reference	3 (1)	2 (1)	reference	10 (1)	3 (1)	reference	0 (0)	reference
Normal weight	136 (38)	85 (31)	81 (24)	62 (16)	217 (31)	93 (22)	41 (22)				
Overweight	99 (28)	79 (29)	1.32 (0.89–1.97)	143 (42)	152 (39)	1.39 (0.93–2.07)	242 (35)	147 (35)	1.45 (1.05–1.98)	59 (32)	1.37 (0.88–2.12)
Obese	115 (32)	109 (39)	1.57 (1.07–2.29)	114 (33)	176 (45)	2.07 (1.38–3.12)	229 (33)	176 (42)	1.83 (1.34–2.50)	85 (46)	2.12 (1.39–3.24)

[a]Adjusted for age (deciles).

[b]Income may include retirement income.

[c]BMI based on weight 2 years prior to diagnosis/reference age.

Table 2. Adjusted ORs for specific types of NSAID use and risk of adult myeloid leukemia among women and men, 2005–2009

	Women				Men			
	Cases, *n* (%)	Controls, *n* (%)	OR[a]	95% CI	Cases, *n* (%)	Controls, *n* (%)	OR[a]	95% CI
Aspirin (regular/extra strength)								
Nonuser	237 (86)	281 (80)	1.00	reference	306 (79)	264 (78)	1.00	reference
User	38 (14)	72 (20)	0.59	0.37–0.93	80 (21)	74 (22)	0.85	0.58–1.24
Tablets per week								
<7	11 (4)	22 (6)	0.56	0.26–1.20	17 (4)	20 (6)	0.73	0.37–1.46
≥7	27 (10)	50 (14)	0.60	0.35–1.02	63 (16)	54 (16)	0.89	0.58–1.36
P_{trend}				0.03				0.50
Duration of use, y								
1–5	9 (3)	16 (5)	0.70	0.30–1.64	21 (5)	17 (5)	1.05	0.53–2.06
6–10	11 (4)	20 (6)	0.61	0.28–1.33	26 (7)	23 (7)	0.83	0.45–1.52
>10	18 (7)	36 (10)	0.53	0.29–0.99	33 (9)	34 (10)	0.76	0.45–1.30
P_{trend}				0.03				0.27
Aspirin (low dose)								
Nonuser	227 (83)	287 (81)	1.00	reference	283 (73)	259 (76)	1.00	reference
User	48 (17)	66 (19)	0.96	0.61–1.50	106 (27)	80 (24)	1.14	0.80–1.64
Tablets per week								
<7	5 (2)	6 (2)	1.09	0.31–3.78	7 (2)	5 (1)	1.26	0.39–4.09
≥7	43 (16)	60 (17)	0.95	0.59–1.51	99 (25)	75 (22)	1.14	0.78–1.65
P_{trend}				0.83				0.48
Duration of use, y								
1–5	26 (9)	39 (11)	0.89	0.51–1.55	53 (14)	33 (10)	1.41	0.87–2.30
6–10	13 (5)	13 (4)	1.18	0.52–2.72	32 (8)	30 (9)	0.87	0.50–1.51
>10	9 (3)	14 (4)	0.93	0.38–2.27	21 (5)	17 (5)	1.10	0.55–2.18
P_{trend}				1.00				0.99
Aspirin (any dose, weighted)								
Nonuser	202 (73)	228 (64)	1.00	reference	221 (57)	202 (59)	1.00	reference
User	74 (27)	128 (36)	0.62	0.42–0.90	169 (43)	139 (41)	1.02	0.74–1.42
Tablets per week								
<7	47 (17)	76 (21)	0.67	0.43–1.04	102 (26)	81 (24)	1.09	0.75–1.58
≥7	27 (10)	52 (15)	0.53	0.31–0.91	67 (17)	58 (17)	0.93	0.60–1.43
P_{trend}				0.02				0.71
Ibuprofen								
Nonuser	203 (75)	260 (75)	1.00	reference	313 (82)	278 (82)	1.00	reference
User	69 (25)	89 (26)	0.89	0.60–1.32	71 (18)	62 (18)	1.02	0.69–1.51
Tablets per week								
<7	27 (10)	36 (10)	0.85	0.49–1.49	32 (8)	27 (8)	1.15	0.66–2.00
≥7	42 (15)	53 (15)	0.92	0.57–1.49	39 (10)	35 (10)	0.92	0.56–1.53
P_{trend}				0.72				0.76
Duration of use, y								
1–5	25 (9)	28 (8)	1.02	0.56–1.87	30 (8)	17 (5)	1.71	0.91–3.21
6–10	25 (9)	24 (7)	1.22	0.66–2.27	22 (6)	24 (7)	0.78	0.41–1.45
>10	19 (7)	37 (11)	0.59	0.32–1.09	19 (5)	21 (6)	0.74	0.38–1.44
P_{trend}				0.19				0.32
Acetaminophen								
Nonuser	209 (77)	289 (83)	1.00	reference	341 (88)	304 (89)	1.00	reference
User	63 (23)	61 (17)	1.60	1.04–2.47	45 (12)	37 (11)	1.09	0.67–1.77
Tablets per week								
<7	24 (9)	34 (10)	1.06	0.59–1.89	22 (6)	18 (5)	1.08	0.56–2.07
≥7	39 (14)	27 (8)	2.37	1.34–4.18	23 (6)	19 (6)	1.09	0.57–2.12
P_{trend}				0.003				0.77

(Continued on the following page)

Table 2. Adjusted ORs for specific types of NSAID use and risk of adult myeloid leukemia among women and men, 2005–2009 (Cont'd)

	Women				Men			
	Cases, *n* (%)	Controls, *n* (%)	OR[a]	95% CI	Cases, *n* (%)	Controls, *n* (%)	OR[a]	95% CI
Duration of use, y								
1–5	21 (8)	22 (6)	1.70	0.87–3.29	20 (5)	11 (3)	1.66	0.77–3.59
6–10	19 (7)	21 (6)	1.24	0.63–2.44	14 (4)	9 (3)	1.44	0.60–3.47
>10	23 (8)	18 (5)	1.96	1.00–3.84	11 (3)	17 (5)	0.55	0.25–1.21
P_{trend}				0.04				0.32
Other anti-inflammatory analgesics								
Nonuser	252 (94)	305 (88)	1.00	reference	367 (94)	324 (96)	1.00	reference
User	17 (6)	43 (12)	0.45	0.24–0.83	22 (6)	15 (4)	1.15	0.58–2.30
Tablets per week								
<7	9 (3)	8 (2)	1.35	0.49–3.70	5 (1)	4 (1)	1.08	0.28–4.10
≥7	8 (3)	35 (10)	0.26	0.11–0.58	17 (4)	11 (3)	1.18	0.53–2.61
P_{trend}				0.001				0.68
Duration of use, y								
1–5	12 (4)	25 (7)	0.54	0.26–1.12	13 (3)	8 (2)	1.26	0.51–3.14
>5	5 (2)	18 (5)	0.32	0.11–0.90	9 (2)	7 (2)	1.02	0.37–2.83
P_{trend}				0.01				0.90
COX-2 inhibitors								
Nonuser	247 (90)	319 (90)	1.00	reference	370 (95)	325 (96)	1.00	reference
User	26 (10)	34 (10)	1.08	0.60–1.93	21 (5)	15 (4)	1.10	0.55–2.21
Tablets per week								
<7	1 (0.5)	9 (3)	0.13	0.02–1.12	2 (0.5)	3 (1)	0.88	0.12–6.72
≥7	25 (9)	25 (7)	1.45	0.77–2.72	19 (5)	12 (4)	1.13	0.54–2.36
P_{trend}				0.35				0.76
Duration of use, y								
1–2	15 (5)	17 (5)	1.25	0.59–2.67	11 (3)	7 (2)	1.23	0.46–3.30
>2	11 (4)	17 (5)	0.90	0.39–2.05	10 (3)	8 (2)	0.99	0.38–2.57
P_{trend}				0.87				0.97

NOTE: For each type of analgesic, a user is defined as someone who reported use at least 1 time per week for at least 1 year. Duration of use was asked in terms of years; 1 person was excluded for reporting 0 years.

[a]Adjusted for age (continuous), BMI (underweight/normal, overweight, and obese), and other analgesic use (yes/no for each of the other 5 types).

analgesics for women for both AML and CML (OR = 0.47; 95% CI = 0.22–0.99.0; OR = 0.31; 95% CI = 0.10–0.92, respectively), which was strongest amongst frequent (≥7 tablets) users ($P_{trend} = 0.006$ and $P_{trend} = 0.02$, respectively).

Further analyses compared risk estimates for women and men by age (≥60 and <60 years), as well as by AML and WHO and FAB subtypes (data not shown). Of note, the reduced risk of myeloid leukemia associated with aspirin use seemed more apparent for the younger women (OR = 0.50, 95% CI = 0.27–0.92) rather than for the older (OR = 0.70, 95% CI = 0.42–1.15) women ($P_{interaction} = 0.56$). There was no pattern for men, nor were there any remarkable age patterns for other analgesics. There were also no obvious patterns when AML was further stratified by subtype.

Discussion

In our study, regular/extra strength aspirin as well as other anti-inflammatory analgesic use was associated with a decreased risk of myeloid leukemia in women but not in men. In contrast, acetaminophen use was associated with an increased risk of myeloid leukemia for women only. We found no associations with low-dose aspirin or ibuprofen with either sex or leukemia subtype.

We are aware of only 3 studies that have explored the association between over-the-counter analgesic use and risk of adult leukemia. In a prospective cohort study of more than 28,000 postmenopausal women in Iowa, Kasum and colleagues (10) reported a 55% (95% CI = 0.27–0.75) decreased risk of leukemia (81 cases, mostly AML and CLL) in women who reported using

Table 3. Adjusted ORs for specific types of NSAID use and risk of adult myeloid leukemia, by sex and leukemia subtype, 2005–2009

	Women							Men						
	Controls, *n* (%)	AML, *n* (%)	OR[a]	95% CI	CML, *n* (%)	OR[a]	95% CI	Controls, *n* (%)	AML, *n* (%)	OR[a]	95% CI	CML, *n* (%)	OR[a]	95% CI
Aspirin (any dose, weighted)														
Nonuser	228 (64)	127 (75)	1.00	reference	55 (71)	1.00	reference	202 (59)	138 (56)	1.00	reference	62 (58)	1.00	reference
User	128 (36)	43 (25)	0.61	0.39–0.96	23 (29)	0.61	0.34–1.11	139 (41)	109 (44)	1.00	0.69–1.44	45 (42)	1.33	0.80–2.22
Tablets per week														
<7	76 (21)	28 (16)	0.68	0.41–1.15	12 (15)	0.55	0.26–1.14	81 (24)	66 (27)	1.06	0.70–1.63	25 (23)	1.25	0.70–2.24
≥7	52 (15)	15 (9)	0.51	0.26–0.99	11 (14)	0.71	0.33–1.54	58 (17)	43 (17)	0.91	0.56–1.48	20 (19)	1.47	0.76–2.83
P_{trend}				0.05			0.37				0.68			0.26
Ibuprofen														
Nonuser	260 (75)	123 (74)	1.00	reference	58 (74)	1.00	reference	278 (82)	198 (82)	1.00	reference	88 (83)	1.00	reference
User	89 (26)	44 (26)	0.94	0.59–1.49	20 (26)	0.92	0.50–1.68	62 (18)	44 (18)	1.03	0.66–1.61	18 (17)	0.79	0.42–1.47
Tablets per week														
<7	36 (10)	20 (12)	1.00	0.54–1.87	6 (8)	0.72	0.28–1.86	27 (8)	22 (9)	1.26	0.68–2.34	7 (7)	1.07	0.36–3.21
≥7	53 (15)	24 (14)	0.89	0.50–1.58	14 (18)	1.04	0.51–2.11	35 (10)	22 (9)	0.86	0.48–1.54	11 (10)	1.32	0.54–3.22
P_{trend}				0.69			0.88				0.56			0.55
Acetaminophen														
Nonuser	289 (83)	133 (79)	1.00	reference	59 (78)	1.00	reference	304 (89)	217 (89)	1.00	reference	94 (89)	1.00	reference
User	61 (17)	35 (21)	1.46	0.87–2.44	17 (22)	1.24	0.64–2.42	37 (11)	28 (11)	1.06	0.61–1.83	12 (11)	1.07	0.51–2.23
Tablets per week														
<7	34 (10)	14 (8)	0.98	0.49–1.96	5 (7)	0.66	0.24–1.86	18 (5)	17 (7)	1.29	0.64–2.61	3 (3)	0.54	0.15–1.92
≥7	27 (8)	21 (13)	2.16	1.11–4.23	12 (16)	1.98	0.88–4.45	19 (6)	11 (4)	0.82	0.37–1.84	9 (8)	1.64	0.67–4.05
P_{trend}				0.03			0.10				0.44			0.36
Other anti-inflammatory analgesics														
Nonuser	305 (88)	155 (94)	1.00	reference	73 (95)	1.00	reference	324 (96)	233 (94)	1.00	reference	101 (96)	1.00	reference
User	43 (12)	10 (6)	0.47	0.22–0.99	4 (5)	0.31	0.10–0.92	15 (4)	16 (6)	1.28	0.61–2.70	4 (4)	0.83	0.26–2.63
Tablets per week														
<7	8 (2)	6 (4)	1.51	0.49–4.69	2 (3)	0.84	0.17–4.26	4 (1)	2 (1)	0.70	0.13–3.92	2 (2)	1.55	0.27–8.99
≥7	35 (10)	4 (2)	0.23	0.08–0.69	2 (3)	0.19	0.04–0.83	11 (3)	14 (6)	1.48	0.64–3.39	2 (2)	0.55	0.11–2.67
P_{trend}				0.01			0.02				0.38			0.47
COX-2 inhibitors														
Nonuser	319 (90)	154 (92)	1.00	reference	68 (88)	1.00	reference	325 (96)	234 (94)	1.00	reference	100 (93)	1.00	reference
User	34 (10)	14 (8)	1.02	0.50–2.08	9 (12)	1.54	0.66–3.62	15 (4)	14 (6)	1.16	0.53–2.50	7 (7)	1.47	0.56–3.85
Tablets per week														
<7	9 (3)	1 (1)	0.24	0.03–2.00	0 (0)	–	–	2 (1)	2 (1)	1.49	0.19–11.6	0 (0)	–	–
≥7	25 (7)	13 (8)	1.34	0.63–2.88	9 (12)	2.17	0.88–5.33	13 (4)	12 (5)	1.11	0.49–2.53	7 (7)	1.75	0.66–4.66
P_{trend}				0.47			0.13				0.73			0.31

NOTE: For each type of medication, a user is defined as someone who reported use at least 1 time per week for at least 1 year.

[a]Adjusted for age (continuous), BMI (underweight/normal, overweight, and obese), and other NSAID use (yes/no for each of the other 5 types).

aspirin 2 or more times weekly compared with women who never used aspirin. In contrast, the authors found a slight 31% (95% CI = 0.77–2.22) increased risk of leukemia with the use of nonaspirin NSAIDs. In a case–control study of acute leukemia (169 cases and 676 controls) in New York, Weiss and colleagues (11) reported a 16% (95% CI = 0.59–1.21) nonstatistically significant decreased risk of acute leukemia with aspirin use; results were stronger for ALL than AML and were found for both sexes. Furthermore, they reported a statistically significant 53% (95% CI = 1.03–2.26) increased risk of acute leukemia associated with the use of acetaminophen. Finally, in a prospective cohort study, Walter and colleagues (12) reported a statistically significant 130% increased risk (95% CI = 1.12–4.73) of AML and myelodysplastic syndromes combined ($N = 90$) with high ($\geq$4 d/wk for $\geq$4 years) acetaminophen use compared with lower use. They found no evidence of an association with NSAID use, including aspirin. Of note, the increased risk of hematologic malignancy associated with acetaminophen in the overall cohort seemed confined mostly to women.

Although based on a small number of cases, we also found an increased risk of CML associated with the use of COX-2 inhibitors in women. Only 3 studies to our knowledge have evaluated the risk of adult leukemia and the use of prescription NSAIDs. In the United Kingdom, Bhayat and colleagues (17) linked data from more than 330 general practices, which included medical and prescribed drug histories on more than 5 million patients. More than 3,200 leukemia patients were identified along with 4 age-, gender-, and practice-matched controls per case. In an examination of NSAID prescription rate prior to leukemia diagnosis and risk of leukemia, the authors found no overall associations, with the possible exception of an increased risk of CLL with 2 to 5 NSAID prescriptions per year. Pogoda and colleagues (18) reported a 50% decreased risk of AML in a case–control study (299 matched pairs) with the use of a prescription NSAID at least 2 years prior to diagnosis. Finally, Traversa and colleagues (19), in a linkage study in Italy of adult leukemia (202 cases and 2,020 controls) and prescription drugs, reported a nonstatistically significant 60% decreased risk of leukemia associated with prior use of prescription NSAIDs for more than 180 days. Unfortunately, none of these studies provided NSAID-specific analyses.

In addition to anti-inflammatory properties, aspirin, ibuprofen, COX-2 inhibitors, and other NSAIDs possess antipyretic and analgesic properties (20, 21). Acetaminophen also possesses the latter 2 properties, but it is considered only a weak anti-inflammatory drug (21). All of these drugs target the COX enzymes, COX-1, -2, and -3, although to varying degrees. For example, aspirin irreversibly inhibits both COX-1 and COX-2 whereas binding by other NSAIDs is reversible (22); acetaminophen preferentially inhibits COX-3. COX enzymes produce prostaglandins that are formed at sites of inflammation. Although it is unclear why cancer risk might be decreased by regular use of certain analgesics, analgesic-associated reductions in prostaglandin synthesis and oxidative cell damage, inhibition of angiogenesis, and disruption of signal transduction pathways have all been speculated to influence risk of malignancy (23, 24). Inverse associations we observed with aspirin and other anti-inflammatory analgesics, in light of positive associations observed with COX-2 and COX-3 inhibitors, may suggest that COX-1 inhibition is most relevant. However, inhibition seems to vary by drug class as well as target tissue (e.g., brain and gastrointestinal tract), which adds to the complexity of understanding mechanisms (21).

Specific to hematopoiesis, there is evidence that certain drugs have differential effects on leukemia cells. For example, aspirin has been shown to induce apoptosis in AML cell lines (25) whereas COX-2 inhibitors induce apoptosis in CML cell lines (24). The increased risk of myeloid leukemia with acetaminophen could be due to the genotoxic effects of a metabolite, *N*-acetyl-*p*-benzoquinone imine, which has been shown to be a DNA topoisomerase II poison (26). DNA topoisomerase II chemotherapy poisons, including etoposide, are associated with secondary leukemias, particularly AML (27). In addition, a few experimental studies suggest that acetaminophen is genotoxic to bone marrow and could increase risk of leukemia (reviewed in ref. 28). Taken in toto, however, it is difficult to speculate on how each of these drugs may influence myeloid leukemia risk, especially in the context of a population-based study.

It is also not clear why we observed significant associations for women but not for men. It is possible that these are chance findings, but given the differing directions by analgesic type (i.e., aspirin vs. acetaminophen), this seems less likely. In studies of the cardioprotective effects of aspirin, there is evidence that men and women respond differently, which could be related to metabolic and/or hormonal differences (reviewed in ref. 29). For example, in contrast to effects observed in men, aspirin has been shown to significantly reduce the risk of stroke but has little influence on the risk of myocardial infarction or mortality in women (30). Related to our findings, sex-specific differences have been reported with regard to analgesic use and risk of certain malignancies, such as lung cancer, non–Hodgkin lymphoma, and most recently, hematopoietic malignancies (31, 32). Moreover, because of the discovery of the cardioprotective benefits identified in clinical trials decades ago, at-risk men have been (and continue to be) advised by their physicians to begin an aspirin regimen early. However, women have lagged behind in these global recommendations and still have a 5% to 10% lower overall prevalence of aspirin use compared with men (33, 34). It is possible that long-term increasing aspirin prevalence among men could diminish the ability to detect an association, assuming that at least some of these men will now never develop leukemia. We acknowledge that we carried out numerous comparisons

and thus our statistically significant results could be false-positive findings. In a few instances, there was a lack of dose response. It will be important to confirm these sex-specific differences, ideally through pooled cohort studies.

Recall bias is a potential limitation to our study, which could further be influenced by conditions associated with disease status. Given the broad scope of the questionnaire, and the lack of readily available public information regarding associations between NSAIDs and leukemia, it seems unlikely that recall would be differential amongst cases and controls. Furthermore, our observations differed by sex and leukemia subtype, and it would be unlikely that selective recall would be associated with specific groups. To diminish the possibility that disease status affected analgesic use, we focused on a period at least 2 years prior to study enrollment. Nevertheless, there is the possibility of nondifferential misclassification. Furthermore, the primary reason for using each type of analgesic was collected using an open-ended question, which resulted in a variety of responses along with some missing values. Adjustment for broad categories of reasons for analgesic use did not materially alter our risk estimates, although some residual confounding by indication could remain.

Although our participation rates (58% for cases and 64% for controls) are comparable if not better than other case–control studies of rapidly fatal malignancies including leukemia and pancreatic cancer (18, 35, 36), selection bias is still a concern. Our controls were recruited from the population and represent an accurate base from which cases arose; importantly, participating cases and controls were comparable in education and income. Moreover, the prevalence of reported aspirin use by controls in our study is comparable with that reported in a national survey (33). Nevertheless, controls or cases who participated could still be fundamentally different with regard to analgesic use compared with those who did not participate. We controlled for age, body mass index (BMI), and other analgesic use in our analyses but cannot rule out residual confounding. It is also important to note that no proxy interviews were conducted in our study. Proxy interviews are prone to misclassification and bias, which is difficult to quantify, particularly if the proportion of proxy interviews between cases and controls differs (37). Thus, our study results may be difficult to compare with others, such as Pogoda and colleagues, for whom 49% of interviews were completed by proxy (18).

In conclusion, this is the largest population-based study to evaluate the use of NSAIDs and risk of adult myeloid leukemia. We found further evidence of a protective association with aspirin (at least in women), and we confirm previous findings of a positive association with acetaminophen. Given the interest in understanding the potential benefits and harm associated with over-the-counter analgesics, and the fact that leukemia is ranked fifth in person-years of life lost due to cancer, further studies of these associations are warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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