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ORIGINAL REPORT

Long-Term Use of Acetaminophen, Aspirin, and Other Nonsteroidal Anti-Inflammatory Drugs and Risk of Hematologic Malignancies: Results From the Prospective Vitamins and Lifestyle (VITAL) Study

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ABSTRACT

Purpose
Among previous studies examining the associations of over-the-counter analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) and incident hematologic malignancies, results were inconsistent for NSAIDs but suggested an increased risk with acetaminophen (paracetamol). Herein, we used a large prospective cohort study to examine these associations.

Patients and Methods
In total, 64,839 men and women age 50 to 76 years were recruited from 2000 to 2002 to the Vitamins and Lifestyle (VITAL) study. Incident hematologic malignancies (n = 577) were identified through December 2008 by linkage to the Surveillance, Epidemiology and End Results cancer registry. Hazard ratios (HRs) associated with use of analgesics for total incident hematologic malignancies and cancer subcategories were estimated by Cox proportional hazards models. Models were adjusted for age, sex, race/ethnicity, education, smoking, self-rated health, arthritis, chronic musculoskeletal pain, migraines, headaches, fatigue, and family history of leukemia/lymphoma.

Results
After adjustment, there was an increased risk of incident hematologic malignancies associated with high use (≥ 4 days/week for ≥ 4 years) of acetaminophen (HR, 1.84; 95% CI, 1.35 to 2.50 for high use; *P* trend = .004). This association was seen for myeloid neoplasms (HR, 2.26; 95% CI, 1.24 to 4.12), non-Hodgkin's lymphomas (HR, 1.81; 95% CI, 1.12 to 2.93), and plasma cell disorders (HR, 2.42; 95% CI, 1.08 to 5.41), but not chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; HR, 0.84; 95% CI, 0.31 to 2.28). By comparison, there was no association with risk of incident hematologic malignancies for increasing use of aspirin, nonaspirin NSAIDs, or ibuprofen.

Conclusion
High use of acetaminophen was associated with an almost two-fold increased risk of incident hematologic malignancies other than CLL/SLL. Neither aspirin nor nonaspirin NSAIDs are likely useful for prevention of hematologic malignancies.

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INTRODUCTION

Increasing evidence from experimental studies links inflammation to the development, survival, and progression of tumors.[1] This notion is corroborated by epidemiologic studies showing that chronic inflammation predisposes to various types of cancer.[1] Accordingly, regular use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with decreased risk of, and mortality from, several tumor types.[1] However, although compelling in some neoplasms such as colorectal cancers, the chemopreventive role of these drugs in other cancers remains unclear. This is particularly true for hematologic malignancies, for which previous studies[2,3] yielded inconsistent results. For example, several case-control studies examined the association between NSAIDs and development of non-Hodgkin's lymphoma (NHL) and found either an increased risk, a decreased risk, or no association, whereas the only prospective study[2,3] reported an increased risk. Findings from a limited number of

studies conducted in Hodgkin's lymphoma suggested a reduced risk with use of aspirin but not with use of other NSAIDs.[2,4] Similarly, a small number of studies[2] suggested a reduced risk of acute leukemia with use of aspirin but yielded conflicting findings for use of nonaspirin NSAIDs.

By comparison, a relatively small number of studies have examined the association between risk of hematologic malignancies and use of acetaminophen (paracetamol), one of the most widely used analgesics. Nevertheless, these results have raised concerns that acetaminophen may increase the risk of several types of these malignancies.[2] Specifically, use of acetaminophen has been found to be associated with an increased risk of some hematologic malignancies in some but not all case-control studies[2,5]; however, no prior prospective studies have examined this association.

Given these conflicting findings and the relative lack of cohort studies on this topic, we examined the association of aspirin, nonaspirin NSAIDs, and acetaminophen use with incident hematologic malignancies in the prospective Vitamins and Lifestyle (VITAL) study.[6]

PATIENTS AND METHODS

Study Cohort

Details of the VITAL study, which was approved by the institutional review board of the Fred Hutchinson Cancer Research Center, have been published previously.[6] Briefly, we mailed questionnaires to 364,418 men and women age 50 to 76 years who lived in the 13-county area in western Washington State covered by the Surveillance, Epidemiology and End Results (SEER) cancer registry. Between October 2000 and December 2002, 79,300 questionnaires were returned, of which 77,719 were deemed eligible. To avoid treatment for an earlier cancer as a cause of blood cancer, we excluded 11,487 participants with prior history of any cancer other than nonmelanoma skin cancer reported at baseline (n = 11,273) and those with missing cancer information at baseline (n = 214). We additionally excluded 1,388 participants with missing information regarding use of all medications and five cases with postbaseline blood cancer on death certificate only without a diagnosis date, leaving 64,839 men and women available for study.

Data Collection

Participants completed a 24-page self-administered, sex-specific, optically scanned questionnaire at baseline that covered three content areas: medication and supplement use, health history and risk factors, and diet. Participants were asked about their regular use ($\geq$ 1 days/week for $\geq$ 1 years) of any of the following NSAIDs and other analgesics, including frequency (days/week) and duration of use over the previous 10 years: low-dose aspirin (81 mg), regular or extra-strength aspirin, ibuprofen, naproxen, celecoxib or rofecoxib, other pain relievers (piroxicam or indomethacin), and acetaminophen. For each drug type, the most common brand names were given as examples, including both over-the-counter and prescription brands. Ten-year average use (continuous) was computed by multiplying the reported frequency of use by years of use and dividing the product by 10. These data were also categorized as "no use," "low use" ($<$ 4 days/week or $<$ 4 years), and "high use" ($\geq$ 4 days/week and $\geq$ 4 years). Two summary NSAID variables were created by combining all NSAIDs except low-dose aspirin and all nonaspirin NSAIDs.

We also ascertained information on age, race/ethnicity, education, smoking, self-rated health, medical history, family history of leukemia or lymphoma, and other lifestyle characteristics. Medical conditions that may be associated with analgesic use were ascertained as self-report of health complaints over the prior year, including chronic neck, back, or joint pain; fatigue or lack of energy; frequent headaches; or self-report of ever having a physician diagnosis of selected conditions, including rheumatoid arthritis, arthritis other than rheumatoid, coronary artery disease defined as history of heart attack, coronary bypass surgery, angioplasty and/or angina, stroke, and migraine headaches. Diabetes was defined as current insulin use or drug treatment for diabetes.

Case Ascertainment

Incident cases of hematologic and other malignancies were identified through December 2008 by annual linkage to the western Washington SEER cancer registry by using matching algorithms described previously.[6] Cases were categorized by using the 2008 WHO classification system.[7]

Follow-Up for Censoring

The end date of follow-up was the earliest date of the following: diagnosis of hematologic malignancy (0.9%), withdrawal from study (0.03%), emigration from the SEER region (5.3%), cancer diagnosis other than hematologic malignancy or nonmelanoma skin cancer (9.4%), death (3.1%), or last linkage to the SEER registry (December 31, 2008; 81.3%). Moves out of the SEER region were identified via linkage to the US Post Office National Change of Address file, follow-up letters, and phone calls. Deaths were ascertained via linkage to the Washington State death file.

Statistical Analysis

Sex- and multivariable-adjusted Cox proportional hazards models that used robust standard errors[8] were used to estimate hazard ratios (HRs) and 95% CIs for the associations between medication use and risk of hematologic malignancies. Age was the time metric in regression models, with participants entering at the age of completing the baseline questionnaire and exiting at their age at end of follow-up. We selected a priori potential confounders, including known and suspected risk factors, for hematologic malignancies and medical conditions that may be indications for use of NSAIDs for adjustment in multivariable regression models. Specifically, for all models except low-dose aspirin, we adjusted for sex, race/ethnicity (white, Hispanic, other), education (high school graduate or less, some college, college, or advanced degree), smoking (pack-years), self-rated health (excellent, very good, good, fair, poor), history of rheumatoid arthritis, history of nonrheumatoid arthritis or chronic neck/back/joint pain, history of fatigue or lack of energy, history of migraines or frequent headaches, and number of first-degree relatives with a history of leukemia or lymphoma (none, one, two or more). For low-dose aspirin, which is primarily used for cardiovascular disease prevention rather than pain, we used the same covariates except a history of rheumatoid or nonrheumatoid arthritis or chronic pain but additionally included a history of coronary artery

Table 1. Classification of Incident Hematologic Malignancies

Disease	Patients	
	No.	%
Myeloid neoplasms	136	23.6
MDS	54	9.4
AML	36	6.2
Myeloproliferative neoplasms*	46	8.0
Mature B-cell neoplasms	389	67.4
CLL/SLL	88	15.3
Plasma cell disorders	66	11.4
Other mature B-cell neoplasm entities	235	40.7
Hodgkin's lymphoma	22	3.8
Mature natural killer/T-cell neoplasms	17	3.0
Others†	13	2.3
Total	577	100

Abbreviations: AML, acute myeloid leukemia; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MDS, myelodysplastic syndrome.
*Includes the diagnostic category of myelodysplastic/myeloproliferative neoplasms.
†Includes cases of malignant lymphoma, not otherwise specified (NOS); leukemia, NOS; acute biphenotypic leukemia; and precursor B-cell lymphoblastic leukemia.

Table 2. Associations Between Baseline Characteristics and Risk of Hematologic Malignancies

Characteristic	Cases (n = 577)		Noncases (n = 64,262)		HR Adjusted for Age and Sex	95% CI	*P*
	No.	%	No.	%			
Demographic factors							
Age at baseline, years					N/A		
< 55	47	8.2	16,126	25.09			
55 to < 60	110	19.1	15,232	23.7			
60 to < 65	95	16.5	11,694	18.2			
65 to < 70	116	20.1	10,131	15.8			
≥ 70	209	36.2	11,079	17.2			
Sex							
Women	231	40.0	33,061	51.5	Ref.*		
Men	346	60.0	31,201	48.6	1.67	1.41 to 1.97	< .001
Race/ethnicity							
White	534	92.6	58,885	91.6	Ref.*		
Hispanic	8	1.4	568	0.9	1.86	0.92 to 3.74	.083
Other	26	4.5	3,757	5.9	0.81	0.54 to 1.20	.287
Missing information	9	1.6	1,052	1.6			
Education							
High school graduate or less	125	21.7	12,219	19.0	Ref.*		
Some college	196	34.0	24,226	37.7	0.95	0.76 to 1.19	.665
College or advanced degree	247	42.8	26,780	41.7	1.07	0.85 to 1.33	.574
Missing information	9	1.6	1,037	1.6			
Lifestyle							
Smoking status (cigarettes)							
Never smoker	254	44.0	30,728	47.8	Ref.*		
Current or former smoker	317	54.9	33,130	51.6			
Pack-years†					1.00	1.00 to 1.00	.625
Mean	28.1		25.7				
SD	24.1		23.2				
Missing information	6	1.0	404	0.6			
Medical history							
Self-reported health							
Excellent	66	11.4	10,009	15.6	Ref.*		
Very good	216	37.4	24,971	38.9	1.23	0.93 to 1.62	.145
Good	203	35.2	21,175	33.0	1.30	0.99 to 1.72	.063
Fair	66	11.4	6,148	9.6	1.46	1.04 to 2.06	.028
Poor	14	2.4	1,006	1.6	2.18	1.23 to 3.86	.008
Missing information	12	2.1	953	1.5			
History of rheumatoid arthritis							
No	540	93.6	61,868	96.3	Ref.*		
Yes	37	6.4	2,383	3.7	1.63	1.17 to 2.28	.004
Missing information	0	0	11	0.02			
History of nonrheumatoid arthritis/chronic joint pain							
No	267	46.3	33,259	51.8	Ref.*		
Yes	310	53.7	30,992	48.2	1.23	1.04 to 1.45	.016
Missing information	0	0	11	0.02			
History of migraines/frequent headaches							
No	489	84.7	54,192	84.3	Ref.*		
Yes	88	15.3	10,059	15.7	1.25	1.00 to 1.58	.054
Missing information	0	0	11	0.02			
History of fatigue/lack of energy							
No	471	81.6	52,695	82.0	Ref.*		
Yes	106	18.4	11,556	18.0	1.15	0.93 to 1.42	.203
Missing information	0	0	11	0.02			
Family history of leukemia/lymphoma							
None	528	91.5	60,308	93.9	Ref.*		
One first-degree relative	34	5.9	3,300	5.1	1.16	0.82 to 1.64	.410
Two or more first-degree relatives	6	1.0	147	0.2	4.09	1.82 to 9.16	.001
Missing information	9	1.6	507	0.8			

Abbreviations: HR, hazard ratio; N/A, not applicable; Ref., reference; SD, standard deviation.
*Reference value of 1.00.
†Among smokers and former smokers.

Table 3. Associations Between 10-Year Acetaminophen, Aspirin, and Nonaspirin NSAID Use and Risk of Hematologic Malignancies

	Cases (n = 577)		Noncases (n = 64,262)		Adjusted for Age and Sex				Multivariable Adjusted†			
Use in 10 Years Prior to Baseline*	No.	%	No.	%	HR	95% CI	*P*	*P* Trend	HR	95 CI	*P*	*P* Trend
Acetaminophen								< .001				.004
Nonuser	405	73.2	48,523	77.9	Ref.‡				Ref.‡			
Low	96	17.4	10,552	16.9	1.22	0.97 to 1.52	.086		1.16	0.92 to 1.47	.201	
High	52	9.4	3,206	5.2	2.04	1.53 to 2.72	< .001		1.84	1.35 to 2.50	< .001	
Low-dose aspirin								.759				.840
Nonuser	371	68.0	43,717	71.8	Ref.‡				Ref.‡			
Low	89	16.3	9,895	16.3	0.97	0.77 to 1.22	.791		0.97	0.77 to 1.23	.795	
High	86	15.8	7,270	11.9	1.05	0.83 to 1.34	.664		1.04	0.82 to 1.33	.739	
Total NSAID excluding low-dose aspirin								.852				.642
Nonuser	271	49.8	31,613	52.0	Ref.‡				Ref.‡			
Low	160	29.4	17,879	29.4	1.13	0.93 to 1.37	.215		1.08	0.88 to 1.32	.466	
High	113	20.8	11,319	18.6	1.03	0.83 to 1.29	.768		0.96	0.77 to 1.21	.737	
Regular-dose aspirin								.474				.324
Nonuser	404	72.3	47,018	75.4	Ref.‡				Ref.‡			
Low	82	14.7	8,090	13.0	1.14	0.90 to 1.45	.272		1.13	0.89 to 1.44	.312	
High	73	13.1	7,281	11.7	0.89	0.69 to 1.15	.368		0.86	0.66 to 1.11	.251	
Total nonaspirin NSAID								.357				.976
Nonuser	393	70.7	41,923	67.9	Ref.‡				Ref.‡			
Low	118	21.2	15,095	24.5	0.98	0.80 to 1.20	.849		0.91	0.73 to 1.13	.387	
High	45	8.1	4,696	7.6	1.20	0.88 to 1.64	.247		1.06	0.77 to 1.45	.742	
Ibuprofen								.607				.988
Nonuser	447	79.3	46,858	75.2	Ref.‡				Ref.‡			
Low	87	15.4	12,009	19.3	0.92	0.73 to 1.16	.472		0.89	0.70 to 1.13	.343	
High	30	5.3	3,420	5.5	1.10	0.76 to 1.60	.599		0.99	0.68 to 1.44	.972	

Abbreviations: HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.
*Low use, less than 4 days/week or less than 4 years; high use, at least 4 days/week and at least 4 years.
†All models except for low-dose aspirin adjusted for age, sex, race/ethnicity, education, smoking, self-reported health, history of rheumatoid arthritis, history of nonrheumatoid arthritis or chronic neck/back/joint pain, history of migraines or frequent headaches, history of fatigue/lack of energy, and family history of leukemia/lymphoma. Model for low-dose aspirin adjusted for age, sex, race/ethnicity, education, smoking, self-reported health, history of coronary artery disease, diabetes, stroke, use of antihypertensive or cholesterol-lowering medications, history of fatigue/lack of energy, and family history of leukemia/lymphoma.
‡Reference value of 1.00.

disease, stroke, diabetes, and use of antihypertensive or lipid-lowering medications. *P* values for trend were computed by using the continuous 10-year average use variable in the model. Finally, we examined whether the associations between medication use and incident hematologic malignancies differed by tumor morphology by treating various disease entities as separate outcomes. In these analyses, patients with the other morphologies were censored at the time of cancer diagnosis. All reported *P* values are two-sided, and $P < .05$ was considered statistically significant. All analyses were performed by using STATA 11 (StataCorp, College Station, TX).

RESULTS

Overall, 64,839 men and women, age 61.5 ± 7.4 years (mean ± standard deviation), were included in this study. After a mean follow-up of 6.5 ± 1.8 years, 577 (0.89%) developed a hematologic malignancy (Table 1). Participants who developed a hematologic malignancy were older at baseline (65.6 ± 7.2 *v* 61.4 ± 7.3 years; $P < .001$), were more likely male ($P < .001$), and more often had at least two first-degree relatives with a family history of leukemia or lymphoma ($P < .001$; Table 2). Cases also more often rated their health in the lower three of five categories ($P = .0124$) and more often had a history of rheumatoid arthritis ($P = .001$) or osteoarthritis and/or chronic joint pain ($P = .0097$) than did noncases.

The associations between acetaminophen, aspirin, and nonaspirin NSAIDs and incidence of hematologic malignancies are summarized in Table 3. After adjustment, there was an increased risk of hematologic malignancies associated with high use (≥ 4 days/week for ≥ 4 years) of acetaminophen (HR, 1.84; 95% CI, 1.35 to 2.50; *P* trend = .004). There was no association with risk of hematologic malignancies for increasing use of low-dose aspirin, total NSAID use excluding low-dose aspirin, regular-dose aspirin, nonaspirin NSAIDs, or ibuprofen. To address the possibility of reverse causation (ie, the possibility that these analgesics and antipyretics were used to treat symptoms of a yet undiagnosed hematologic malignancy), we repeated these analyses after exclusion of the 146 incident cases that occurred within 2 years of baseline. After multivariate adjustment, there was an increased risk of incident hematologic malignancies associated with high use of acetaminophen (HR, 1.50; 95% CI, 1.04 to 2.18; data not shown).

When we stratified malignancies by WHO disease classification (Table 4), we found that high use of acetaminophen was associated with increased risk of myeloid neoplasms (HR, 2.26; 95% CI, 1.24 to 4.12); restriction of myeloid neoplasms to patients with myelodysplastic syndrome or acute myeloid leukemia yielded similar findings (HR, 2.30; 95% CI, 1.12 to 4.73 for high use). High use of acetaminophen

Table 4. Multivariable-Adjusted HRs of 10-Year Acetaminophen, Aspirin, and Nonaspirin NSAID Use and Risk of Individual Hematologic Malignancies

Use in 10 Years Prior to Baseline*	Myeloid Neoplasms (n = 136)						CLL/SLL (n = 88)						Plasma Cell Disorders (n = 66)						Mature B-Cell Neoplasms Other Than CLL/SLL or Plasma Cell Disorders (n = 235)					
	No.	%	HR	95% CI	*P*	*P* Trend	No.	%	HR	95% CI	*P*	*P* Trend	No.	%	HR	95% CI	*P*	*P* Trend	No.	%	HR	95% CI	*P*	*P* Trend
Acetaminophen						.102						.261						.007						.055
Nonuser	88	67.7	Ref.†				70	80.5	Ref.†				44	67.7	Ref.†				169	76.1	Ref.†			
Low	28	21.5	1.55	0.98 to 2.43	.060		13	14.9	0.93	0.50 to 1.73	.820		14	21.5	1.63	0.88 to 3.04	.120		30	13.5	0.84	0.56 to 1.26	.403	
High	14	10.8	2.26	1.24 to 4.12	.008		4	4.6	0.84	0.31 to 2.28	.732		7	10.8	2.42	1.08 to 5.41	.031		23	10.4	1.81	1.12 to 2.93	.016	
Low-dose aspirin						.113						.004						.024						.159
Nonuser	77	60.2	Ref.†				47	56.0	Ref.†				49	76.6	Ref.†				163	73.1	Ref.†			
Low	25	19.5	1.24	0.78 to 1.97	.357		13	15.5	1.13	0.60 to 2.10	.708		11	17.2	0.93	0.48 to 1.80	.832		33	14.8	0.83	0.57 to 1.22	.338	
High	26	20.3	1.40	0.88 to 2.22	.157		24	28.6	2.26	1.35 to 3.79	.002		4	6.3	0.39	0.14 to 1.08	.069		27	12.1	0.75	0.49 to 1.15	.184	
Total NSAID excluding low-dose aspirin						.931						.195						.196						.460
Nonuser	57	46.3	Ref.†				70	80.5	Ref.†				44	67.7	Ref.†				156	68.7	Ref.†			
Low	37	30.1	1.23	0.81 to 1.89	.334		9	10.3	1.18	0.72 to 1.91	.510		9	13.9	1.48	0.84 to 2.61	.180		35	15.4	0.93	0.67 to 1.30	.675	
High	29	23.6	1.08	0.68 to 1.71	.753		8	9.2	0.76	0.42 to 1.35	.346		12	18.5	1.38	0.73 to 2.58	.319		36	15.9	1.11	0.78 to 1.57	.559	
Regular-dose aspirin						.366						.057						.308						.341
Nonuser	93	72.7	Ref.†				45	51.7	Ref.†				28	43.1	Ref.†				107	49.1	Ref.†			
Low	18	14.1	1.07	0.64 to 1.77	.808		28	32.2	0.71	0.35 to 1.42	.334		21	32.3	1.18	0.57 to 2.43	.663		59	27.1	1.25	0.86 to 1.81	.235	
High	17	13.3	0.76	0.45 to 1.29	.314		14	16.1	0.55	0.27 to 1.14	.108		16	24.6	1.31	0.67 to 2.58	.433		52	23.9	1.17	0.80 to 1.71	.423	
Total Nonaspirin NSAID						.188						.516						.617						.325
Nonuser	85	66.4	Ref.†				59	67.8	Ref.†				44	66.7	Ref.†				165	73.7	Ref.†			
Low	28	21.9	1.08	0.69 to 1.68	.740		21	24.1	1.14	0.67 to 1.92	.634		17	25.8	1.27	0.73 to 2.21	.392		43	19.2	0.70	0.49 to 1.01	.054	
High	15	11.7	1.69	0.95 to 3.02	.075		7	8.1	1.17	0.54 to 2.54	.687		5	7.6	1.19	0.40 to 3.13	.831		16	7.1	0.79	0.47 to 1.33	.382	
Ibuprofen						.605						.607						.154						.456
Nonuser	101	77.7	Ref.†				67	76.1	Ref.†				48	72.7	Ref.†				187	81.3	Ref.†			
Low	20	15.4	0.96	0.59 to 1.57	.867		17	19.3	1.18	0.68 to 2.03	.555		13	19.7	1.31	0.71 to 2.41	.387		32	13.9	0.74	0.50 to 1.09	.129	
High	9	6.9	1.31	0.65 to 2.63	.450		4	4.6	0.93	0.34 to 2.50	.880		5	7.6	1.67	0.62 to 4.52	.310		11	4.8	0.81	0.44 to 1.49	.503	

NOTE. All models except for low-dose aspirin adjusted for age, sex, race/ethnicity, education, smoking, self-reported health, history of rheumatoid arthritis, history of nonrheumatoid arthritis or chronic neck/back/joint pain, history of migraines or frequent headaches, history of fatigue/lack of energy, and family history of leukemia/lymphoma. Model for low-dose aspirin adjusted for age, sex, race/ethnicity, education, smoking, self-reported health, history of coronary artery disease, diabetes, stroke, use of antihypertensive or cholesterol-lowering medications, history of fatigue/lack of energy, and family history of leukemia/lymphoma.

Abbreviations: CLL, chronic lymphocytic leukemia; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug; Ref., reference; SLL, small lymphocytic lymphoma.

*Low use, less than 4 days/week or less than 4 years; high use, at least 4 days/week and at least 4 years.

†Reference value of 1.00.

was also associated with increased risk of mature B-cell neoplasms other than chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or plasma cell disorders (HR, 1.81; 95% CI, 1.14 to 2.93); furthermore, there was an increased risk of plasma cell disorders (HR, 2.42; 95% CI, 1.08 to 5.41). There was no association between acetaminophen use and risk of CLL/SLL (HR, 0.84; 95% CI, 0.31 to 2.28 for high use). Furthermore, in these stratified analyses, high use of low-dose aspirin was associated with an increased risk of CLL/SLL (HR, 2.26; 95% CI, 1.35 to 3.79; $P = .004$ for trend) and a trend toward decreased risk of plasma cell disorders ($P = .069$ for high use; $P = .024$ for trend); however, there was no clear association of these conditions with use of regular-dose aspirin. We observed no associations between use of nonaspirin NSAIDs or ibuprofen and any individual hematologic malignancy category.

When the entire cohort was stratified by sex (Table 5), the association between acetaminophen use and total incident hematologic malignancies was stronger for females (HR for high use, 2.15; 95% CI, 1.41 to 3.28) than for males, in whom statistical significance was not reached (HR for high use, 1.55; 95% CI, 0.97 to 2.50). Low use but not high use of total NSAIDs excluding low-dose aspirin was associated with an increased risk in females (HR, 1.53; 95% CI, 1.12 to 2.09); otherwise, there was no association with risk of incident hematologic malignancies for use of the other medications studied when we stratified the analysis by sex. We also examined the associations of medication use with mature B cell neoplasms (excluding CLL/SLL and plasma cell disorders), the largest disease category, stratified by sex. High use of regular-strength aspirin was associated with a nonsignificantly increased risk of such neoplasms in women (HR, 1.62; 95% CI, 0.86 to 3.04), whereas no such effect was seen in men (HR, 0.96; 95% CI, 0.61 to 1.53). In contrast, high use of total nonaspirin NSAIDs was not associated with increased risk of these B-cell neoplasms in either women (HR, 0.76; 95% CI, 0.37 to 1.57) or men (HR, 0.83; 95% CI, 0.39 to 1.78).

DISCUSSION

Previous results of the role of aspirin or nonaspirin NSAIDs on incident hematologic malignancies have been inconsistent across several case-control studies.[2,3] In the only other prospective study among the 27,290 postmenopausal women who were followed for 7 years as part of the Iowa Women's Health Study, use of nonaspirin NSAIDs (HR, 2.39; 95% CI, 1.18 to 4.83) and aspirin (HR, 1.71; 95% CI, 0.94 to 3.13) were associated with increased risk of NHL.[9] In our large, prospective cohort study, we found no evidence that long-term use of regular-strength aspirin or nonaspirin NSAIDs was associated with risk of total hematologic malignancies or most subtypes classified by using the WHO system. In sex-stratified analyses, however, high use of regular-strength aspirin was associated with a nonsignificantly increased risk

Table 5. Associations Between 10-Year Acetaminophen, Aspirin, and Nonaspirin NSAID Use and Risk of Hematologic Malignancies, Stratified by Sex

Use in 10 Years Prior to Baseline*	Men								Women							
	Cases (n = 346)		Noncases (n = 31,201)		Multivariable-Adjusted HR	95% CI	*P*	*P* Trend	Cases (n = 231)		Noncases (n = 33,061)		Multivariable-Adjusted HR	95% CI	*P*	*P* Trend
	No.	%	No.	%					No.	%	No.	%				
Acetaminophen								.549								.001
Nonuser	265	79.8	25,308	83.1	Ref.†				140	63.4	23,215	72.9	Ref.†			
Low	48	14.5	4,077	13.4	1.12	0.81 to 1.54	.490		48	21.7	6,475	20.3	1.22	0.87 to 1.73	.250	
High	19	5.7	1,065	3.5	1.55	0.97 to 2.50	.070		33	14.9	2,141	6.7	2.15	1.41 to 3.28	< .001	
Low-dose aspirin								.490								.216
Nonuser	231	70.9	20,673	70.0	Ref.†				140	63.6	23,044	73.5	Ref.†			
Low	44	13.5	4,649	15.7	0.79	0.57 to 1.10	.156		45	20.5	5,246	16.7	1.21	0.86 to 1.72	.273	
High	51	15.6	4,207	14.3	0.88	0.65 to 1.20	.419		35	15.9	3,063	9.8	1.35	0.91 to 2.00	.141	
Total NSAID excluding low-dose aspirin								.163								.209
Nonuser	181	55.2	15,793	53.1	Ref.†				90	41.7	15,820	50.9	Ref.†			
Low	75	22.9	7,847	26.4	0.83	0.63 to 1.10	.202		85	39.4	10,032	32.3	1.53	1.12 to 2.09	.007	
High	72	22.0	6,099	20.5	0.83	0.63 to 1.09	.181		41	19.0	5,220	16.8	1.29	0.87 to 1.90	.206	
Regular-dose aspirin								.122								.524
Nonuser	235	70.8	21,246	70.3	Ref.†				169	74.5	25,772	80.1	Ref.†			
Low	46	13.9	4,203	13.9	1.01	0.73 to 1.39	.946		36	15.9	3,887	12.1	1.35	0.94 to 1.94	.099	
High	51	15.4	4,778	15.8	0.77	0.57 to 1.05	.094		22	9.7	2,503	7.8	1.10	0.70 to 1.74	.679	
Total nonaspirin NSAID								.669								.604
Nonuser	263	77.4	22,470	74.1	Ref.†				130	60.2	19,453	62.0	Ref.†			
Low	53	15.6	6,209	20.5	0.73	0.54 to 1.00	.048		65	30.1	8,886	28.3	1.15	0.83 to 1.59	.406	
High	24	7.1	1,658	5.5	1.12	0.74 to 1.71	.596		21	9.7	3,038	9.7	1.03	0.63 to 1.68	.904	
Ibuprofen								.487								.476
Nonuser	288	84.2	24,030	78.9	Ref.†				159	71.6	22,828	71.8	Ref.†			
Low	39	11.4	5,129	16.8	0.70	0.50 to 0.98	.037		48	21.6	6,880	21.6	1.15	0.82 to 1.62	.421	
High	15	4.4	1,313	4.3	0.91	0.54 to 1.53	.719		15	6.8	2,107	6.6	1.10	0.64 to 1.87	.740	

NOTE. All models except for low-dose aspirin adjusted for age, sex, race/ethnicity, education, smoking, self-reported health, history of rheumatoid arthritis, history of nonrheumatoid arthritis or chronic neck/back/joint pain, history of migraines or frequent headaches, history of fatigue/lack of energy, and family history of leukemia/lymphoma. Model for low-dose aspirin adjusted for age, sex, race/ethnicity, education, smoking, self-reported health, history of coronary artery disease, diabetes, stroke, use of antihypertensive or cholesterol-lowering medications, history of fatigue/lack of energy, and family history of leukemia/lymphoma.

Abbreviations: HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug; Ref., reference.

*Low use, less than 4 days/week or less than 4 years; high use, at least 4 days/week and at least 4 years.

†Reference value of 1.00.

of mature B-cell neoplasms (excluding CLL/SLL and plasma cell disorders) of magnitude similar to that in the results from the Iowa Women's Health Study. In contrast, no such effect was seen in men in our study, nor was high use of total nonaspirin NSAIDs associated with increased risk of mature B-cell neoplasm in either women or men. Thus, our findings provide some support to the earlier prospective study showing a positive association between use of aspirin and risk of some B-cell neoplasms in women, although the mechanism underlying this observation remains unclear. We also found low-dose aspirin use to be associated with an increased risk of CLL/SLL and a reduced risk of plasma cell disorders among men and women combined. Given the relatively small number of incident cases in these two disease subgroups, we cannot exclude the possibility of chance findings, and further studies will be necessary to confirm these observations. Similarly, we found low use of total NSAIDs excluding low-dose aspirin to be associated with an increased risk of total hematologic malignancies in females; this finding should be interpreted cautiously because the scientific basis for such a sex-specific negative effect of low but not high drug use is unclear.

The strongest and most consistent finding from our study was that high use of acetaminophen is associated with an almost two-fold increased risk of total hematologic malignancies and of myeloid neoplasms, plasma cell disorders, and other mature B-cell neoplasms except CLL/SLL. The association of acetaminophen use with total hematologic malignancies was greater among women than among men; the reason for this modifying effect of sex is currently unclear and will require further study. Several case-control studies have examined the association between acetaminophen use and risk of hematologic malignancies. Studying 169 cases and 676 controls, Weiss et al[10] found an increased risk of acute leukemia for ever-use of acetaminophen (odds ratio [OR], 1.53; 95% CI, 1.03 to 2.26). In a large study of 2,362 lymphoma cases and 2,458 controls,[5] an increased risk was found for intake of acetaminophen (OR, 2.29; 95% CI, 1.49 to 3.51). Regular use of acetaminophen was also associated with increased risk of Hodgkin's lymphoma in a study of 525 cases and 679 controls (OR, 1.72; 95% CI, 1.29 to 2.31)[11] as well as with NHL among women (OR, 1.71; 95% CI, 1.18 to 2.50) but not men (OR, 0.75; 95% CI, 0.48 to 1.17) in another study[12] comprising 625 cases and 2,512 controls. In contrast, two studies[13,14] reported no association of use of acetaminophen with NHL. Finally, Moysich et al[15] found an increased risk among regular users of acetaminophen for development of multiple myeloma in a study comprising 117 cases and 483 controls (OR, 2.95; 95% CI, 1.72 to 5.08). To the best of our knowledge, ours is the first prospective study of acetaminophen use and hematologic malignances, and our results support the majority of prior case-control studies.

The genotoxic effects of acetaminophen, a major metabolite of phenacetin, which has been linked to the development of cancer of the upper and lower urinary tract,[16,17] remain poorly understood. However, acetaminophen inhibits replicative DNA synthesis and DNA repair synthesis and increases the frequency of chromosomal damage in cell lines and experimental animals, possibly due to inhibition of ribonucleotide reductase.[18] The major reactive metabolite of acetaminophen, *N*-acetyl-*p*-benzoquinone imine, has been shown to cause extensive DNA single-strand breaks and to strongly enhance DNA cleavage by topoisomerase II in vitro.[18,19] Similarly, *p*-aminophenol, another metabolite of acetaminophen, has been reported to be mutagenic in the L5178Y mouse lymphoma assay and may induce single-strand breaks and chromosome aberrations.[20,21] Studies in experimental animals suggest that acetaminophen is genotoxic in vivo in bone marrow cells and, with long-term exposure, may increase the incidence of mononuclear cell leukemia and have carcinogenic effects on liver and bladder.[18] Moreover, some epidemiologic studies have reported acetaminophen use to be associated with several types of cancer of the kidneys or the urothelial system.[18,22]

This study has several strengths, including its prospective design, the large cohort size, case ascertainment through the SEER cancer registry, and the use of the most recent WHO disease classification system. Furthermore, the availability of baseline information on personal lifestyle and medical history allowed adjustment for major potential confounding factors, including adjustment for confounding by indication. On the other hand, some limitations need to be acknowledged. Although we ascertained years of use and days per week for several types of analgesics and separated use of low-dose from regular-strength and extra-strength aspirin, we did not ascertain dose per day; moreover, medication use was self-reported. However, measurement error from these sources and from poor recall would be nondifferential in a prospective study and therefore would lead to attenuation of results.

Of some concern is the possibility of reverse causation, that is, disease and/or symptoms could lead to exposures (eg, acetaminophen use) rather than the reverse. For example, fever and night sweats, as part of constitutional ("B") symptoms, may precede the diagnosis of a hematologic malignancy, particularly in some advanced and aggressive lymphoid neoplasms.[23,24] However, we required at least 4 years of drug use for categorization as "high user," and although a prolonged period of B symptoms preceding a cancer diagnosis may occur in some cases, two recent studies of patients with lymphoma suggest that the median time from symptoms to diagnosis is about 2.5 to 4 months.[25,26] In contrast, fevers are a rare presenting symptom in multiple myeloma (< 1%); however, many of these patients present with bone pain, although the vast majority of patients are diagnosed within 1 year of onset of symptoms.[27] As another argument against reverse causality, one might expect that disease-associated symptoms would lead to use of any type of NSAID or acetaminophen rather than acetaminophen alone. Nonetheless, we additionally excluded cases arising in the first 2 years of follow-up in an analysis of acetaminophen use; this ensures that those classified as high users had begun use at least 6 years before diagnosis. In this analysis, the HR was attenuated although it remained significantly increased throughout the later part of the follow-up period (HR for high use, 1.50; 95% CI, 1.04 to 2.18). Thus, it is possible that reverse causation explains part but not all of the increased risk of hematologic malignancies found in this study (and other studies) of acetaminophen use. Alternatively, the attenuation of risk in our study after removing the first 2 years of follow-up could be due to increased exposure measurement error caused by changes in use of specific analgesics as one moves farther from the time of the questionnaire.

In conclusion, high use of acetaminophen was associated with increased risk of incident hematologic malignancies other than CLL/SLL, with an almost two-fold risk for use at least 4 days/week for at least 4 years. Case-control studies, in vitro studies, and one long-term animal experiment support these results. Nonetheless, supporting evidence from other prospective studies would be needed before any recommendations about acetaminophen use could be made. Neither regular aspirin nor nonaspirin NSAIDs were associated with decreased risk, implying that these drugs are unlikely to be useful for prevention of hematologic malignancies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Financial support: Roland B. Walter, Emily White
Provision of study materials or patients: Emily White
Collection and assembly of data: Emily White
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