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Cancer risk associated with long-term use of acetaminophen in the prospective VITamins And Lifestyle (VITAL) study

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Abstract

Background—Acetaminophen (paracetamol) is a widely used over-the-counter drug, but concerns of genotoxic effects have been raised. After we recently found an almost 2-fold increased risk of hematologic malignancies associated with high use of acetaminophen in the prospective VITamins And Lifestyle (VITAL) study, we herein further examined the association between acetaminophen and cancer risk in the VITAL cohort.

Methods—62,841 men and women aged 50 to 76 years were recruited from 2000–2002, and incident malignancies other than non-melanoma skin cancer (n=5,750) were identified through December 2008 via linkage to the Surveillance, Epidemiology, and End Results cancer registry. Hazards ratios associated with acetaminophen use for incidence of total cancers and non-hematologic cancer subcategories were estimated with Cox proportional hazards models that were adjusted for age, demographics, cancer risk factors, and medical conditions that may be indications for acetaminophen use.

Results—Use of acetaminophen was not associated with total cancer risk. We also observed no associations for most major non-hematologic cancer sites, including cancers of the gastrointestinal system, lung, urinary tract, skin, prostate, or female organs.

Conclusion—This study failed to provide evidence of an association between acetaminophen use and total cancer risk and incidence of non-hematologic malignancies.

Impact—Together with our previous findings, the findings from the VITAL study suggest a particular sensitivity of the hematopoietic system to the mutagenic effects of acetaminophen.

Keywords

acetaminophen (Paracetamol) ; cancer risk; prospective cohort study; epidemiology; VITAL study

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Authorship and Disclosures

All authors designed and performed research, analyzed and interpreted data, and drafted the manuscript.

Introduction

Acetaminophen (paracetamol) is one of the most widely used over-the-counter analgesic-antipyretics. However, as the active metabolite of phenacetin, which is considered carcinogenic to humans (1), significant genotoxic effects have long been a concern. This possibility has been investigated by a number of epidemiological studies, primarily with case-control design, with inconsistent results (2–4). Recently, we found an almost 2-fold increased risk of hematologic malignancies other than chronic lymphocytic leukemia/small lymphocytic lymphoma associated with high use of acetaminophen in the prospective VITamins And Lifestyle (VITAL) study (5). We have now examined the association of acetaminophen use with incidence of total cancers and individual solid tumors in this cohort.

Methods

Study Cohort

Details of the VITAL study have been published previously (6). Among 77,719 men and women deemed eligible for study participation, 11,463 were excluded because of a prior history of any cancer other than non-melanoma skin cancer or missing cancer information at baseline. We additionally excluded 3,394 participants with missing exposure information and 21 cases with post-baseline cancer on death certificate only without a diagnosis date, leaving 62,841 participants, aged 61.5±7.3 (mean±SD), available for study.

Data Collection

Participants completed a baseline questionnaire on demographics, health history, cancer risk factors, diet, and medications that encompassed questions on regular use, defined as ≥1 day/week for ≥1 year, of acetaminophen and other analgesics, including frequency and duration of use over the previous 10 years. 10-year use was categorized as “no use”, “low use” (<4 days/week or <4 years), and “high use” (≥4 days/week and ≥4 years).

Case Ascertainment

After a mean follow-up of 6.5±1.7 years, a diagnosis of incident, invasive malignancies other than non-melanoma skin cancer was identified in 5,750 (9.2%) participants via annual linkage to the Surveillance, Epidemiology, and End Results (SEER) cancer registry (6). The remainders were censored at the earliest date of the following events: withdrawal from study (n=19), emigration from the SEER region (n=4,290), death (n=1,900), or December 31, 2008 (the date of complete case ascertainment at time of linkage to the SEER registry; n=50,882).

Statistical Analysis

Cox proportional hazards models using participants’ age as the time metric estimated hazard ratios (HRs) and 95% confidence intervals (95% CI) for the associations between acetaminophen use and incident malignancies. For analyses of individual tumor types, various cancer entities were treated as separate outcomes, and cases of other malignancies were censored at their respective time of diagnosis. *P*-values for trend were computed by using the categorized 10-year acetaminophen use variable as ordinal in regression models. All reported *P*-values are two-sided, and $P<0.05$ was considered statistically significant.

Results

High use of acetaminophen was not associated with total cancer risk either overall (HR 1.02 [0.89–1.17]), or by gender (for women, HR 0.97 [0.80–1.17]; for men, HR 1.08 [0.88–1.31]) (Table 1). The associations between acetaminophen use and risk of individual solid tumors,

stratified by site and gender, are summarized in Table 2. There were no statistically significant associations with risks of total gastrointestinal, lung, urinary tract, female, prostate, or melanoma skin cancers. We additionally performed exploratory cancer subgroup analyses, acknowledging the low power to detect significant associations because of the small number of cases of individual cancer types. With this limitation in mind, high use of acetaminophen was associated with statistically non-significantly increased risk of bladder cancer (HR=1.50 [0.57–3.89]) and decreased risk of aggressive prostate cancer (HR=0.74 [0.45–1.21]) or pancreatic cancer (HR=0.40 [0.12–1.31]).

Discussion

In our study, there was no evidence for an association between acetaminophen use and total cancer risk overall or by gender. This finding is comparable to that from a retrospective population-based cohort study showing no association for overall cancers (SIR=1.1 [1.06–1.15]) with acetaminophen use (7). We also found no statistically significant association with cancer development for most cancer subgroups other than hematologic malignancies. Of note, some studies on acetaminophen suggested a decreased risk with certain cancers. Most prominently, Jacobs *et al*. recently reported a decreased risk of overall prostate cancer (RR=0.62 [0.44–0.87]) and aggressive prostate cancer (RR=0.49 [0.27–0.88]) among long-term regular users of acetaminophen (as defined as current use of ≥ 30 pills per month for ≥ 5 years) in the Cancer Prevention Study II Nutrition Cohort (8). In our study, which had 80% power to detect a HR of 0.74 for overall prostate cancer and 0.64 for aggressive subforms, there was no association with overall prostate cancer, although there was a statistically non-significant trend towards reduced risk for aggressive prostate cancer; this comparison may be limited given the differences in definition of acetaminophen use between the 2 studies.

Despite the large cohort size, however, our study had limited power in detecting associations between acetaminophen use and risk of individual cancers or cancer subtypes. Nonetheless, it is reassuring that we did not find an association between high acetaminophen use and specific cancers other than hematologic malignancies. The latter observation suggests a particular sensitivity of the hematopoietic system to acetaminophen. The reason for this predisposition is unclear and will deserve further study.

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Table 1

Associations between acetaminophen use and total cancer incidence, stratified by gender

	10-year Use Prior to Baseline[a]			
	No Use	**Low Use**	**High Use**	***P* trend**
All participants (n=62,841)				
Cases (n=5,750)	4,467 (77.7%)	978 (17.0%)	305 (5.3%)	
Non-cases (n=57,091)	44,467 (77.9%)	9,671 (16.9%)	2,953 (5.2%)	
HR (95% CI)[b]	1.00 (reference)	1.08 (0.99–1.17)	1.02 (0.89–1.17)	0.25
Women (n=32,059)				
Cases (n=2,441)	1,741 (71.3%)	523 (21.4%)	177 (7.3%)	
Non-cases (n=29,618)	21,620 (73.0%)	6,002 (20.3%)	1,996 (6.7%)	
HR (95% CI)[b]	1.00 (reference)	1.04 (0.92–1.17)	0.97 (0.80–1.17)	0.97
Men (n=30,782)				
Cases (n=3,309)	2,726 (82.4%)	455 (13.8%)	128 (3.9%)	
Non-cases (n=27,473)	22,847 (83.2%)	3,669 (13.4%)	957 (3.5%)	
HR (95% CI)[b]	1.00 (reference)	1.18 (0.99–1.26)	1.08 (0.88–1.31)	0.11
			P interaction = 0.88	

[a] Low use, use for either less than 4 days/week or less than 4 years; high use, use for at least 4 days/week and at least 4 years.

[b] *A priori* potential confounders were selected, including known and suspected cancer risk factors and medical conditions that may be indications for use of acetaminophen, for adjustment in multivariable regression models. Specifically, all models were adjusted for age, education, race, marital status, height, body mass index, physical activity, pack-years of smoking, alcohol intake at 45y, fruit and vegetable intake, red meat intake, multivitamin use, self-rated health, family history of colon, lung, and hematological cancers (as separate terms), sigmoidoscopy in the past 10 years, diabetes, osteoarthritis/chronic joint pain, migraine/chronic headaches, and use of non-steroidal anti-inflammatory drugs (NSAIDs). The models were additionally adjusted for family history of breast cancer, mammogram in the past 2 years, age at menarche, age at menopause, age at first birth, years of estrogen therapy, years of combined hormone therapy, and hysterectomy (for women); and family history of prostate cancer and PSA test in the past 2 years (for men).

Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 2

Associations between acetaminophen use and cancer incidence, stratified by cancer site and gender

	10-year Use Prior to Baseline[a]			
Cancer Site[b]	**No Use**	**Low Use**	**High Use**	***P* trend**
Gastrointestinal (n=783)[1]				
Cases / Non-cases	623 / 48,311	120 / 10,529	40 / 3,218	
HR (95% CI)[c]	1.00 (reference)	0.90 (0.71–1.14)	0.84 (0.57–1.22)	0.24
Women				
Cases / Non-cases	265 / 23,096	72 / 6,453	20 / 2,153	
HR (95% CI)[c]	1.00 (reference)	0.93 (0.67–1.29)	0.75 (0.45–1.26)	0.29
Men				
Cases / Non-cases	358 / 25,215	48 / 4,076	20 / 1,065	
HR (95% CI)[c]	1.00 (reference)	0.86 (0.60–1.23)	0.94 (0.54–1.64)	0.53
			P interaction = 0.35	
Colon and rectum (n=419)				
Cases / Non-cases	344 / 48,590	56 / 10,593	19 / 3,239	
HR (95% CI)[c]	1.00 (reference)	0.79 (0.56–1.12)	0.80 (0.46–1.37)	0.18
Pancreas (n=132)				
Cases / Non-cases	105 / 48,829	21 / 10,628	6 / 3,252	
HR (95% CI)[c]	1.00 (reference)	0.90 (0.51–1.58)	0.40 (0.12–1.31)	0.16
Lung (n=622)				
Cases / Non-cases	458 / 48,476	122 / 10,527	42 / 3,216	
HR (95% CI)[c]	1.00 (reference)	1.22 (0.95–1.55)	1.06 (0.73–1.54)	0.32
Women				
Cases / Non-cases	170 / 23,191	67 / 6,458	28 / 2,145	
HR (95% CI)[c]	1.00 (reference)	1.18 (0.83–1.67)	1.18 (0.72–1.95)	0.36
Men				
Cases / Non-cases	288 / 25,285	55 / 4,069	14 / 1,071	
HR (95% CI)[c]	1.00 (reference)	1.24 (0.88–1.75)	0.93 (0.52–1.67)	0.64
			P interaction = 0.65	
Urinary tract (n=282)[2]				
Cases / Non-cases	214 / 48,720	50 / 10,599	18 / 3,240	
HR (95% CI)[c]	1.00 (reference)	1.10 (0.76–1.59)	1.05 (0.60–1.83)	0.72
Women				
Cases / Non-cases	57 / 23,304	21 / 6,504	8 / 2,165	
HR (95% CI)[c]	1.00 (reference)	1.07 (0.58–1.97)	0.89 (0.38–2.11)	0.89
Men				

	10-year Use Prior to Baseline[a]			
Cancer Site[b]	**No Use**	**Low Use**	**High Use**	***P* trend**
Cases / Non-cases	157 / 25,416	29 / 4,095	10 / 1,075	
HR (95% CI)[c]	1.00 (reference)	1.17 (0.73–1.87)	1.15 (0.54–2.41)	0.53
			P interaction = 0.88	
Kidney (n=161)				
Cases / Non-cases	120 / 48,814	30 / 10,619	11 / 3,247	
HR (95% CI)[c]	1.00 (reference)	1.11 (0.69–1.79)	0.96 (0.46–1.98)	0.91
Bladder (n=101)				
Cases / Non-cases	76 / 48,858	19 / 10,630	6 / 3,252	
HR (95% CI)[c]	1.00 (reference)	1.39 (0.74–2.60)	1.50 (0.57–3.89)	0.24
Melanoma (n=279)				
Cases / Non-cases	229 / 48,705	38 / 10,611	12 / 3,246	
HR (95% CI)[c]	1.00 (reference)	0.90 (0.60–1.33)	0.79 (0.39–1.58)	0.42
Women				
Cases / Non-cases	84 / 23,277	17 / 6,508	6 / 2,167	
HR (95% CI)[c]	1.00 (reference)	0.76 (0.42–1.39)	0.63 (0.22–1.82)	0.26
Men				
Cases / Non-cases	145 / 25,428	21 / 4,103	6 / 1,079	
HR (95% CI)[c]	1.00 (reference)	1.02 (0.61–1.71)	1.04 (0.41–2.62)	0.92
			P interaction = 0.33	
Female cancers (n=1,225)[3]				
Cases / Non-cases	880 / 22,481	269 / 6,256	70 / 2,103	
HR (95% CI)[c]	1.00 (reference)	1.07 (0.91–1.26)	0.85 (0.64–1.13)	0.68
Breast (n=901)				
Cases / Non-cases	646 / 22,715	196 / 6,329	53 / 2,120	
HR (95% CI)[c]	1.00 (reference)	1.10 (0.91–1.33)	0.83 (0.59–1.15)	0.74
Uterus (n=214)				
Cases / Non-cases	156 / 23,205	47 / 6,478	11 / 2,162	
HR (95% CI)[c]	1.00 (reference)	1.07 (0.71–1.63)	0.99 (0.48–2.01)	0.88
Prostate cancer (n=1,587)				
Cases / Non-cases	1,321 / 24,252	216 / 3,908	50 / 1,035	
HR (95% CI)[c]	1.00 (reference)	1.10 (0.93–1.30)	1.00 (0.73–1.37)	0.51
Aggressive prostate cancer (n=768)[d]				
Cases / Non-cases	649 / 48,285	99 / 10,550	20 / 3,238	
HR (95% CI)[c]	1.00 (reference)	0.97 (0.76–1.25)	0.74 (0.45–1.21)	0.32

[a] Low use, use for either less than 4 days/week or less than 4 years; high use, use for at least 4 days/week and at least 4 years.

[b] Major categories do not add to 5,750 due to exclusion of 571 cases with hematologic malignancies and 393 cases with cancers of the head and neck, connective tissue, brain, thyroid, and unspecified primary site.

[c] All models were adjusted as described in footnote to Table 1.

[d] To compare our findings on prostate cancer risk with those from Jacobs *et al.* (8), we considered aggressive prostate cancers to be those with a Gleason grade ≥7, AJCC stages III/IV, or fatal prostate cancer. For cancers diagnosed between 2000 and 2003, Gleason grade was identified using a SEER differentiation variable. From 2000 to 2002, well or moderately differentiated tumors were those with Gleason grades of 2 to 7, while poorly differentiated tumors had scores between 8 and 10. In 2003, this coding scheme changed so that a Gleason grade of 7 was considered poorly differentiated. We therefore re-abstracted Gleason scores from the original SEER reports for cancers diagnosed from 2000 to 2002 in order to properly classify Gleason grades of ≥7 as poorly differentiated. AJCC stage was not available from SEER until 2004. Before 2004, we classified aggressive tumors as those with distant SEER summary stage, which identifies *metastatic* AJCC stage IV tumors. Prostate cancers diagnosed from 2004 to 2008 were classified as aggressive using Gleason grade (≥7) and AJCC stage (III/IV) data. Fatal prostate cancer was defined by cause of death and was available for all years.

[1] Besides cancers of colon/rectum and pancreas, contains cancers of esophagus (n=56), stomach (n=56), liver (n=47), small intestines (n=21), anus and anal canal (n=15), gall bladder (n=11), biliary tract (n=9), and other or ill-defined digestive organs (n=17).

[2] Besides cancers of kidney and bladder, contains cancers of renal pelvis (n=10), ureter (n=5), and other or unspecified urinary organs (n=5).

[3] Besides cancers of breast and uterus, contains cancers of ovary (n=74), cervix (n=11), vulva (n=7), vagina (n=3), and other or unspecified female genital organs (n=15).

Abbreviations: CI, confidence interval; HR, hazard ratio.