

Letter to the Editor

Paracetamol, nonsteroidal anti-inflammatory drugs, and risk of asthma in adult survivors of childhood cancer*To the Editor:*

A number of cross-sectional, longitudinal, and ecologic studies have reported an association between paracetamol and risk of asthma in children or adults, and pathophysiological mechanisms specific to paracetamol have been proposed.¹⁻³ Whether the observed association is a result of a causal effect of paracetamol, however, remains unclear because of the possibility of confounding by indication—for example, subjects with asthma or predisposed to asthma might more often use paracetamol because of more frequent respiratory tract infections or other comorbidities that have increased prevalence among patients with asthma.⁴

The literature on risk of asthma and intake of nonsteroidal anti-inflammatory drugs (NSAIDs) is scarcer. While aspirin is known to trigger bronchospasm in sensitive patients, it has been suggested that exclusive use of nonaspirin NSAIDs in children with asthma might be associated with a lower risk of asthma compared with those taking paracetamol only. However, results remain inconclusive, and randomized clinical trials are lacking.^{5,6}

We had a dataset of young adults cured from childhood cancer in whom asthma (ever, current, year of onset, and asthma medication in the past 2 years), intake of different analgesics, and frequency of intake during the past 2 years had been assessed in detail, providing an opportunity to examine this question. We used these data to determine whether prevalence of asthma differed between persons taking different types of analgesics: paracetamol alone, nonaspirin NSAIDs alone, aspirin alone, or different combinations of these 3.

The Swiss Childhood Cancer Survivor Study is a detailed questionnaire survey of all persons registered in the Swiss Childhood Cancer Registry who were age <16 years when diagnosed with cancer and ≥16 years at the time of the survey and had at least 5 years elapsed since diagnosis. Persons with a relapse, second cancer, or current immunosuppressive therapy were excluded from this analysis.⁷ Asthma was defined as a report of asthma or use of asthma medication during the last 2 years. We assessed detailed information on intake of different types of analgesics and frequency of intake during the last 2 years. Intake was classified as “no analgesics,” “paracetamol alone,” “nonaspirin NSAIDs alone,” “aspirin alone,” “paracetamol and nonaspirin NSAIDs,” “paracetamol and aspirin,” “aspirin and nonaspirin NSAIDs,” and “paracetamol, aspirin, and nonaspirin NSAIDs.” Frequency of intake was classified as “no intake,” “less than once a week,” and “once a week or more.” Indications for analgesics intake were not assessed.

We assessed the association between asthma and intake of analgesics and frequency of intake by using logistic regression adjusting for potential demographic, socioeconomic, and clinical confounders. Associations with *P* values <.05 were considered statistically significant.

A total of 1293 young adults participated in the study. For this analysis, we included those who had complete data on analgesics intake and asthma (*n* = 1065). Their mean age was 26.2 years (range, 16.0-49.1), 53.2% were men, 230 (21.6%) were current smokers, 243 (22.8%) had a migration background (meaning that

TABLE I. Characteristics of the study population (*N* = 1065)

Variables	No.	Percentage
Sex		
Male	567	53.2
Initial diagnosis*		
Leukemias	411	38.6
Lymphomas	205	19.2
CNS tumors	109	10.2
Embryonal tumors (renal, hepatic, neuroblastoma, retinoblastoma)	170	16.0
Bone tumors and soft tissue sarcomas	116	10.9
Other†	54	5.1
Treatment		
Chemotherapy only	537	50.4
Radiotherapy only	46	4.3
Chemotherapy + radiotherapy	347	32.6
Surgery only; unknown	91	8.6
BMT	44	4.1
Time since diagnosis		
<10 y	123	11.5
10-19 y	519	48.7
20-29 y	369	34.7
>30 y	54	5.1
Smoking		
Never	684	64.2
Yes, but not current	123	11.6
Current	230	21.6
Missing	28	2.6
Migration background		
No migration background	822	77.2
Migration background	243	22.8
Number of older siblings		
None	383	36.0
1-2	506	47.5
3 or more	53	4.9
Missing	123	11.6
Asthma during the last 2 y		
No	989	92.9
Yes	76	7.1
Analgesics intake during the last 2 y		
None	294	27.6
Paracetamol alone	242	22.7
Nonaspirin NSAIDs alone	76	7.2
Aspirin alone	81	7.6
Paracetamol + nonaspirin NSAIDs	141	13.2
Paracetamol + aspirin	96	9.0
Nonaspirin NSAIDs + aspirin	55	5.2
Paracetamol + nonaspirin NSAIDs + aspirin	80	7.5
Frequency of intake of analgesics during the last 2 y		
None	294	27.6
Less than once a week	549	51.6
Once a week or more	71	6.7
Missing	151	14.1

BMT, Bone marrow transplantation; CNS, central nervous system; ICC-3, International Classification of Childhood Cancer, Third Edition.

*According to ICC-3 Classification; ICC-3 reduced diagnostic group.

†Including other malignant epithelial neoplasms, other and unspecified malignant neoplasms, and Langerhans cell histiocytosis.

participants or their parents had immigrated to Switzerland), 559 (52.4%) had at least 1 older sibling, and their mean body mass index was 23.2 kg/m² (range, 16.8-38.8). Regarding their cancer history, the most common initial diagnoses were leukemia

TABLE II. Association between intake of analgesics and asthma during the last 2 years (N = 1065)

Analgesics	N total	With asthma, n (%)	Unadjusted			Adjusted*		
			OR	95% CI	P value	OR	95% CI	P value
None	294	12 (4.1)	1.00		.037†	1.00		.006†
Paracetamol only	242	21 (8.7)	2.23	1.08-4.64	.031	2.60	1.17-5.78	.019
Nonaspirin NSAIDs only	76	8 (10.5)	2.76	1.09-7.03	.033	3.28	1.21-8.83	.019
Aspirin only	81	3 (3.7)	0.90	0.25-3.28	.878	0.75	0.16-3.54	.716
Paracetamol + nonaspirin NSAIDs	141	18 (12.8)	3.44	1.61-7.36	.001	3.33	1.36-8.12	.008
Paracetamol + aspirin	96	5 (5.2)	1.29	0.44-3.76	.640	1.33	0.40-4.42	.644
Nonaspirin NSAIDs + aspirin	55	3 (5.5)	1.36	0.37-4.97	.646	1.70	0.44-6.58	.442
Paracetamol + nonaspirin NSAIDs + aspirin	80	6 (7.5)	1.91	0.69-5.25	.212	2.43	0.83-7.10	.104

*N = 891, adjusted for sex, age, initial cancer diagnosis, cancer therapy, time since diagnosis, body mass index, smoking, number of older siblings, and migration background.

†Global P value for an association between asthma and the intake variable as a whole (likelihood ratio test comparing models with and without the intake variable).

(38.6%) and lymphoma (19.2%). For most (88.5%), ≥ 10 years had passed since diagnosis, and they can be considered as cured. In total, 76 (7.1%) reported asthma or use of asthma medication during the past 2 years, 771 (72.4%) reported use of analgesics of any type, and 71 (6.7%) reported weekly or more frequent intake of analgesics (Table I).

In univariate analysis, intake of any analgesics was positively associated with asthma (odds ratio [OR], 2.1; 95% CI, 1.1-4.0; $P = .019$). Intake of paracetamol alone, nonaspirin NSAIDs alone, and paracetamol and nonaspirin NSAIDs in combination were each significantly associated with asthma, whereas associations with combinations including aspirin were weaker and not significant (Table II). After adjusting for age, sex, initial cancer diagnosis, cancer therapy, time since diagnosis, smoking status, body mass index, number of older siblings, and migration background, the associations remained statistically significant for persons using paracetamol alone (OR, 2.6; 95% CI, 1.2-5.8; $P = .019$), nonaspirin NSAIDs alone (OR, 3.3; 95% CI, 1.2-8.8; $P = .019$), and combinations of the 2 (OR, 3.3; 95% CI, 1.4-8.1; $P = .008$; Table II). There was no statistically significant difference in strength of association with asthma between exclusive intake of paracetamol and exclusive intake of nonaspirin NSAIDs ($P = .607$). Compared with “no intake,” less frequent intake of analgesics was significantly associated with the prevalence of asthma (OR, 2.4; 95% CI, 1.2-5.1; $P = .017$), whereas the estimated association for weekly or more frequent intake was similar in strength but not significant (OR, 2.5; 95% CI, 0.8-8.1; $P = .116$).

In summary, this study showed a higher prevalence of asthma in young adult cancer survivors using paracetamol and/or nonaspirin NSAIDs compared with a similar group who did not report taking these drugs during the previous 2 years. No evidence of an association between asthma and aspirin-only use was found.

Previous studies on analgesics and asthma had mainly focused on paracetamol.^{1-3,8} The oxidant effect of paracetamol in lung tissue has been proposed as the underlying mechanism.^{1-2,5} Whether analgesics of other pharmacologic groups such as nonaspirin NSAIDs are also associated with asthma is still poorly evaluated, and published results are conflicting. Lesko et al⁶ reported that children with asthma taking ibuprofen were at lower risk of asthma than those taking paracetamol, and Kanabar et al⁵ concluded in their review that the available data support a protective rather than a harmful effect of ibuprofen. A large cross-sectional study using the Third National Health and Nutrition Examination Survey found an association between intake of paracetamol and asthma prevalence and decreased lung function, whereas intake of aspirin or ibuprofen was not associated with asthma.⁹ However,

a recent Danish study reported an increased risk of adult-onset asthma for persons with regular use of nonaspirin NSAIDs.¹⁰ These studies did not distinguish between combinations of analgesics as we have.

Like most other studies,^{3,6,8,10} our survey was based on self-reported analgesics use and asthma. Reported prevalence of asthma (7%) was very comparable to results from general population samples of schoolchildren and young adults in Switzerland.¹¹ Some drugs used might have been forgotten or misclassified. The nature of our study population, childhood cancer survivors, may also have affected the results. Although the participants were generally healthy and had been off cancer treatment for many years, their frequency of analgesics intake may differ from that in the general population. It is therefore possible that our findings on frequency of analgesics use cannot be generalized to the whole population. However, it is unlikely that this has biased differences in strength of association between asthma and specific types of analgesics.

The association found in this study might not be a result of a causal effect of paracetamol and nonaspirin NSAIDs on the risk of asthma. Because of the cross-sectional design, we could not distinguish between patients with asthma before intake of these drugs and patients who developed asthma subsequently. We did not find a clear dose-response relationship that might be indicative of a causal relationship. Analgesics are often taken for viral infections. People with asthma are more often affected by lower respiratory tract symptoms during viral infections, and these tend to be more severe and longer-lasting than those in healthy individuals.¹² Furthermore, patients with asthma are known to have a range of comorbidities associated with pain or fever more often.⁴ For these reasons, patients with asthma may more frequently use analgesics, leading to an apparent association with asthma that is not causal (confounding by indication). The finding that the association is not restricted to a particular class of drugs in our data is to be expected if confounding by indication were the explanation. Of interest is the comparatively weak association between aspirin and asthma. Among all NSAIDs, aspirin has received most publicity as a potential trigger of acute bronchospasm. The weak or lacking association between aspirin and asthma may therefore represent a selective avoidance of aspirin by patients with asthma.

In conclusion, we found a positive association between the intake of nonaspirin NSAIDs and current asthma that was of similar magnitude as that for paracetamol. Whether this association between analgesics and asthma is causal remains unclear. Confounding by indication is a plausible explanation, and

randomized clinical trials are needed to disentangle cause and effect.

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