Original Article

Nonsteroidal Anti-Inflammatory Drugs and the Risk Of Skin Cancer

A Population-Based Case-Control Study

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BACKGROUND: Nonsteroidal anti-inflammatory drugs (NSAIDs) may prevent the development of cancer by inhibiting cyclooxygenase (COX) enzymes, which are involved in carcinogenesis. Therefore, the authors of this report examined the association between NSAID use and the risk of squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and malignant melanoma (MM). **METHODS:** From 1991 through 2009, all incident cases of SCC (n = 1974), BCC (n = 13,316), and MM (n = 3242) in northern Denmark were identified. Approximately 10 population controls (n = 178,655) were matched to each case by age, gender, and county of residence. The use of aspirin, other nonselective NSAIDs, or selective COX-2 inhibitors was ascertained through a prescription database. Conditional logistic regression analyses adjusted for potential confounders were used to compute odds ratios as estimates of incidence rate ratios (IRRs). **RESULTS:** For NSAIDs overall, ever use (>2 prescriptions) compared with nonuse (≤2 prescriptions) was associated with a decreased risk of SCC (IRR, 0.85; 95% confidence interval [CI], 0.76-0.94) and MM (IRR, 0.87; 95% CI, 0.80-0.95), especially for long-term use (≥7 years) and high-intensity use (>25% prescription coverage during the total duration of use). NSAID use was not associated with a reduced risk of BCC overall (IRR, 0.97; 95% CI, 0.93-1.01), but the risk of BCC at sites other than the head and neck was reduced in association with long-term use (IRR, 0.85; 95% CI, 0.76-0.95) and high-intensity use (IRR, 0.79; 95% CI, 0.69-0.91). All estimates of reduced risk were driven primarily by the use of nonselective NSAIDs and older COX-2 inhibitors (diclofenac, etodolac, and meloxicam). **CONCLUSIONS:** The current results indicated that NSAID use may decrease the risk of SCC and MM. ***Cancer* 2012;000:000–000.** © *2012 American Cancer Society.*

KEYWORDS: case-control study, chemoprevention, epidemiology, nonsteroidal anti-inflammatory drugs, skin neoplasm.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) have potential cancer-preventive effects by inhibiting cyclooxygenase (COX) enzymes, which are involved in detrimental processes, such as inhibition of apoptosis, immunosuppression, and stimulation of angiogenesis and invasiveness.[1,2] Moreover, COX-independent pathways that involve lipoxygenases and extracellular signal-regulated kinases also may be involved.[2] The cancer-preventive properties of NSAIDs have been observed particularly for colorectal cancer among users of COX-2 inhibitors or aspirin but also may extend to other cancers.[1,2]

Previous studies largely support a protective role of NSAIDs in development of keratinocyte carcinomas, ie, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), as well as malignant melanoma (MM).[3-13] Thus, the results from 1 randomized controlled study indicated a lower risk of keratinocyte carcinomas associated with use of the COX-2 inhibitor celecoxib.[8] However, the previous studies are controversial and are difficult to compare because of differences in outcome measures (eg, inclusion or exclusion of in situ cancers), study design, study populations (eg, high-risk populations vs general populations), and type and measure of NSAID use.[3-13] Therefore, we conducted a population-based, case-control study using validated registry data to examine whether orally administered aspirin, other nonselective NSAIDs, or COX-2 inhibitors are associated with reduced incidence of SCC, BCC or MM.

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DOI: 10.1002/cncr.27406, **Received:** October 7, 2011; **Revised:** December 7, 2011; **Accepted:** December 13, 2011, **Published online** Month 00, 2012 in Wiley Online Library (wileyonlinelibrary.com)

MATERIALS AND METHODS

Setting and Design

We conducted this study in northern Denmark, which has a population of approximately 1.8 million (30% of the Danish population).[14] To ensure that we had at least 2 years of complete prescription history for all study participants, the study period commenced 2 years after establishment of the prescription databases in northern Denmark (all were established between 1989 and 1998) and continued until December 31, 2008. We included only individuals who had resided in the study area for at least 2 years.

In Denmark, a government-funded health care plan guarantees universal tax-supported health care for all residents; and prescribed medication, including NSAIDs, is subsidized to various degrees.[14,15] The unique central personal registration (CPR) number assigned to all Danish residents allows linkage of medical registries.[16]

Skin Cancer Cases

Since 1943, the Danish Cancer Registry (DCR) has recorded all malignancies together with details on morphology and histology.[17] We used the DCR to identify all incident cases of SCC, BCC, and MM diagnosed during the study period in individuals aged $\geq$20 years. Patients who had more than 1 type of skin cancer were included in the analysis of each type. To evaluate the effects of NSAIDs on skin cancer by the approximate level of sun exposure, we extracted information on the anatomic site of skin cancer (ie, head and neck vs other sites). We excluded individuals who had human immunodeficiency virus infection, a previous cancer diagnosis, or a history of solid organ transplantation, because these disorders increase skin cancer risk.[18,19] The date of diagnosis was considered the index date for cases.

Population Controls

Since 1968, the Danish Civil Registration System (CRS) has recorded all changes in vital status, such as death and migration, with daily updates.[16] We used the CRS to match up to 10 population controls to each case by birth year, sex, and county of residence. We sampled controls using risk-set sampling; ie, only individuals who were alive and who had no history of skin cancer registered in the DCR on the index date of the case were eligible for selection.[20] The same inclusion/exclusion criteria that were used to select cases were applied to controls. Controls were assigned an index date identical to that of their corresponding case.

Nonsteroidal Anti-Inflammatory Drug Use

We used the Aarhus University database[14] to identify all NSAID prescriptions that were redeemed by study participants before their index date. Each time a prescription is redeemed at a pharmacy, a record of the patient's CPR number, the date, and the type and quantity of drug prescribed (according to the World Health Organization's *Anatomical Therapeutic Chemical Classification System*) is transmitted to the database.[14]

We identified prescriptions for low-dose aspirin (75 mg, 100 mg, or 150 mg) and high-dose aspirin (500 mg), other nonselective NSAIDs (phenylbutazon, indomethacin, sulindac, aceclofenac, piroxicam, tenoxicam, lornoxicam, ibuprofen, naproxen, ketoprofen, fenoprofen, flurbiprofen, dexibuprofen, tiaprofenic acid, tolfenamic acid, and nabumeton), older selective COX-2 inhibitors (diclofenac, etodolac, and meloxicam), and newer selective COX-2 inhibitors (celecoxib, rofecoxib, and etoricoxib).[21] We examined older and newer COX-2 inhibitors separately as well as together because of overlapping COX-2 selectivity.[2,21]

We categorized exposure according to the number of prescriptions filled by each individual. We excluded prescriptions redeemed within the year before the index date to reduce both surveillance bias[1] and the potential effect of subclinical disease on medication use. "Ever users" redeemed >2 prescriptions during the entire study period and were classified further as either recent users (>2 prescriptions within 1-2 years before the index date) or former users (>2 prescriptions in total, but not within 1-2 years before the index date). We classified duration of use as short-term (<7 years) or long-term ($\geq$7 years) based on the number of days between the first and the last prescriptions plus the average prescription length (assumed to be 30 days).[22] We defined intensity of use as low (<25%) or high ($\geq$25%) according to the number of days of prescription coverage (product of the number of prescriptions and length of prescription) divided by duration of use in days. We defined individuals who had $\leq$2 NSAID prescriptions as nonusers (reference group). Finally, for a comparison analysis, we examined the association between prescribed acetaminophen and the risk of skin cancer.[1]

Patient Characteristics

From the Danish National Registry of Patients,[23] we retrieved patients' medical history between 1977 and the index date and computed their comorbidity burden using the validated Charlson Comorbidity Index (CCI) score.[24] We also identified patients with rheumatoid arthritis, migraines, or cardiovascular disease (myocardial infarction, congestive heart failure, and peripheral vascular disease), using these diseases and the CCI as proxy measures

for chronic use of over-the-counter, low-dose ibuprofen and aspirin. Furthermore, we identified a history of any autoimmune disease, because these diseases are associated with increased NSAID intake[25] and may affect skin cancer risk.[26-28]

Comedication Use

Various drugs other than NSAIDs also may affect skin cancer risk.[18,29-31] Therefore, we used the prescription database to obtain information on use of the following comedications before the index date: glucocorticoids, cytostatic and immunosuppressive drugs, treatments for skin cancer precursor lesions, topical NSAIDs, and drugs with documented adverse effects of photosensitivity, phototoxicity, and/or pigmentation according to Litt's *Drug Eruption Reference Manual*.[25,32] We also identified psoralen and ultraviolet A (UVA) treatment through treatment codes in the Danish National Registry of Patients.

Statistical Analysis

We computed the frequency and proportion of cases and controls in categories of each study variable. We used conditional logistic regression to compute unadjusted odds ratios with 95% confidence intervals (CIs), associating NSAID use with SCC, BCC, and MM occurrence. Given the risk-set sampling design, the odds ratios provide an unbiased estimate of incidence rate ratios (IRRs).[20]

Next, we adjusted for 1 covariate at a time to quantify the confounding effect of each before fitting a multivariate, conditional logistic regression model with adjustment for CCI score and use of systemic glucocorticoids, cytostatic or immunosuppressive medications, and drugs with pigmenting adverse effects. We estimated adjusted IRRs with 95% CIs for skin cancer among ever users, recent users, and former users of NSAIDs. This approach was used for any NSAIDs; low-dose and high-dose aspirin; nonselective NSAIDs; older, newer, and all COX-2 inhibitors; and the most frequently used agents. In the analyses of NSAID subtypes, we ignored use of NSAIDs different from the subtype under consideration; for example, use of aspirin was not taken into account when examining nonselective NSAIDs. In analyses examining intensity and duration of use, we considered all NSAIDs together and reduced bias because of left censoring by focusing only on individuals with a minimum of 10 years of prescription history. To explore the presence of effect measure modification, we performed unconditional logistic regression with additional adjustment for the matching factors and stratified the results by age, sex, or anatomic site. In the comparison analysis of acetaminophen, we considered only nonusers of NSAIDs and defined the reference group as individuals who had ≤ 2 acetaminophen prescriptions. We also estimated the IRR in ever users compared with nonusers of both NSAIDs and acetaminophen.

To examine the robustness of our findings, we performed 3 sensitivity analyses. First, we examined the isolated effect of any NSAIDs, low-dose aspirin, nonselective NSAIDs, and COX-2 inhibitors by examining the associations among patients who did not use other NSAIDs and/or acetaminophen. Second, to reduce potential surveillance bias,[1] we repeated the analyses after excluding prescriptions that were redeemed within 2 years and then within 3 years before the index date, altering the exposure definitions accordingly. Third, we reanalyzed the effects of duration and intensity of use using an average prescription length of 60 days.

RESULTS

Descriptive Data

We identified a total of 1974 patients with SCC, 13,316 patients with BCC, and 3242 patients with MM. The median age at diagnosis was 77 years, 67 years, and 57 years among patients with SCC, BCC, and MM, respectively (Table 1). Men accounted for a greater proportion of patients with SCC (63%) versus patients with BCC (50%) and MM (45%). SCC tumors were located more frequently on the head and neck (56%) compared with BCC tumors (50%) and MM tumors (12%).

Among controls, 38% (67,338 patients) were ever users of NSAIDs. Only 6% had redeemed 1 or more prescriptions for newer COX-inhibitors, and, among these, only 37% had more than 6 months' duration of use; this proportion decreased exponentially to 28%, 14%, and 6% after 1 year, 2 years, and 3 years, respectively.

Nonsteroidal Anti-Inflammatory Drugs and Skin Cancer

Ever use of NSAIDs, compared with nonuse, was associated with slightly reduced risks of SCC (adjusted IRR, 0.85; 95% CI, 0.76-0.94) and MM (IRR, 0.87; 95% CI, 0.80-0.95) but not BCC (IRR, 0.97; 95% CI, 0.93-1.01) (Table 2). We observed no variation in the magnitude of associations according to timing of use, ie, recent use or former use. However, the magnitude of associations depended on the duration and intensity of use (Table 3). Decreased IRRs for SCC were observed in all subgroups of duration and intensity of use, especially among high-

Table 1. Characteristics of Skin Cancer Cases and Matched Controls in Northern Denmark, 1991-2008

Characteristic	No. of Patients (%)					
	Squamous Cell Carcinoma		Basal Cell Carcinoma		Malignant Melanoma	
	Cases, n = 1921	Controls, n = 19,163	Cases, n = 12,864	Controls, n = 128,609	Cases, n = 3089	Controls, N = 30,883
Sex						
Men	1209 (63)	12,052 (63)	6452 (50)	64,505 (50)	1390 (45)	13,893 (45)
Women	712 (37)	7111 (37)	6412 (50)	64,104 (50)	1699 (55)	16,990 (55)
Anatomic site of skin cancer						
Head and neck	1078 (56)	—	6374 (50)	—	378 (12)	—
Other	843 (44)	—	6490 (50)	—	2711 (88)	—
Age at index date, y						
Median	77	77	67	67	57	57
Mean±SD	75±12	75±12	66±14	66±14	57±16	57±16
Age group at index date, y						
<50	67 (3.5)	664 (3.5)	1746 (14)	17,414 (14)	1065 (35)	10,666 (35)
50-59	165 (8.6)	1628 (8.5)	2498 (19)	25,042 (19)	681 (22)	6796 (22)
60-69	342 (18)	3469 (18)	3249 (25)	32,515 (25)	628 (20)	6334 (21)
70-79	598 (31)	5928 (31)	3147 (24)	31,417 (24)	434 (14)	4303 (14)
≥80	749 (39)	7474 (39)	2224 (17)	22,221 (17)	281 (9.1)	2784 (9)
Calendar period of index date						
1991-1995	300 (16)	2993 (16)	1506 (12)	15,060 (12)	309 (10)	3090 (10)
1996-2000	379 (20)	3780 (20)	2915 (23)	29,146 (23)	683 (22)	6830 (22)
2001-2005	801 (42)	7981 (42)	5166 (40)	51,656 (40)	1340 (43)	13,393 (43)
2006-2008	441 (23)	4409 (23)	3277 (25)	32,747 (25)	757 (25)	7570 (25)
Charlson comorbidity level[a]						
Low	385 (20)	4492 (23)	2923 (23)	32,724 (25)	655 (21)	7774 (25)
Moderate	1281 (67)	12,565 (66)	9001 (70)	86,397 (67)	2297 (74)	21,522 (70)
High	255 (13)	2106 (11)	940 (7.3)	9488 (7.4)	137 (4.4)	1587 (5.1)
Comorbidities						
Cardiovascular disease[b]	299 (16)	2832 (15)	1163 (9)	12,206 (9.5)	177 (5.7)	1911 (6.2)
Migraines	12 (0.62)	83 (0.43)	89 (0.69)	874 (0.68)	26 (0.84)	237 (0.77)
Rheumatoid arthritis	39 (2)	193 (1)	180 (1.4)	1255 (0.98)	33 (1.1)	215 (0.70)
Juvenile rheumatoid arthritis	0 (0)	1 (0.010)	2 (0.020)	14 (0.010)	1 (0.030)	6 (0.020)
Any autoimmune disease	178 (9.3)	1277 (6.7)	882 (6.9)	7889 (6.1)	179 (5.8)	1659 (5.4)
Comedications[c]						
PUVA-treatment[d]	0 (0)	6 (0.030)	2 (0.020)	28 (0.020)	2 (0.060)	8 (0.030)
Systemic glucocorticoids	507 (26)	4289 (22)	2918 (23)	26,423 (21)	550 (18)	5288 (17)
Glucocorticoid suppositories and foam	4 (0.21)	61 (0.32)	72 (0.56)	525 (0.41)	18 (0.58)	141 (0.46)
Cytostatic and immunosuppressive drugs	52 (2.7)	152 (0.79)	222 (1.7)	1319 (1)	34 (1.1)	260 (0.84)
Topical NSAIDs[e]	2 (0.10)	22 (0.11)	9 (0.070)	99 (0.080)	4 (0.13)	19 (0.060)
Topical treatment of precursor neoplastic lesions	11 (0.57)	24 (0.13)	50 (0.39)	235 (0.18)	11 (0.36)	128 (0.41)
Photosensitizing medications[d]	1448 (75)	13,753 (72)	9243 (72)	87,408 (68)	1978 (64)	19,386 (63)
Phototoxic medications[d]	1147 (60)	10,539 (55)	6370 (50)	61,459 (48)	1279 (41)	12,373 (40)
Pigmenting medications[d]	1363 (71)	12,698 (66)	8935 (69)	82,294 (64)	1840 (60)	18,504 (60)

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; PUVA, psoralen plus ultraviolet light therapy; SD, standard deviation.
[a] The Charlson Comorbidity Index score was categorized as follows: 0, low; 1-2, medium; and ≥3, high.
[b] Cardiovascular diseases included myocardial infarction, congestive heart failure, and peripheral vascular disease.
[c] Any prescription redemption was included.
[d] These included drugs with documented adverse effects of photosensitivity, phototoxicity, and/or pigmentation according to the 17th edition of Litt's *Drug Eruption Reference Manual*.

intensity users. For MM, long-term and high-intensity use, particularly in combination, was associated with the strongest inverse association. Long-term and/or high-intensity use was associated with a 10% to 17% reduced risk of BCC.

Aspirin, nonselective NSAIDs, and older and newer COX-2 inhibitors had similar inverse associations with the risk of SCC. The same was observed for MM, except that no association was observed for newer COX-2 inhibitors. An analysis of the most frequently

Table 2. Nonsteroidal Anti-Inflammatory Drug Use and Adjusted Incident Ratios with 95% Confidence Intervals of Skin Cancer in Northern Denmark, 1991-2008[a]

	Squamous Cell Carcinoma			Basal Cell Carcinoma			Malignant Melanoma		
	No. (%)			No. (%)			No. (%)		
NSAID Use	Cases, n = 1921	Controls, n = 19,163	IRR [95% CI][b]	Cases, n = 12,864	Controls, n = 128,609	IRR [95% CI][b]	Cases, n = 3089	Controls, n = 30,883	IRR [95% CI][b]
Reference group[c]	1082 (56)	10,666 (56)	Ref	7822 (61)	79,666 (62)	Ref	2157 (70)	20,985 (68)	Ref
Any NSAIDs									
Ever[d]	839 (44)	8497 (44)	0.85 [0.76-0.94]	5042 (39)	48,943 (38)	0.97 [0.93-1.01]	932 (30)	9898 (32)	0.87 [0.80-0.95]
Recent[e]	437 (23)	4560 (24)	0.81 [0.71-0.92]	2232 (17)	22,227 (17)	0.94 [0.89-0.99]	339 (11)	3,937 (13)	0.79 [0.69-0.90]
Former[f]	402 (21)	3937 (21)	0.89 [0.78-1.01]	2810 (22)	26,716 (21)	1.00 [0.95-1.05]	593 (19)	5961 (19)	0.92 [0.83-1.02]
Low-dose aspirin									
Ever[d]	457 (24)	4493 (23)	0.86 (0.76-0.99)	1989 (15)	19,468 (15)	0.97 (0.91-1.02)	288 (9.3)	3044 (9.9)	0.89 [0.76-1.03]
Recent[e]	326 (17)	3220 (17)	0.86 (0.75-1.00)	1413 (11)	13,958 (11)	0.96 (0.90-1.02)	201 (6.5)	2,214 (7.2)	0.85 [0.72-1.01]
Former[f]	131 (6.8)	1273 (6.6)	0.87 (0.71-1.06)	576 (4.5)	5510 (4.3)	0.99 (0.90-1.08)	87 (2.8)	830 (2.7)	0.97 [0.76-1.23]
High-dose aspirin									
Ever[d]	4 (0.21)	55 (0.29)	0.61 [0.22-1.70]	31 (0.24)	313 (0.24)	0.92 [0.64-1.34]	3 (0.10)	43 (0.14)	0.64 [0.20-2.08]
Recent[e]	1 (0.050)	13 (0.070)	0.70 [0.09-5.35]	9 (0.070)	73 (0.060)	1.14 [0.57-2.28]	0 (0)	12 (0.04)	—
Former[f]	3 (0.16)	42 (0.22)	0.59 [0.18-1.92]	22 (0.17)	240 (0.19)	0.86 [0.55-1.33]	3 (0.10)	31 (0.10)	0.88 [0.27-2.89]
Nonselective NSAIDs									
Ever[d]	388 (20)	3893 (20)	0.85 [0.75-0.97]	2541 (20)	26,128 (20)	0.91 [0.87-0.96]	523 (17)	5694 (18)	0.85 [0.76-0.94]
Recent[e]	79 (4.1)	896 (4.7)	0.74 [0.58-0.94]	501 (3.9)	5530 (4.3)	0.84 [0.76-0.93]	89 (2.9)	1101 (3.6)	0.74 [0.59-0.93]
Former[f]	309 (16)	2997 (16)	0.89 [0.77-1.03]	2040 (16)	20,598 (16)	0.93 [0.88-0.99]	434 (14)	4593 (15)	0.87 [0.78-0.98]
All COX-2 inhibitors									
Ever[d]	205 (11)	2051 (11)	0.84 [0.71-1.00]	1418 (11)	13,035 (10)	1.01 [0.95-1.08]	259 (8.4)	2733 (8.9)	0.87 [0.75-1.00]
Recent[e]	64 (3.3)	601 (3.1)	0.90 [0.68-1.18]	372 (2.9)	3366 (2.6)	1.02 [0.91-1.14]	61 (2)	664 (2.2)	0.83 [0.63-1.09]
Former[f]	141 (7.3)	1450 (7.6)	0.82 [0.67-1.00]	1046 (8.1)	9669 (7.5)	1.01 [0.94-1.09]	198 (6.4)	2069 (6.7)	0.88 [0.75-1.03]
Older COX-2 inhibitors									
Ever[d]	156 (8.1)	1622 (8.5)	0.81 [0.68-0.98]	1163 (9)	10,674 (8.3)	1.02 [0.95-1.09]	218 (7.1)	2325 (7.5)	0.86 [0.74-1.00]
Recent[e]	44 (2.3)	427 (2.2)	0.88 [0.64-1.22]	269 (2.1)	2479 (1.9)	1.00 [0.88-1.14]	42 (1.4)	499 (1.6)	0.76 [0.55-1.04]
Former[f]	112 (5.8)	1195 (6.2)	0.79 [0.64-0.98]	894 (7)	8195 (6.4)	1.02 [0.95-1.10]	176 (5.7)	1826 (5.9)	0.89 [0.75-1.05]
Newer COX-2 inhibitors									
Ever[d]	58 (3)	537 (2.8)	0.87 [0.65-1.17]	344 (2.7)	2796 (2.2)	1.13 [1.00-1.27]	53 (1.7)	477 (1.5)	1.01 [0.75-1.36]
Recent[e]	20 (1)	179 (0.93)	0.89 [0.55-1.44]	103 (0.80)	863 (0.67)	1.08 [0.87-1.33]	18 (0.58)	166 (0.54)	0.99 [0.60-1.63]
Former[f]	38 (2)	358 (1.9)	0.86 [0.60-1.23]	241 (1.9)	1933 (1.5)	1.15 [1.00-1.33]	35 (1.1)	311 (1)	1.02 [0.71-1.47]

Abbreviations: CI, confidence interval; COX-2, cyclooxygenase-2; IRR, incident rate ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; Ref, reference group.

[a] IRRs and CIs were computed with conditional logistic regression. Controls were matched on birth year, sex, and county of residence.

[b] Analyses were adjusted for Charlson Comorbidity Index, use of systemic glucocorticoids, cytostatic or immunosuppressive medication, and drugs with pigmenting adverse effects.

[c] The reference group was patients who received ≤2 prescriptions of any NSAID in total.

[d] Ever use indicates a total of >2 prescriptions.

[e] Recent use indicates >2 prescriptions within the period 1 to 2 years before the index date.

[f] Former use indicates >2 prescriptions overall but ≤2 during the recent period.

Table 3. Adjusted Incidence Rate Ratios With 95% Confidence Intervals for the Duration and Intensity of Nonsteroidal Anti-Inflammatory Drug (NSAID) Use (Aspirin, Nonselective NSAIDs, and Selective Cyclooxygenase 2 Inhibitors) Among Skin Cancer Cases and Matched Controls With ≥10 Years of Prescription History: Northern Denmark, 1991-2008

	IRR (95% CI)		
Variable	Squamous Cell Carcinoma	Basal Cell Carcinoma	Malignant Melanoma
Reference group[b]	Ref	Ref	Ref
NSAID duration			
Short term[c]	0.75 (0.59-0.95)	1.00 (0.92-1.09)	0.89 (0.74-1.06)
Long term[d]	0.84 (0.68-1.03)	0.90 (0.83-0.97)	0.84 (0.71-1.00)
NSAID intensity			
Low[e]	0.89 (0.73-1.09)	0.96 (0.90-1.04)	0.92 (0.79-1.06)
High[f]	0.66 (0.52-0.85)	0.89 (0.80-0.97)	0.70 (0.56-0.89)
Combinations			
Short-term, low-intensity	0.79 (0.58-1.07)	1.04 (0.94-1.15)	0.87 (0.71-1.08)
Short-term, high-intensity	0.69 (0.50-0.94)	0.95 (0.84-1.07)	0.88 (0.66-1.16)
Long-term, low-intensity	0.94 (0.75-1.18)	0.92 (0.85-1.00)	0.93 (0.78-1.11)
Long-term, high-intensity	0.65 (0.48-0.88)	0.83 (0.73-0.93)	0.54 (0.38-0.75)

Abbreviations: CI, confidence interval; IRR, incident rate ratio; Ref, reference group.
[a] IRRs and CIs were computed with conditional logistic regression. Controls were matched on birth year, sex, and county of residence. Analyses were adjusted for Charlson Comorbidity Index score, use of systemic glucocorticoids, cytostatic or immunosuppressive medication, and drugs with pigmenting adverse effects.
[b] The reference group was patients who received a total of ≤2 prescriptions of any nonsteroidal anti-inflammatory drug.
[c] Short-term indicates <7 years between redemption of the first prescription and the end of the last prescription.
[d] Long-term indicates ≥7 years between the redemption of the first prescription and the end of the last prescription.
[e] Low-intensity indicates <25% prescription coverage during the total duration of use.
[f] High-intensity indicates ≥25% prescription coverage during the total duration of use.

Table 4. The Most Frequently Used Nonsteroidal Anti-Inflammatory Drugs and Incidence Rate Ratios of Skin Cancer in Northern Denmark, 1991-2008[a]

	IRR (95% CI)		
NSAID Ever Use[b]	Squamous Cell Carcinoma	Basal Cell Carcinoma	Malignant Melanoma
Reference group[c]	Ref	Ref	Ref
Ibuprofen	0.81 (0.69-0.94)	0.87 (0.82-0.93)	0.86 (0.75-0.97)
Naproxen	0.84 (0.60-1.17)	0.90 (0.79-1.02)	0.99 (0.77-1.29)
Ketoprofen	0.85 (0.55-1.30)	0.91 (0.77-1.06)	0.73 (0.49-1.08)
Diclofenac	0.85 (0.69-1.04)	0.99 (0.91-1.06)	0.87 (0.73-1.02)
Etodolac	0.81 (0.56-1.17)	1.18 (1.04-1.34)	0.77 (0.54-1.08)
Piroxicam	0.49 (0.27-0.88)	0.82 (0.67-1.01)	0.87 (0.55-1.37)
Celecoxib	0.83 (0.54-1.26)	1.13 (0.95-1.33)	0.99 (0.65-1.51)
Rofecoxib	1.02 (0.71-1.48)	1.18 (1.00-1.39)	0.94 (0.61-1.44)
Indomethacin	1.26 (0.87-1.83)	0.86 (0.71-1.05)	0.74 (0.46-1.20)

Abbreviations: CI, confidence interval; IRR, incident rate ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; Ref, reference group.
[a] IRRs and CIs were computed by using conditional logistic regression. Controls were matched on birth year, sex, and county of residence. Analyses were adjusted for Charlson Comorbidity Index score, use of systemic glucocorticoids, cytostatic or immunosuppressive medication, and drugs with pigmenting adverse effects.
[b] Ever use indicates a total of >2 prescriptions.
[c] The reference group was patients who had a total of ≤2 prescriptions of any NSAID.

used individual agents supported the overall results (Table 4).

The stratified analysis revealed that the inverse association between NSAIDs and BCC was limited to cancers that occurred on less UV-exposed areas of the body (sites other than the head and neck) in long-term users (IRR, 0.85; 95% CI, 0.76-0.95), high-intensity users (IRR, 0.79; 95% CI, 0.69-0.91), and long-term/high-intensity users (IRR, 0.72; 95% CI, 0.60-0.87). For SCC and MM, the reduced IRRs were independent of anatomic

site. We observed no apparent modification of the effect estimates by age or sex.

Acetaminophen and Skin Cancer

Unexpectedly, we observed an inverse association between acetaminophen use and the risk of BCC at sites other than the head and neck (IRR, 0.68; 95% CI, 0.56-0.83). This decreased risk was observed in high-intensity and/or long-term users. Overall, ever use of acetaminophen was not associated with the risk of MM (IRR, 0.98; 95% CI, 0.74-1.31), but the analyses of duration and intensity of use revealed a 20% to 30% risk reduction in high-intensity and/or long-term users. No association was observed between acetaminophen use and the risk of SCC (IRR, 0.96; 95% CI, 0.74-1.23). IRRs for ever use of both NSAIDs and acetaminophen were 0.81 (95% CI, 0.68-0.96) for SCC, 0.89 (95% CI, 0.83-0.96) for BCC, and 0.77 (95% CI, 0.64-0.93) for MM.

Sensitivity Analyses

Taking concurrent use of other NSAIDs into account weakened the inverse association between low-dose aspirin, newer COX-2 inhibitors, and the risk of SCC but strengthened the inverse association with older COX-2 inhibitors. The effect estimates remained similar for BCC and MM, except for an attenuation of the association between nonselective NSAIDs and the risk of MM. The results were not affected meaningfully by changing the average prescription length to 60 days or by excluding NSAIDs prescribed within 2 years or 3 years before the index date.

DISCUSSION

We observed that use of NSAIDs overall, including aspirin, nonselective nonaspirin NSAIDs, and COX-2 inhibitors, was associated with a decreased risk of skin cancer, particularly SCC and MM. The effect increased with greater duration and intensity of use, which may reflect a cumulative biologic effect (ie, a dose-response effect) exerted in the initiation of carcinogenesis. In line with the approved treatment of actinic keratosis with topical diclofenac,[25] we also observed that older COX-2 inhibitors (including diclofenac) were associated with a greater isolated reduction in the risk of SCC versus BCC and MM.

The various associations for skin cancer subtypes and anatomic sites may be explained by dissimilarities in the expression of COX enzymes. For example, laboratory studies consistently have reported elevated COX-2 levels in SCC and its precursor lesions (eg, actinic keratosis and Bowen disease), whereas results have been conflicting for BCC and MM.[2,33,34] Another explanation may be that the phototoxic adverse effects of some NSAIDs preclude their protective effects at sun-exposed sites, especially in MM and BCC, because they are associated more strongly with sunburns (ie, intermittent, intense sun exposure) than SCC.[18,19] Also, the harmful effect of sun exposure itself at such sites may be so strong that the protective effects of NSAIDs are reduced.

A recent trial investigated the risk of BCC, SCC, and actinic keratosis after 11 months of follow-up in 240 high-risk patients who were randomized to receive either a placebo or 200 mg celecoxib administered orally twice daily for 9 months.[8] The trial indicated that there was a protective effect of celecoxib on both SCC (relative risk [RR], 0.42; 95% CI, 0.19-0.93) and BCC (RR, 0.40; 95% CI, 0.18-0.93),[8] similar to the results from 2 observational studies in high-risk populations.[6,12] Our results do not support an association between newer COX-2 inhibitors and skin cancer or NSAIDs overall and BCC. However, our findings are in accordance with studies conducted in the general population.[3,4,13,35] Thus, the effects of NSAIDs may depend on the baseline risk of skin cancer. In addition, newer COX-2 inhibitors are rarely used continuously for a longer time; were commercially available for only part of the study period; and in, some instances (rofecoxib), were withdrawn from the market.[25] Therefore, duration of use in our study population may not have been sufficient to demonstrate a protective effect of these agents.

Five previous studies have examined the association between aspirin and other nonaspirin NSAIDs and the risk of MM.[5,7,9-11] Only 1 of those studies failed to demonstrate an inverse association.[5] Like us, Curiel-Lewandrowski et al[7] observed that the inverse association was cumulative and that the association remained even after taking into account concurrent use of other NSAIDs. On average, previous studies reported a higher prevalence of NSAID use.[3-13] This discrepancy is likely attributable to differences in defining "ever users," age and sex distributions, and the source of exposure data (self-reported vs prescription records).

The major limitation of the current study is that cases were ascertained through the DCR, in which only an estimated 60% of SCC and BCC cases are recorded.[28,29,36] This incompleteness hypothetically may bias our results in 2 ways. On 1 hand, if NSAID users have higher comorbidity than nonusers, then some clinicians may deem the detection of a keratinocyte carcinoma relatively trivial and not as important to register as other comorbidities, thereby producing a false inverse association between NSAIDs and SCC or BCC risk. Conversely,

NSAID users may be in more frequent contact with the health care system and, thus, may have a greater chance of skin cancer detection—a scenario that would cause us to underestimate the actual inverse association with NSAID use.[1] In any case, the completeness of data in the DCR is high for other cancers, including MM[17]; therefore, the inverse association with MM strengthens the validity of our results.

Our study relied on dispensed prescriptions, which may not be equivalent to actual drug use. However, the finding that patients partially paid for and repeatedly redeemed prescriptions suggests adherence with the medications and increases our confidence that we accurately classified chronic, long-term use of NSAIDs—the exposure of greatest interest in our study. Over-the-counter use of aspirin and low-dose ibuprofen also may have affected our results. However, regular users typically are registered in the prescription database, because the cost is automatically partly refunded when a physician prescribes the drug.[15] We also lacked data on length of prescriptions and, thus, could not classify daily or weekly doses of each drug. Finally, we may have misclassified some former users as nonusers because of left censoring through the prescription database. Nonetheless, at the most, these limitations in exposure classification would have led us to underestimate a protective effect of NSAIDs on skin cancer.

We had no information on lifestyle factors, skin phenotype, or UV radiation exposure. However, matching on county of residence and the limited geographic variation in northern Denmark minimizes geographic differences in ambient UV radiation exposure.[37] To explain our results, unmeasured confounders would have to be associated with both long-term NSAID use and decreased risk of skin cancer. In this context, a Danish study previously demonstrated that continuous analgesic use is more frequent in individuals with poor self-reported health, smoking, and low levels of education and physical activity,[38] suggesting that a healthy user effect is unlikely. The comparison analysis of acetaminophen was used as an indicator of a potential healthy user effect. Unexpectedly, we observed an inverse association between acetaminophen and BCC and MM risk, possibly suggesting confounding by unmeasured factors. Conversely, an actual protective effect of acetaminophen is plausible, eg, through COX-3 inhibition or activation by tyrosinase to cytotoxic metabolites in melanocytes.[39,40] The clinical data on this association, however, are limited and conflicting.[4,13,35,41] When interpreting these discrepancies, our lack of information on over-the-counter acetaminophen should be taken into account.

Given the high skin cancer incidence and the widespread and frequent use of NSAIDs, a preventive effect of these agents may have important public health implications. We observed that NSAIDs overall, including aspirin, other nonselective NSAIDs, and older COX-2 inhibitors, were associated with a decreased risk of skin cancer, particularly SCC and MM. The risk reduction was greatest among long-term and high-intensity users, suggesting a cumulative and dose-dependent, protective effect.

FUNDING SOURCES

Supported by the Clinical Epidemiological Research Foundation.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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