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Association of Use of Nonsteroidal Anti-inflammatory Drugs and Cutaneous Squamous Cell Carcinoma

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Abstract

OBJECTIVE—To examine the association between non-steroidal anti-inflammatory drug (NSAID) use and cutaneous squamous cell carcinoma (SCC).

DESIGN—Retrospective case-control.

SETTING—Kaiser Permanente Northern California (KPNC), a large population based-health maintenance organization.

PATIENTS—Random sample of 415 KPNC members diagnosed with a pathology-verified SCC in 2004 and 415 age-, sex, and race-matched controls with no history of skin cancer.

MAIN EXPOSURE MEASURE—Self-reported NSAID use in the 10 years prior to baseline. NSAID use was categorized based on type (any NSAIDs, aspirin, ibuprofen, non-aspirin NSAIDs). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression to estimate the association of SCC with regular use, dose and duration of exposure to the different NSAID types. Information on pharmacy-dispensed NSAIDs was also

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examined to assess its association with SCC risk. Models were adjusted for all ascertained SCC risk factors (fully adjusted model) and only those variables associated with both SCC risk and NSAID use (parsimonious model).

RESULTS—Fully adjusted analyses showed no statistically significant reduction in SCC risk with self-reported regular use of any NSAID (OR=1.32, 95% CI: 0.92–1.89), aspirin (OR=1.38, 95% CI: 0.96–1.97), ibuprofen (OR=0.74, 95% CI: 0.46–1.19), or non-aspirin NSAIDs (OR=0.84, 95% CI: 0.56–1.26). Analyses examining duration, dose, and variables combining duration and dose of NSAID exposure did not appreciably change results. Analysis using the parsimonious model showed similar results. The data on pharmacy dispensed NSAIDs also showed no association with SCC risk.

CONCLUSIONS—Neither self-reported, nor pharmacy-dispensed NSAID exposure was associated with cutaneous SCC risk.

INTRODUCTION

Nonsteriodal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX), blocking the synthesis of proinflammatory prostaglandins. In addition to their anti-inflammatory properties, NSAIDs also inhibit neoplastic proliferation by inducing apoptosis and inhibiting angiogenesis.[1,2] Epidemiologic studies and randomized trials have shown protective effects of NSAIDs for several cancers including colorectal,[3,4] breast,[5] prostate,[6] and lung.[7] Laboratory studies suggest that NSAIDs exert protective effects against cutaneous squamous cell carcinomas (SCCs) both *in vitro*[2,8] and in animal models.[10–12] However, few epidemiologic studies have examined the association between NSAID use and SCC risk, and these have yielded conflicting information.[13–18] The conflicting results may be due, in part, to differing methods for ascertaining NSAID exposure (for example, relying solely on pharmacy dispensed NSAIDs),[13,14] differing definitions of regular NSAID use,[16,18] and lack of adjustment for potential confounding variables such as sun-sensitivity.[18]

We conducted a case-control study to investigate whether NSAID use is associated with SCC using the Kaiser Permanente Northern California (KPNC) population. KPNC electronic records include a comprehensive pathology database through which cutaneous SCCs can be accurately identified. The epidemiology of cutaneous SCCs is otherwise difficult to study because unlike most malignancies, cutaneous SCCs are not reportable to national registries such as the Surveillance Epidemiology and End Results (SEER) program, they do not have unique International Classification of Disease (ICD-9) identifiers, and patients' self-report of a history of SCC are not accurate.[19] We used a self-administered questionnaire to ascertain SCC risk factors and exposure to NSAIDs by type, dose, and duration over the 10 years preceding the diagnosis date. Based on previously published literature,[20] we hypothesized that NSAID use would be associated with a reduction in risk of SCC.

METHODS

Study Population

This investigation was a case-control study of 415 KPNC members (ages 43 to 85) with a pathology-confirmed squamous cell carcinoma diagnosed in 2004 and 415 control subjects matched to cases by year of birth, sex and self-reported race. To minimize risk of exposure misclassification due to poor recall of NSAID use, we excluded members greater than 85 years of age and those with a diagnosis of dementia from January 1, 1994 to December 31, 2004. Members whose native language was not English were also excluded to reduce the likelihood of error in completing the self-administered questionnaire. This study was approved by the Kaiser Foundation Research Institute Institutional Review Board (IRB)

(CN-05MAsga-01-H, approved December 8, 2005) and was conducted according to the Declaration of Helsinki principles.

A pool of potential cases were identified from KPNC electronic pathology records by querying all electronic pathology reports of specimens collected between January 1, 2004 and December 31, 2004 that contained the word “skin” in the specimen line and the phrase “squamous cell carcinoma” or “SCC” in the diagnosis line. Each pathology report was reviewed by a dermatologist (MA), and only those tumors that were extra-genital, non-mucosal, and had a definitive diagnosis of SCC were included in the pool of eligible cases. The index date was defined as the date of SCC diagnosis.

In keeping with an IRB mandate that potential subjects with SCC be approached through their primary care provider, 1052 eligible cases were grouped and randomly selected by primary care provider. Of the 581 cases selected, 472 (81%) completed the questionnaire, and those, 422 were able to be matched with a responding control. Control subjects were drawn from respondents to the 2005 Member Health Survey (MHS), a general health survey mailed to a random sample of KPNC adult members. We chose MHS participants because this survey asked questions on self-identified race and history of prior cancer. Of the MHS respondents who reported no history of cancer, potential controls were matched by year of birth ±1 year, sex and race to cases (n=1801). One control was randomly selected within the case-control pairing and contacted to participate in the study. If they refused, another control was randomly selected within the pairing until a case-control pair was completed. We contacted 736 controls in order to achieve a matched control for all 422 cases (57% response).

Each participant was contacted by mail and asked to complete a 3-page self-administered questionnaire regarding various personal characteristics, medication use, health history, skin cancer history and risk factors. The survey instrument was modeled off of a validated questionnaire to ascertain supplement use developed for the Vitamins and Lifestyle Study.[21] For non-responders who did not opt out of the study, the questionnaire was mailed a second time 3 weeks after initial contact. If no response was obtained from the second mailing and the patient did not opt out, the subject was contacted by telephone and the questionnaire administered by trained study personnel. Participants were offered a $5 gift-card for completing the questionnaire. Subjects who had mailed in the questionnaire but had missing pertinent variables on NSAID exposure and SCC risk factors were contacted by phone and, if they agreed, the missing items were administered to them.

Exclusions

Given the significantly increased risk profile of organ transplant patients, case-control pairs in which one member reported a history of an organ transplant were excluded (6 cases). In addition, one case-control pair had discrepant self-reported race on the questionnaire and was excluded, leaving 415 case-control pairs for analysis.

NSAID Exposure

Self-Reported Exposure—Information was ascertained on over-the-counter and prescription NSAID use through a self-administered questionnaire which inquired about the use of aspirin, ibuprofen, naproxen, bismuth subsalicylate, diclofenac, etodolac, indomethacin, nabumetone, piroxicam, salsalate, sulindac, celecoxib, rofecoxib, and valdecoxib. Common brand names were given as examples to facilitate recall. Acetaminophen use was also ascertained as a comparison drug, as it is used for many of the same indications as NSAIDs (analgesic, antipyretic) but is not hypothesized to have chemoprotective properties for skin cancer. For each drug, individuals were asked about

their patterns of use over the preceding 10 years including years taken (categorical variable: <1, 1–3, 4–6, 7–9, 10+), days per week of use (categorical variable: 1–2, 3–5, 6+), pills taken per day (1, 2, 3–4, 5–6, 7+), and dose (in mg, dose categories provided based on medication in question).

We categorized the different NSAIDs into four groups: 1) any NSAIDs, 2) aspirin, 3) ibuprofen, and 4) non-aspirin NSAIDs. For each type, we examined three exposure measures. “Regular use” was defined as taking the medication at least once a week for at least one year. “Duration” represented categorized years of use in the past 10 years (range 0 year to 10 years). For subjects reporting more than one type of NSAID use, the longest reported duration was used for the exposure variable. The “dose” was the average strength in mg per pill over the reported period of use and was calculated as days per week/7 × pills per day × dose per pill. The dose variable was further categorized for aspirin as “low-dose” (≤ 81 mg) and “high-dose” (> 81 mg) and for ibuprofen as “low-dose” (≤ 200 mg) and “high-dose” (> 200 mg) based on dosage during the stated period of use.

To simultaneously account for duration and frequency, the variable “pill-years” was defined by multiplying number of pills per day × days per week × years of use using the midpoint of each duration category. The pill-year variable was divided into 4 categories (0, >0 to < 2, 2 to ≤ 5, > 5). If the respondent indicated that they had taken a specific NSAID but failed to complete the remaining information regarding that NSAID on the questionnaire, the lowest category of the missing frequency, dose, and/or duration was assumed.

The two most commonly reported NSAIDs, aspirin and ibuprofen, had wide variations in dose. To capture dose in addition to frequency and duration of use, we defined the variable “pill-year-dose” as follows: pill-years × the common strength per pill (in mgs). Since a pill-year is equivalent to taking one pill each day for one year, one pill-year-dose for aspirin corresponds to intake of one 325 mg tablet per day for one year, and for ibuprofen as intake of one 200 mg tablet per day for one year. There were not enough respondents to allow for meaningful analysis of pill-year-dose exposure for the remaining NSAIDs.

Pharmacy-Dispensed NSAIDs—Longitudinal exposure to NSAIDs was ascertained for each study member using information found in automated KPNC pharmacy databases on filled prescriptions from the date the questionnaire was returned (baseline) to 10 years prior to baseline (encompassing 1995–2005). We searched for all known available pharmacy-dispensed NSAIDs requiring a prescription during the study period including nabumetone, etodolac, sulindac, indomethacin, piroxicam, salsalate, diclofenac, celecoxib, rofecoxib, and valdecoxib. We determined the number of refills for each medication type in the 10 years prior to the date the survey was returned. If the individual had at least 1 refill for a given NSAID, they were considered to be exposed. We also determined the cumulative days supply for each NSAID type during the 10 years and calculated the years of exposure as a continuous variable. Additionally, we created an ever/never exposure variable for any pharmacy-dispensed prescription NSAID (“any NSAID”) and used the maximum duration of any pharmacy-dispensed NSAID as the duration measure for the “any NSAID” variable.

Covariates

Participants answered questions on variables known to influence SCC risk including skin type, history of freckling (yes/no), eye color, natural hair color, education, family history of skin cancer, history of sunburns, outdoor sun exposure, occupational sun exposure, tanning bed use (yes/no), high-risk exposures (UV light, burn scar, non-healing ulcers, radiation treatment, arsenic exposure, exposure to industrial chemicals), and smoking (current vs. former/never). For occupational exposure, we asked participants if their main occupation involved daily sun exposure of at least 2 hours between 10 am–4 pm (yes/no). We also

inquired if respondents regularly (at least once a week) spent at least 2 hours outdoors between 10 am and 4 pm, and if so, ascertained the average number of hours per week.

Statistical Analysis

Differences in distributions of categorical covariates between cases and controls were analyzed using Pearson chi-square tests. For the matched case-control analysis, we used conditional logistic regression to estimate unadjusted and adjusted odds ratios and Wald 95% confidence intervals for each of the four NSAID exposure types with regular use, dose, duration, and pill-years as exposure measures. To ensure that our multivariate analysis was not over-adjusted, we also analyzed the multivariate model limiting the number of variables to only those that were associated with both NSAID exposure and SCC risk at the $p<0.20$ level (parsimonious model). The referent category for all analyses involving regular use and duration were users who reported consuming NSAIDs less than once a week for less than one year. The referent category for analyses involving dose were low-dose users (81 mg or less for aspirin, 200 mg or less for ibuprofen). *P* values were two-sided. Power calculations indicated that a sample size of 415 cases and 415 controls with 59% of controls exposed to NSAIDs would result in a maximum detectable SCC risk reduction of SCC of 0.64, or a minimum detectable risk reduction of 36% (two sided test; alpha=0.05; power=0.80, within matched pair phi correlation of 0.20). All statistical analyses were performed using SAS, version 9.1, (SAS Institute Inc., Cary, NC).

RESULTS

The average age of participants at index date was 72.5 years ± 8.6 SD (range: 43–85). The majority of participants were male (n=514, 61.9%). Compared to controls, cases were more likely to have red or blond hair, blue or grey eyes, and lighter skin types. Cases were also more likely to report current smoking, a family history of skin cancer and a history of childhood freckles, routine sun exposure and severe sunburns (Table 1).

The majority of study participants (60.8%) self-reported regular use of NSAID in the 10 years prior to baseline. The most commonly reported regularly used NSAIDs were aspirin (48%), ibuprofen (18%), naproxen (5%), and nabumetone (4%). Other NSAIDs (bismuth subsalicylate, diclofenac, etodolac, indomethacin, piroxicam, salsalate, sulindac, celecoxib, rofecoxib, and valdecoxib) were regularly used by less than 2% of the participants. Acetaminophen was regularly used by 19% of participants. There were no significant differences in sex, age at index date, or any measured SCC risk factors between regular and non-users of any NSAID. Regular NSAID users were more likely to take acetaminophen (p=0.005). There were no significant differences in reported type of NSAID regularly used between cases and controls except that seven cases reported regular celecoxib use compared to only one control.

Regular use of any NSAID was not associated with a reduction in SCC risk (fully adjusted OR=1.32, 95% CI: 0.92–1.89, Table 2). Although NSAID users whose exposure was of short duration (1–3 years) appeared to be at somewhat *increased* risk for SCC (adjusted OR=1.94, 95% CI: 1.10–3.44), we found no consistent effects of duration of use of any NSAID on SCC risk (p for linear trend 0.69). In comparing regular aspirin users to non-users, there was no negative association with SCC risk (adjusted OR=1.38, 95% CI: 0.96–1.97). Duration of aspirin use was also not associated with SCC risk (p for trend 0.52). High-dose aspirin users did not have a different SCC risk than low-dose users. Regular ibuprofen users had a non-significant slightly lower risk of SCC than never/occasional users (adjusted OR=0.74, 95% CI: 0.46–1.19). Although there were no consistent effects of dose or duration, all ORs suggested a protective association with ibuprofen exposure. Among non-aspirin NSAIDs, there was also no significant SCC risk reduction (adjusted OR 0.84,

95% CI: 0.56–1.26). For all four of our exposure variables, we found no evidence of a dose-response effect by duration of use. As expected, there was no association between regular use of acetaminophen (the control medication without COX activity) and SCC risk (OR=1.15; 95% CI: 0.74–1.81) nor any association between dose and duration of acetaminophen use.

We examined which of the co-variables served as potential confounding factors by virtue of being associated with both NSAID use and SCC risk at the p≤.20 level. Only two variables emerged as potential confounding variables: hair color and occupational sun exposure. We analyzed all multivariate models using only those two potential confounding variables (parsimonious multivariable model) and found no significant associations between NSAID use (categorized as any NSAID, aspirin, ibuprofen, non-aspirin NSAIDs) and SCC risk (data not shown). Of note, the slightly protective effect of ibuprofen use on SCC risk was not evident in the parsimonious multivariable model (adjusted OR: 1.03, 95% CI: 0.71–1.50).

Finally, we examined the association of pharmacy-dispensed NSAIDs and SCC risk. In total, 27% of cases and 26% of controls were prescribed an NSAID (not including aspirin, ibuprofen or naproxen) and had refilled the prescription for the NSAID at least once during the 10-year observation period. There was no association between any pharmacy dispensed NSAID use and SCC risk whether examining overall NSAIDs, or examining individual NSAID types (ever/never use). There was also no statistically significant effect of duration (Table 3).

DISCUSSION

Results from this case-control study do not support the hypothesis that NSAIDs are inversely associated with risk of cutaneous SCC. For self-reported NSAID exposure, there was no clear effect of dose, duration, or combined dose-duration variables for any of the four NSAID exposure categories on SCC risk. Short-term, low dose use of any NSAID as well as acetaminophen were both associated with an increased risk of SCC, suggesting that the effect is not class specific and possibly confounded by indication.[22] Furthermore, there was no association between pharmacy-dispensed NSAIDs and SCC risk during the same observation period (10 years prior to baseline).

Our results are largely consistent with three of the four published papers examining the association of NSAIDs with SCC risk.13¯16 Two large population-based cohort studies examined the association of NSAID exposure, both non-aspirin NSAIDs13 and low-dose aspirin14 and found no association with non-melanoma skin cancer (NMSC). They defined NMSC using diagnosis codes and were therefore unable to separately analyze basal cell carcinomas and SCCs, which may have different sensitivities to chemoprevention with NSAIDs. In a study of 132 SCCs arising among 1,093 participants of the Skin Cancer Prevention Study, a randomized trial of oralβ-carotene for the prevention of NMSC, NSAID use in the year prior to diagnosis was not associated with a statistically significant risk reduction of SCC (adjusted OR= 0.71, 95% CI 0.48–1.04).[15] The analysis did not differentiate between aspirin and non-aspirin NSAIDs, although the majority of NSAID users (87%) were aspirin users. The trial was limited to people with a history of skin cancer, which may limit generalizability of the findings. Our point estimates are consistent with a published abstract which reported regular NSAID use for more than 24 months to be associated with an increased risk of NMSC.18 The full study has not been published to date, prohibiting more detailed comparison of their findings and ours.

Our results differ from those of a case-control study that compared 86 subjects with SCC to 187 age- and sex-matched controls drawn from 1621 sun-exposed residents of Queensland,

Australia and ascertained NSAID use over the previous 10 years with face-to-face interviews.[16] They reported that NSAID use more than eight times a week for more than a year was associated with a significantly reduced SCC risk (adjusted OR= 0.07; 95% CI 0.01–0.71). Full-dose NSAID use 2 or more times per week for more than 5 years was also associated with a risk reduction for SCC (OR, 0.20; 95% CI, 0.04–0.96). Limitations of this study include its small sample size (n= 86 cases, 187 controls) and the fact that their exposure measurement strictly relied on recall and was also not validated against an external source, such as pharmacy records. The difference between our results and their results may be also be attributed to study populations (community-based cohort in Australia vs. U.S.), which may have different risk profiles, such as sun-exposure history. Also, the type of NSAID used by their participants differed from our sample: the most common non-aspirin NSAID reported in their sample was celecoxib (17%) whereas less than 1% of our participants reported celecoxib use. In their analysis, they did not distinguish among different types of NSAIDs, and it may be that different subsets of NSAIDs may have differential chemoprotective properties.

Strengths of this study include a large sample size (n=830) and thorough measurement of exposure including type, dose, and duration over the preceding 10-year period. Our exposure measurement included both self-reported NSAID use, which captures over-the-counter and prescription NSAIDs, as well as detailed information on pharmacy-dispensed NSAIDs, derived from KPNC's comprehensive electronic pharmacy database. Both datasets yielded consistent findings of no association of SCC risk with NSAID exposure. Our data on self-reported NSAID use adjusting for only those variables shown to be potential confounders (parsimonious model) as well as all ascertained SCC risk factors (fully adjusted model) showed similar findings.

There are several potential limitations to this study, including the possibility of recall bias, selection bias, and limitations of generalizability. The high response rates from both cases (81%) and controls (57%) combined with the fact that both groups largely conformed to established risk factors for SCC suggests minimal selection bias. Our control population came from respondents to the Member's Health Survey and not from the Kaiser Permanente membership at large and may be prone to selection bias. However, previously published papers have reported that respondents to the MHS are representative of the KPNC population.[23] Recall bias is also a potential problem for the self-reported variables. Although our questionnaire was modeled on a previous self-administered questionnaire on supplement use (including NSAIDs) and cancer risk24 which has shown high test-retest reliability and validity in capturing supplement intake over the past 10 years,21 the validity of using a self-administered questionnaire to retrospectively collect information on drug use may need further study. Differential misclassification would result if the cancer diagnosis served as a stimulus for cases to recall NSAID exposures more or less thoroughly than controls. However, the questionnaire collected data on a variety of exposures and NSAIDs are not recognized to be an important factor in the risk of skin cancer. The generalizability of our study may be limited because we only studied KPNC members, although previous studies have shown that the KPNC membership is highly representative of the surrounding region except for the tail ends of the income distribution.25,26

In this case-control study, we did not detect any consistent relationships between SCC risk and overall NSAID use, aspirin use, ibuprofen use, or non-aspirin NSAID use. Dose and duration of NSAID use did not appear to alter risk of SCC. Given the potential toxicity of NSAIDs, including platelet dysfunction and gastric ulcers, more uniformly efficacious chemopreventative agents with safer side effect profiles need to be explored.

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Table 1

Distribution of Risk Factors for Cutaneous Squamous Cell Carcinomas among Cases and Controls

Covariates	SCC n = 415	Controls n = 415	p value*
Hair color (% red/blond)	102 (24.6)	67 (16.2)	0.003
Eye color (% blue/grey)	191 (46.1)	165 (40.0)	0.073
Skin type⊕			
1	58 (14.0)	20 (4.8)	<0.001
2	76 (18.3)	40 (9.6)	
3	244 (58.8)	253 (61.0)	
4	36 (8.7)	90 (21.7)	
Missing	1 (0.2)	12 (2.9)	
Education (% 4-year college degree or above)	158 (38.1)	176 (42.5)	0.193
Cigarette smoking (% current)	29 (7.0)	16 (3.9)	0.046
Sunburns (% > 2 severe sunburns)	263 (63.5)	184 (44.7)	<0.001
Childhood freckles (% yes)	224 (54.5)	111 (27.2)	<0.001
Occupational sun exposure§ (% yes)	96 (23.2)	85 (20.6)	0.365
Routine sun exposure◇ (% yes)	312 (75.2)	284 (68.6)	0.035
Average # hrs/week outdoors 10am–4pm			
1–2	150 (36.2)	161 (38.8)	0.009
3–5	92 (22.2)	113 (27.2)	
6–10	82 (19.8)	71 (17.1)	
>10	91 (21.9)	70 (16.9)	
Tanning bed use (% yes)	49 (11.8)	36 (8.7)	0.137
History of actinic keratoses¶ (% yes)	333 (84.1)	80 (19.9)	<0.001
Family history of skin cancer^			
No	172 (41.6)	315 (75.9)	<0.001
Yes	136 (32.9)	59 (14.2)	
Don't Know▰	106 (25.6)	41 (9.9)	

*Pearson Chi-squared test for proportions

⊕Reaction of skin after exposure to 1 hour of mid-day sun for the first time in the summer with 1=painful or blistering sunburn with no tan, 2=painful sunburn followed by a light tan, 3= mild sunburn followed by a moderate tan, 4= no sunburn followed by a deep tan

§At least 2 hours/day of sun-exposure between 10am–4 pm for primary occupation

◇At least 2 hours/day once-a-week of sun-exposure between 10am–4 pm in the past 10 years

[¶] Treatment by a doctor for a precancerous skin lesion

[^] Including natural parents, brothers, and sisters only

[▰] More cases than controls reported not knowing their family history of skin cancer. Examination of the survey did not reveals any issues with survey design that would have caused subjects to skip the question differentially. The reasons for the discrepancy are unknown.

Table 2

Self-Reported NSAID use among Cases and Controls

NSAID use	SCC n = 415	Controls n = 415	Crude OR (95% CI)	Adjusted OR* (95% CI)
Any NSAID				
Any use				
Never/occasional	153 (37%)	172 (41%)	1.0 (referent)	1.0 (referent)
Regular▰	262 (63%)	243 (59%)	1.21(0.92, 1.60)	1.32 (0.92, 1.89)
Duration (yrs)◇				
<1	149 (36%)	172 (42%)	1.0 (referent)	1.0 (referent)
1–3	57 (14%)	39 (9%)	1.68 (1.06,2.67)	1.94 (1.10,3.44)
4–9	95 (23%)	99 (24%)	1.09 (0.76, 1.55)	1.20 (0.76, 1.89)
10+	114 (27%)	105 (25%)	1.25 (0.88,1.76)	1.30 (0.82,2.07)
P for Trend			0.70	0.69
Pill-years¶				
0	125 (30%)	151 (37%)	1.0 (referent)	1.0 (referent)
>0–2	49 (12%)	33 (8%)	1.82 (1.09,3.04)	2.40 (1.26, 4.57)
>2–5	49 (12%)	51 (12%)	1.13 (0.72,1.78)	1.60 (0.89, 2.89)
>5	192 (46%)	180 (43%)	1.29 (0.94, 1.76)	1.25 (0.83, 1.90)
P for Trend			0.63	0.71
Aspirin				
Any use				
Never/occasional	207 (50%)	226 (54%)	1.0 (referent)	1.0 (referent)
Regular▰	208 (50%)	189 (46%)	1.21 (0.92, 1.60)	1.38 (0.96, 1.97)
Dose▲				
Low dose (≤81 mg)	342 (82%)	339 (82%)	1.0 (referent)	1.0 (referent)
High dose(> 81 mg)	73 (18%)	76 (18%)	0.95 (0.66, 1.36)	0.86 (0.54, 1.38)
Duration (yrs)◇				
<1	207 (50%)	226 (55%)	1.0 (referent)	1.0 (referent)
1–3	50 (12%)	35 (8%)	1.56 (0.97,2.49)	1.53 (0.86,2.75)
4–9	74 (18%)	75 (18%)	1.08 (0.74,1.56)	1.41 (0.88,2.28)
10+	84 (20%)	79 (19%)	1.17 (0.81,1.69)	1.23 (0.75,2.02)
P for Trend			0.88	0.52
Pill-years¶				
0	207 (50%)	226 (54%)	1.0 (referent)	1.0 (referent)
>0 – 2	49 (12%)	33 (8%)	1.62 (1.00, 2.61)	1.79 (0.98, 3.26)
>2 – 5	52 (13%)	51 (12%)	1.12 (0.72, 1.72)	1.33 (0.75, 2.34)
>5	107 (26%)	105 (25%)	1.11 (0.79, 1.55)	1.24 (0.79, 1.92)
P for Trend			0.92	0.67

NSAID use	SCC n = 415	Controls n = 415	Crude OR (95% CI)	Adjusted OR* (95% CI)
Pill-years-dose¤				
0	226 (54%)	207 (50%)	1.0 (referent)	1.0 (referent)
>0 – 2.5	132 (32%)	152 (37%)	1.26 (0.93, 1.71)	1.60 (1.07,2.39)
>2.5 – 10	47 (11%)	45 (11%)	1.06 (0.66, 1.70)	1.00 (0.53,1.88)
>10	10 (2%)	11 (3%)	1.15 (0.49, 2.72)	0.75 (0.23,2.38)
P for Trend			0.85	0.46
Ibuprofen				
Any use				
Never/occasional	340 (82%)	343 (83%)	1.0 (referent)	1.0 (referent)
Regular◢	75 (18%)	72 (17%)	1.05 (0.73, 1.52)	0.74 (0.46, 1.19)
Dose▲				
Low dose (≤200 mg)	355 (86%)	364 (88%)	1.0 (referent)	1.0 (referent)
High dose(>200 mg)	60 (14%)	51 (12%)	1.21 (0.81, 1.83)	0.85 (0.50, 1.43)
Duration (yrs)◇				
<1	340 (82%)	343 (83%)	1.0 (referent)	1.0 (referent)
1–3	15 (4%)	19 (5%)	0.79 (0.39, 1.60)	0.74 (0.32, 1.71)
4–9	33 (8%)	32 (8%)	1.05 (0.61, 1.79)	0.63 (0.31, 1.24)
10+	27 (7%)	21 (5%)	1.28 (0.72, 2.27)	0.90 (0.43, 1.89)
P for Trend			0.30	0.70
Pill-years¶				
0	340 (82%)	343 (83%)	1.0 (referent)	1.0 (referent)
>0 – 2	12 (3%)	12 (3%)	1.01 (0.45, 2.26)	0.69 (0.26, 1.80)
>2 – 5	23 (6%)	23 (6%)	1.02 (0.57, 1.83)	0.85 (0.40, 1.80)
>5	40 (10%)	37 (9%)	1.09 (0.68, 1.75)	0.70 (0.38, 1.30)
P for Trend			0.76	0.44
Pill-years-dose¤				
0	340 (82%)	343 (83%)	1.0 (referent)	1.0 (referent)
>0 – 2.5	12 (3%)	15 (4%)	0.82 (0.38, 1.77)	0.66 (0.27, 1.64)
>2.5 – 10	24 (6%)	20 (5%)	1.19 (0.66, 2.17)	0.95 (0.45, 2.04)
>10	39 (9%)	37 (9%)	1.05 (0.65, 1.72)	0.64 (0.33, 1.23)
P for Trend			0.54	0.38
Non-aspirin NSAID				
Any use				
Never/occasional	307 (74%)	313 (75%)	1.0 (referent)	1.0 (referent)
Regular◢	108 (26%)	102 (25%)	1.08 (0.79, 1.48)	0.84 (0.56, 1.26)
Duration (yrs)◇				
<1	299 (72%)	313 (75%)	1.0 (referent)	1.0 (referent)
1–3	26 (6%)	21 (5%)	1.29 (0.72,2.31)	1.34 (0.65, 2.77)

NSAID use	SCC n = 415	Controls n = 415	Crude OR (95% CI)	Adjusted OR* (95% CI)
4–9	47 (11%)	47 (11%)	1.05 (0.68, 1.64)	0.68 (0.38, 1.12)
10+	43 (10%)	34 (8%)	1.31 (0.83,2.07)	1.05 (0.57, 1.91)
P for Trend			0.45	0.59
Pill-years¶				
0	322 (78%)	333 (80%)	1.0 (referent)	1.0 (referent)
>0 – 2	14 (3%)	14 (3%)	1.53 (0.84,2.76)	1.66 (0.81, 3.42)
>2 – 5	30 (7%)	25 (6%)	1.13 (0.66,1.91)	1.03 (0.52, 2.05)
>5	49 (12%)	43 (10%)	1.35 (0.97, 1.87)	1.02 (0.66, 1.57)
P for Trend			0.36	0.61
Acetaminophen				
Any use				
Never/occasional	329 (79%)	344 (83%)	1.0 (referent)	1.0 (referent)
Regular▰	86 (21%)	71 (17%)	1.25 (0.89, 1.77)	1.15 (0.74, 1.81)
Duration (yrs) ◇				
<1	329 (79%)	344 (83%)	1.0 (referent)	1.0 (referent)
1–3	23 (6%)	21 (5%)	1.13 (0.60,2.15)	1.14 (0.52,2.50)
4–9	30 (7%)	27 (7%)	1.15 (0.68, 1.96)	1.14 (0.57,2.30)
10+	33 (8%)	23 (6%)	1.45 (0.85,2.46)	1.18 (0.58,2.40)
P for Trend			0.22	0.68
Pill-years¶				
0	329 (79%)	344 (83%)	1.0 (referent)	1.0 (referent)
>0 – 2	22 (5%)	13(3%)	1.80 (0.86, 3.76)	2.74 (1.06, 7.10)
>2 – 5	20 (5%)	26 (6%)	0.78 (0.41, 1.46)	0.59 (0.26, 1.32)
>5	44 (11%)	32 (8%)	1.41 (0.88, 2.25)	1.18 (0.64, 2.19)
P for Trend			0.83	0.35

*Adjusted for eye color (blue/grey vs. other), natural hair color (red/blond vs. other), skin type (1–4 as described in Table 1), education (4-year college or above vs. not), history of sunburns (> 2 severe vs. ≤ 2 severe), history of high-risk exposures such as UV light, burn scar, non-healing ulcers, radiation treatment, arsenic exposure, exposure to industrial chemicals (yes/no), history of smoking (current vs. former/none), history of freckling (yes/no), outdoor sun exposure (> 2 hours per week between 10am and 4 pm), occupational sun exposure (yes/no), tanning bed use (yes/no), and family history of skin cancer (yes/no). Dummy variables were created for all missing values. 95% CI values are Wald estimates.

◇Years of use in past 10 years

▰At least once/week for at least one year

▲Average daily dose over the period of reported use

¶Number of pills per day x days per week x years of use. 1 pill-year is equivalent to 1 pill per day for one year.

▫Number of pills per day x days per week x years of use x strength per pill. 1 pill-years-dose is equivalent to 1 regular strength pill per day for 1 year

Table 3

Pharmacy-Dispensed NSAID Exposure among Cases and Controls[@]

NSAID use[¤]	SCC n = 415	Controls n = 415	Crude OR (95% CI)	Adjusted OR[*] (95% CI)
Any prescription NSAID				
Any use	112 (27%)	106 (25%)	1.08 (0.79, 1.48)	1.12 (0.76, 1.66)
Duration (yrs)[◇]			0.96 (0.81, 1.14)	1.04 (0.86, 1.25)
Nabumatone				
Any use	53 (13%)	58 (14%)	0.89 (0.59,1.36)	0.97 (0.58,1.63)
Duration (yrs)[◇]			1.03 (0.73, 1.45)	1.33 (0.90, 1.97)
Indomethacin				
Any use	29 (7%)	22 (5%)	1.33 (0.76,2.35)	1.26 (0.63,2.55)
Duration (yrs)[◇]			1.08 (0.49, 2.38)	1.72 (0.64, 4.62)
Sulindac				
Any use	16 (4%)	23 (6%)	0.68 (0.35,1.31)	0.54 (0.25,1.20)
Duration (yrs)[◇]			0.79 (0.57, 1.09)	0.72 (0.45, 1.15)
Etodolac				
Any use	14 (3%)	7 (2%)	2.00 (0.81, 4.96)	1.88 (0.55, 6.42)
Duration (yrs)[◇]			1.00 (0.25, 4.00)	2.65 (0.51, 13.72)
Salsalate				
Any use	13 (3%)	11 (3%)	1.18 (0.53, 2.64)	1.47 (0.51,4.18)
Duration (yrs)[◇]			1.11 (0.45, 2.75)	1.42 (0.51, 3.95)
Piroxicam				
Any use	8 (2%)	9 (2%)	0.89 (0.34,2.30)	1.15 (0.33,4.05)
Duration (yrs)[◇]			3.40 (0.53, 21.80)	3.20 (0.41, 24.72)
Celecoxib				
Any use	10 (2%)	8 (2%)	1.25 (0.49, 3.17)	1.85 (0.60, 5.73)
Duration (yrs)[◇]			1.41 (0.71, 2.79)	1.29 (0.63, 2.65)
Rofecoxib				
Any use	6 (1%)	3 (1%)	2.00 (0.50,8.00)	3.42 (0.73,16.05)
Duration (yrs)[◇]			1.52 (0.23, 10.01)	1.78 (0.20, 16.26)

[@] All exposures are based on having had at least one refill for a given medication.

[*] Adjusted for eye color (blue/grey vs. other), natural hair color (red/blond vs. other), skin type (1–4 as described in Table 1), education (4-year college or above vs. not), history of sunburns (> 2 severe vs. ≤ 2 severe), history of high-risk exposures such as UV light, burn scar, non-healing ulcers, radiation treatment, arsenic exposure, exposure to industrial chemicals (yes/no), history of smoking (current vs. former/none), history of freckling (yes/no), outdoor sun exposure (> 2 hours per week between 10am and 4 pm), occupational sun exposure (yes/no), tanning bed use (yes/no), and family history of skin cancer (yes/no). Dummy variables were created for all missing values. 95% CI values are Wald estimates.

[◇] Duration in years as a continuous variable.

[¤] Valdecoxib and diclofenac not reported due to too few numbers of participants using drug (≤1%) making models unstable.