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Use of non-steroidal anti-inflammatory drugs and risk of basal cell carcinoma in the United States Radiologic Technologists study

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with reduced risk of colorectal and other cancers, but the association with basal cell carcinoma (BCC) is unclear. Previous epidemiological studies have been small in size, conducted in especially vulnerable populations, or have not accounted for solar UV exposure, a major risk factor for BCC. In the United States Radiologic Technologists cohort, we followed subjects to assess NSAID use on risk of first incident BCC. We included Caucasian participants who responded to both second and third questionnaires (administered from 1994–1998 and 2003–2005, respectively) and who reported no cancer at the time of the second questionnaire, N=58,213. BCC, constituent risk factors (e.g., eye color, complexion, hair color) and sun exposure history were assessed through self-administered survey. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. Of the 58,213 people in the study population, 2,291 went on to develop BCC. Any NSAID use was not associated with subsequent incidence of BCC (HR = 1.04, 95% CI: 0.92–1.16) after adjusting for age, sex, and estimated lifetime summer sun exposure. No association was observed when stratified by NSAID type (aspirin and other NSAIDs), nor did dose-response patterns emerge by frequency of use (average days per month). Further analyses did not reveal interaction with sex, birth cohort, smoking, alcohol consumption, sun exposure, occupational radiation exposure, or personal risk factors for BCC. In this large nationwide study, we observed no association between NSAID use and subsequent BCC risk.

Keywords

non-steroidal anti-inflammatory drugs; basal cell carcinoma; ultraviolet radiation Article category: Epidemiology

Introduction

Nonmelanoma skin cancer (NMSC) is the most common malignancy in Caucasian populations, with more than 2 million new cases treated annually in the United States[1]. Basal cell carcinoma (BCC) represents about 80% of all NMSCs, with squamous cell carcinomas (SCCs) accounting for another 20%[2]. Despite extensive public health campaigns to reduce sun exposure, the main causative factor in the pathogenesis of BCC[3], incidence has been increasing in both the United States[4] and Europe[5].

Epidemiologic studies and randomized trials have shown protective effects of NSAIDs in human populations for several cancers including colorectal[6], prostate[7], and lung[8]. A number

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of experimental animal[9–13] and *in vitro*[14–15] studies have demonstrated the protective effects of non-steroidal anti-inflammatory drugs (NSAIDs) on NMSC. These effects are believed to stem from NSAIDs abilities to inhibit cyclooxegenase 2 (COX-2), an enzyme found to be over expressed in the epidermis following UV exposure.[16] A few epidemiological studies and randomized trials have also focused on the relationship between NSAID use and BCC. The results of these studies have been mixed, with some finding a reduced risk in certain vulnerable subgroups[10, 17–19] and others finding no statistically significant protective effect[20–21].

The purpose of this study is to examine the association between NSAID use and subsequent risk of first BCC. To our knowledge, the present study is the first to assess the incidence of BCC in a large study population with estimates of past solar UV exposure. This study uses data from the United States Radiologic Technologists (USRT) Study, a large nationwide occupational cohort, to determine whether the prospective occurrence of primary BCC differed by self-reported NSAID use after taking into account established risk factors for BCC such as UV exposure and personal characteristics.

Materials and Methods

Study Population

The USRT comprises a cohort of radiologic technologists living in the United States who were certified by the American Registry of Radiologic Technologists for at least 2 years between 1926 and 1982[22]. Details of the study have been previously described[22–23]. Three different self-administered questionnaires were mailed to participants in the following time periods: 1983–1989, 1994–1998, and 2003–2005. The first questionnaire provided baseline information on, among other factors, sex, age, smoking history, alcohol intake, as well as cancer diagnoses. The second questionnaire, which forms the baseline of our study, updated many of these cancer risk factors, provided self-reported medication use, including NSAID and acetaminophen use, and contained incident cancer diagnoses. The third survey included information related to past solar UV exposure such as time spent outdoors and constitutional factors (i.e., eye and hair color), in addition to cancer diagnosis. The USRT Study has been approved annually by the human subjects review boards at the University of Minnesota and the National Cancer Institute.

Our study population consists of Caucasian participants who reported no cancer at the time of the second questionnaire and responded to both the second and third questionnaires, N=58,213. Exit from follow-up occurred at the earlier of: first primary cancer diagnosis, including all types of NMSC, or at the last completed questionnaire (administrative censoring). Those with an unknown diagnosis date were excluded, including subjects who died between the second and third questionnaire since NMSC is rarely coded on death certificates.

Eligible cases included subjects with an incident first primary BCC. For the 2,255 participants reporting first primary diagnosis of BCC, medical records were obtained for 666 (29.5%). Of these, 638 (95.8%) were confirmed and 28 (4.2%) were denied. In addition, 61 BCCs were not self-reported but were found as a result of the validation effort (they were originally reported as cancers other than NMSC) and included in the study population. Based on the high confirmation rate of self-reported BCC from our validation study, self-reported BCCs that were not validated (n=1,592) were also included in this study. The final case group included a total of 2,291 subjects.

Data Collection

The following information was collected through the self-administered second survey questionnaire (entry into the study population): BMI, smoking history, alcohol use, and occupational work history. NSAID use and acetaminophen use were also collected during the second questionnaire, which was the only time questions on these medications were asked. To address potential exposure misclassification and confounding issues, we include analyses for acetaminophen use and BCC risk as a comparison. Acetaminophen has many of the same indications as NSAIDs in the general population, but its mechanism of action does not involve the hypothesized pathways that NSAID use are believed to affect (i.e., inhibition of COX-2). Medication use was assessed based on the question, "during the past year, on average, how many days each month did you take the following medications?" Potential medications included: aspirin (Anacin, Bufferin, etc.), other anti-inflammatory drugs (Ibuprofen, Motrin, etc.), and acetaminophen (Tylenol). Possible responses in each drug category were: none, <1, 1–4, 5–14, 15–21, or 22+ days per month.

Incident BCC was determined from the third questionnaire along with the following variables: highest education level achieved, eye color, hair color, skin pigmentation, history of severe sunburns, skin reaction to sun exposure, and lifetime solar UV exposure. UV exposures were determined by linking the residential locations reported by respondents for five age periods with the Total Ozone Mapping Spectrometer (TOMS) database (http://toms.gsfc.nasa.gov), which has been used previously in the USRT Study[24]. Lifetime solar UV exposure was estimated by multiplying average hours of summer sun exposure per week by TOMS summer erythemal UV estimates based on residence and weighting by years of life spent at that location.

Statistical analysis

Differences in characteristics between subjects with and without BCC and users and non-users of NSAIDs were tested using two-sample T-tests for continuous variables and Chi-squared tests for categorical variables. Presence of a dose- response trend in these characteristics was examined using the Cochran-Armitage test, which assumes a null hypothesis of no linear trend in binomial proportions of response (BCC vs. no BCC and NSAID users vs. NSAID non-users) for increasing levels of dose.

To analyze the relationship between NSAID use and incidence of BCC, we used Cox proportional hazards regression to compute hazard ratios (HRs) with 95% confidence intervals (CIs) using age at diagnosis of BCC as the response (i.e., age as the time-scale beginning at completion of the second questionnaire)[25]. This method adjusts for age in all models. Subjects were followed from the second questionnaire until the date of BCC diagnosis, completion of the third questionnaire, or the diagnosis of the first cancer (other than BCC), whichever occurred first. The exposure variables of interest were NSAID and acetaminophen use. In addition, all models included sex, since this variable is commonly controlled for in other analyses. We further considered the following variables as potential confounders and effect modifiers of the NSAID BCC relationship: birth cohort (five-year age groups), length of follow-up (0–5 years, > 5 years), education, BMI, smoking status (never, former, current), alcohol intake, acetaminophen use, and the following potential risk factors for skin cancer: skin pigmentation, hair color, eye color, lifetime solar UV exposure, skin reaction to sun exposure, history of severe sunburns, and lifetime occupational radiation exposure. The final adjusted regression models included NSAID or acetaminophen use, sex, and lifetime UV exposure since UV exposure had the greatest effect on the overall HR for any NSAID use and is considered a strong risk factor for BCC. After adjusting for sex and UV exposure, other BCC risk factors did not affect regression estimates. We also tested for

trends across categories of medication variables by assigning equally spaced scores to the categories and treating the variable as continuous in the analyses.

We conducted several sensitivity analyses. We performed an analysis stratified by length of follow-up. We also reran the main analyses in the final models including only the cases (n = 698) that were confirmed through validation. Finally we included a category for missing values for each of the covariates. These analyses did not materially change our findings (data not shown). Hazard models were tested for proportionality using a time interaction term and found to be consistent with the proportionality assumption. Tests were two-sided and P values were considered significant at the 0.05 alpha level. Analyses were conducted with SAS 9.2 software (SAS Institute, Cary, NC, USA).

Results

The study population of Caucasian, cancer-free members of the USRT was comprised primarily of women (80%) and the mean age at entry into the study (i.e. second survey questionnaire completion) was 47.5 (SD 8.3) years of age. Follow-up included 58,213 people with 509,465 person-years at risk. Almost 4% of our cohort (n=2,291) reported first incident BCC during follow-up. Occurrence of BCC was not associated with sex or education, but tended to increase with age, alcohol consumption, and lifetime UV exposure (Table 1). Personal characteristics such as skin, eye and hair color, reaction to sunlight, and history of blistering sunburn were also significantly associated with BCC. The proportion of subjects with BCC decreased significantly with increasing BMI (p for trend <0.001).

NSAID users were statistically significantly more likely to be female, report history of blistering sunburn, have a severe or painful reaction to 30 minutes of strong sunlight, and be in the highest quartile of solar UV exposure (Table 2). NSAID users had slightly greater BMIs than non-users and were on average over a year younger (47.2 vs. 48.6 years). However, NSAID users did not differ from those reporting no NSAID use with regard to person-years of follow-up or complexion.

We observed no significant association between any use of NSAIDs and risk of BCC (adjusted HR=1.04, 95% CI: 0.92–1.16, Table 3). No dose-response patterns emerged when analyses were conducted for aspirin or other NSAID use and adjustment did not significantly alter these results. Sensitivity analyses using only confirmed BCC did not change these conclusions. Further analyses did not reveal statistically significant modification of the NSAID-BCC relationship by sex, birth cohort, smoking, alcohol consumption, BMI, occupational radiation exposure, sun exposure, or constitutional characteristics (i.e., eye color, hair color). When this analysis was stratified by length of follow-up for cases, NSAID-BCC hazard ratios remained null after adjusting for age, sex, and solar UV exposure.

As a comparison, the hazard ratio of BCC related to acetaminophen use was also examined. Any acetaminophen use was significantly and positively associated with BCC (adjusted HR=1.14, 95%CI: 1.04–1.25, Table 3). However, when stratified by average days of acetaminophen use per month, only the lowest category, 0 to 4 days of use per month, was significant after adjustment for sex and UV exposure (HR=1.18, 95% CI: 1.07–1.30) and the dose-response relationship was not statistically significant.

Discussion

In this large cohort study, we did not observe a relationship between BCC and frequency of self-reported baseline NSAID use, for aspirin or other NSAIDs. We also observed no effect modification between BCC and NSAID use by sex, birth cohort, smoking, alcohol

consumption, BMI, occupational radiation exposure, sun exposure, or constitutional characteristics.

BCCs most frequently occur on areas of the body exposed to sunlight[26] and ultraviolet irradiation has been identified as the major risk factor for skin cancer development. A principal event in the development of BCC is the over-expression of enzyme COX-2, which leads to an overproduction of prostaglandins[11]. Both COX-2 expression and prostaglandin levels have been shown to increase during the inflammatory response following UV exposure[27]. The chemoprotective properties of NSAIDs are hypothesized to stem at least in part from their ability to inhibit COX-2[27–28]. Additional evidence indicates that NSAIDs inhibit the survival of existing cancer cells through cyclooxygenase independent mechanisms[29].

Although a few studies have reported a protective effect from NSAIDs[10, 17–19], these findings relate to especially high risk groups that may not reflect risk patterns in the general population. One prospective study on the recurrence of BCCs in genetically predisposed PTCH1+/− humans and mice found a slight protective effect of NSAID use in crude analyses[17]. In another study, investigators assessed the effects of the non-steroidal anti-inflammatory COX-2 inhibitor celecoxib on BCC burden in a 3-year, double-blinded, randomized clinical trial of 60 patients with basal cell nevus syndrome[10]. Among patients with less than 15 BCCs at study entry (n= 36), there was a 20% increase in BCC burden per year in the celecoxib arm compared to a 50% increase in the placebo arm (P for difference = 0.02). Another randomized clinical trial in subjects with at least 10 clinically apparent actinic lesions designed to assess retinol use and skin cancer risk found a significantly decreased risk of BCC among those who used NSAIDs for less than the study duration of 5 years (HR=0.33, 95% CI: 0.13–0.80)[18].

Recently, a randomized controlled trial of the NSAID celecoxib was conducted in high risk subjects with 10 to 40 actinic keratoses (premalignant precursor of nonmelanoma skin cancers) and Fitzpatrick sun-reactive skin types I, II, or III[19]. Investigators found no effect of celecoxib on the incidence of actinic keratoses, but did observe a statistically significant reduction in the number of both BCCs and SCCs, suggesting that celecoxib may prevent the progression of lesions already in the later stages of carcinogenesis. The authors propose that by inhibiting COX-2, celecoxib may promote apoptosis, inactivate myeloid suppressor cells, which promote angiogenesis, or suppress the epithelial–mesenchymal transition, a process characterized by loss of cell adhesion and increased mobility of cells into surrounding tissue.

Given the protective effects of NSAIDs found in experimental studies of high risk groups, our null findings may be partly due to dosing levels of NSAIDs that are too low or irregular to observe a potentially chemoprotective effect of NSAID use on BCC risk in the general population. Study respondents were questioned at one point in time about frequency of medication use and were not asked about specific dose. Use of NSAIDs for 22 days or more per month was reported by less than 10% of our cohort and frequency of NSAID use did not exhibit a dose-response relationship to BCC risk in this cohort. Thus, our study is limited by the time and consistency of exposure, the absence of dose information, and reliance on self-report. At least one study has found, however, that recall validity of prescription NSAID use is adequate, particularly among regular users[30]. In addition, we note that reliance on surveys limited our ability to control fully for long-term UV exposure, which is both difficult to estimate and highly related to BCC risk.

Our results were consistent with other studies measuring the effect of NSAID use on BCC risk in populations not selected for high susceptibility. Vogel and colleagues conducted a nested case–control study that included 322 BCC cases and a similar number of controls in a

prospective cohort of 57,053 individuals in Denmark[20]. They found that ever (vs. never) NSAID use was not associated with risk of BCC (IRR = 0.85, 95% CI: 0.66–1.10). In the Finnish Adult Twin Cohort Study, Milan and colleagues also did not find a significant relationship between NSAID use and BCC in monozygotic or dizygotic case-control pairs[21].

Although we found no association between NSAID use for aspirin or other NSAIDs, we did find an increased risk of BCC for any acetaminophen use (adjusted HR=1.14, 95%CI: 1.04–1.25). When stratified by average days of acetaminophen use per month, the dose-response was not statistically significant (p = 0.8). However, the latter finding suggests the possibility of confounding by indication[31]. For example, self-selection for use of over-the-counter pain relievers may be related to certain risk factors for BCC (e.g. pain from physical activity spent outside or frequent sunburns). In this case, the effect would not be drug class specific and persons with higher levels of risk factors for BCC who take NSAIDs would have an overestimated risk of BCC, masking any protective effect.

There are several strengths to our study. In addition to prospectively identified cases of BCC, a major advantage is the relatively large number of such cases. Self-reported history of NMSC can be unreliable.[32] However, in this population of medical workers, 95.8% of self-reported BCC for which medical records were obtained were confirmed as BCC. A previous study measured the degree of under-reporting of several cancers in the USRT using population-based cancer registry reports as the gold standard[33]. Although the study did not assess the under-reporting of BCCs (they are not typically reported to population-based cancer registries or on death certificates), it found relatively low rates of under-reporting of several other cancers compared to other study populations. In addition, we have information on many well-established risk factors for BCC, including constitutional characteristics and solar UV exposure that varied substantially by geographic region in this nationwide cohort. Also, since data on NSAID exposure was obtained prior to cancer diagnosis, there is no reason to expect differential misclassification by cancer diagnosis or temporal ambiguity, i.e., reverse causation.

In summary, in this large nationwide cohort study, NSAID use was not associated with incident BCC risk. Future observational studies should obtain ongoing reports of NSAID dose and duration, longer follow-up, and more refined long-term prospective, UV exposure measures.

Acknowledgments

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Abbreviations

NSAID	non-steroidal anti-inflammatory drugs
USRT	United States Radiologic Technologists
HR	hazard ratio
CI	confidence interval
COX	cyclooxegenase
UV	ultraviolet
BCC	basal cell carcinoma

NMSC	non-melanoma skin cancer
SCC	squamous cell carcinoma
BMI	body mass index
TOMS	Total Ozone Mapping Spectrometer

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Table 1

Demographic and personal characteristics among basal cell carcinoma cases and non-cases in the United States Radiologic Technologists study

	Without BCC, % (n=55,922)	With BCC, % (n= 2,291)	P-value[a]	P for trend[b]
Sex				
Male	19.9	21.2	0.132	
Female	80.1	78.8		
Age at entry, mean(SD)	47.4 (8.3)	49.6 (9.4)	<.0001	
Age category				
0 to 39	18.3	14.8	<.0001	<.0001
40 to 49	50.4	43.3		
50 to 59	22.5	26.5		
60+	8.8	15.3		
Follow-up (person-yrs), mean (SD)	8.9 (1.6)	5.5 (2.6)	<.0001	
Education				
Two-year rad tech program	44.7	43.8	0.0947	0.0947
College or grad school	39.5	41.8		
Missing	15.8	14.4		
Body Mass Index, (kg/m2)				
Underweight, <18.5	1.4	1.6	<.0001	<.0001
Normal, 18.5–24.9	50.4	56.3		
Overweight, 25–29.9	30.2	28.1		
Obese, ≥30	16.1	12.2		
Missing	1.9	1.9		
Smoking status				
Non-smokers	54.6	54.3	0.0326	0.3747
Former	32.0	33.9		
Current	12.7	11.1		
Unknown	0.7	0.7		
Alcohol				
< 1 drink per week	48.4	44.9	0.0007	0.0001
1–6 drinks per week	25.8	27.1		
7+ drinks per week	8.2	9.9		
Missing	17.65	18.07		
Eye color				
Blue/green/grey	43.7	50.9	<.0001	<.0001
Hazel	14.2	14.2		
Brown	26.2	20.5		
Missing/Other	15.8	14.4		
Natural hair color at age 20				
Red	2.6	4.3	<.0001	<.0001
Blonde	15.3	19.8		

	Without BCC, % (n=55,922)	With BCC, % (n= 2,291)	P-value[a]	P for trend[b]
Brown	78.0	72.0		
Black	3.5	3.1		
Missing/Other	0.7	0.8		
Complexion				
Fair	47.8	57.8	<.0001	<.0001
Medium	49.6	40.7		
Dark	2.0	0.8		
Unknown	0.6	0.7		
Ever blistering sunburn				
Yes	59.5	69.3	<.0001	
No	39.9	30.2		
Unknown	0.6	0.5		
Skin reaction to 30 minutes of strong sunlight				
Severe sunburn	34.0	45.4	<.0001	<.0001
Mild sunburn	52.8	45.9		
Tanned, no sunburn	11.4	7.0		
No change in skin color	1.3	1.1		
Unknown	0.6	0.7		
Average lifetime solar UV, quartile[c]				
Q1 (lowest)	23.6	21.7	0.0006	<.0001
Q2	23.6	22.2		
Q3	23.6	23.9		
Q4 (highest)	23.4	27.0		
Missing	5.8	5.2		
Any NSAID				
No	16.0	15.8	0.8471	
Yes	81.9	81.8		
Missing	2.13	2.44		
Aspirin, days per month				
No	50.3	49.3	0.2367	0.0497
0 to 4	29.1	28.7		
5 to 14	8.2	7.9		
15 to 21	2.6	2.9		
22+	6.7	7.8		
Missing	3.1	3.3		
Other NSAID, days per month				
No	32.3	34.1	0.1153	0.5679
0 to 4	34.5	33.1		
5 to 14	18.0	16.5		
15 to 21	5.0	5.0		
22+	7.8	8.4		

	Without BCC, % (n=55,922)	With BCC, % (n= 2,291)	P-value[a]	P for trend[b]
Missing	2.5	2.9		
Any acetaminophen				
No	34.0	34.0	0.9173	
Yes	63.6	63.4		
Missing	2.5	2.6		
Acetaminophen, days per month				
No	34.0	34.0	0.0125	0.5409
0 to 4	43.4	44.0		
5 to 14	14.2	12.3		
15 to 21	2.9	3.0		
22+	3.1	4.1		
Missing	2.5	2.6		

Abbreviations: BCC, basal cell carcinoma; SD, standard deviation; BMI, body mass index; cGy, centi-Gray

[a] Chi2 test for categorical variables and two sample t-test for continuous variables

[b] P for trend using Cochran-Armitage test

[c] Solar UV exposure quartile calculated from summer erythemal UV values weighted by time outdoors

Table 2

Demographic and personal characteristics among NSAID users and non-users in the United States Radiologic Technologists study[a]

	NSAID non-users (n= 9,285)	NSAID users (n= 47,679)	P-value[b]	P for trend[c]
Sex				
Male	22.3	19.5	<.0001	<.0001
Female	77.7	80.5		
Age at entry, mean(SD)	48.6 (9.1)	47.2 (8.1)	<.0001	
Age category				
0 to 39	17.5	18.5	<.0001	<.0001
40 to 49	45.1	51.4		
50 to 59	25.0	22.1		
60+	12.3	8.1		
Follow-up (person-yrs), mean (SD)	8.7 (1.8)	8.8 (1.8)	0.3849	
Education				
Two-year rad tech	45.3	44.5		
program			0.0014	
College or grad school	37.7	40.1		
Missing	17.1	15.3		
Smoking status				
Non-smokers	55.9	54.3	0.0012	0.0332
Former	30.4	32.4		
Current	12.7	12.7		
Unknown	1.0	0.6		
Alcohol				
< 1 drink per week	49.6	48.1	<.0001	<.0001
1–6 drinks per week	23.2	26.4		
7+ drinks per week	7.9	8.4		
Missing	19.4	17.1		
Body Mass Index, (kg/m2)				
Underweight, <18.5	2.0	1.3	<.0001	<.0001
Normal, 18.5–24.9	53.3	50.1		
Overweight, 25–29.9	29.2	30.3		
Obese, ≥30	13.4	16.5		
Missing	2.2	1.8		
Eye color				
Blue/green/grey	42.3	44.5	0.0354	0.012
Hazel	14.3	14.2		
Brown	26.4	25.9		
Missing/Other	17.0	15.4		
Natural hair color at age 20				
Red	2.5	2.7	0.0363	0.0199

	NSAID non-users (n= 9,285)	NSAID users (n= 47,679)	P-value[b]	P for trend[c]
Blonde	15.1	15.6		
Brown	77.8	77.8		
Black	3.8	3.3		
Missing/Other	0.7	0.7		
Complexion				
Fair	47.7	48.5	0.1032	0.0739
Medium	49.8	49.3		
Dark	2.2	1.9		
Unknown	0.3	0.3		
Ever blistering sunburn				
Yes	55.0	61.0	<.0001	
No	44.4	38.5		
Unknown	0.6	0.5		
Skin reaction to 30 minutes of strong sunlight				
Severe sunburn	33.7	34.6	<.0001	0.0004
Mild sunburn	51.9	52.8		
Tanned, no sunburn	11.9	11.0		
No change in skin color	1.7	1.2		
Unknown	0.9	0.5		
Average lifetime solar UV, quartile[d]				
Q1 (lowest)	24.6	23.3	0.0005	0.0013
Q2	23.2	23.7		
Q3	22.1	24.0		
Q4 (highest)	22.9	23.7		
Missing	7.1	5.4		

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; BMI, body mass index

[a] 1,249 people had missing values for NSAID use

[b] Chi2 test for categorical variables and two sample t-test for continuous variables

[c] P for trend using Cochran-Armitage test

[d] Solar UV exposure quartile calculated from summer erythemal UV values weighted by time outdoors

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Table 3

Hazard ratios of BCC and NSAID or acetaminophen use in the United States Radiologic Technologists study

	Number of cases	Unadjusted HR (95% CI)	P for trend	Adjusted[a] HR (95% CI)	P for trend
Any NSAID					
No	361				
Yes	1874	1.07 (0.96, 1.20)		1.04 (0.92, 1.16)	
Aspirin, days per month					
No	1130				
0 to 4	658	0.99 (0.90, 1.09)	0.33	1.01 (0.91, 1.11)	0.29
5 to 14	182	0.93 (0.79, 1.08)		0.90 (0.77, 1.06)	
15 to 21	66	0.99 (0.77, 1.27)		0.98 (0.76, 1.27)	
22+	179	0.93 (0.79, 1.10)		0.93 (0.79, 1.10)	
Other NSAID, days per month					
No	782				
0 to 4	758	1.08 (0.97, 1.20)	0.66	1.05 (0.94, 1.16)	0.98
5 to 14	377	1.04 (0.91, 1.17)		1.01 (0.89, 1.15)	
15 to 21	115	1.09 (0.90, 1.33)		1.07 (0.87, 1.31)	
22+	193	1.01 (0.87, 1.19)		0.99 (0.84, 1.16)	
Any acetaminophen					
No	779				
Yes	1452	1.15 (1.1, 1.26)		1.14 (1.04, 1.25)	
Acetaminophen, days per month					
No	779				
0 to 4	1009	1.18 (1.08, 1.30)	0.03	1.18 (1.07, 1.30)	0.08
5 to 14	281	1.01 (0.88, 1.16)		1.00 (0.87, 1.16)	
15 to 21	69	1.17 (0.91, 1.50)		1.19 (0.93, 1.52)	
22+	93	1.30 (1.05, 1.61)		1.22 (0.98, 1.53)	

[a] Adjusted for age, sex, solar UV exposure quartile calculated from summer erythemal UV values weighted by time outdoors

[b] P for trend from treating categorical medication variable as continuous in regression