

# Use of Nonsteroidal Anti-Inflammatory Drugs and Incidence of Melanoma in the United States Radiologic Technologists Study



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## ABSTRACT

Although NSAIDs have been associated with both reduced and increased cutaneous melanoma risk, few studies have examined these associations by ultraviolet radiation (UVR) or personal sun-sensitivity. We examined the associations between NSAID use and first primary invasive cutaneous melanoma among 58,227 non-Hispanic white participants in the United States Radiologic Technologists cohort study. Poisson regression was used to calculate rate ratios (RR) and 95% likelihood-based confidence intervals (CI), adjusting for attained age, birth cohort, and ambient UVR. No significant association of melanoma was observed for any use of NSAIDs (RR, 0.87; 95% CI, 0.71–1.09). The relative risks of melanoma for the highest categories of aspirin and other

NSAID use ( $\geq 5$  times per month vs. none) were 0.93 (95% CI, 0.74–1.16) and 1.02 (95% CI, 0.83–1.25), respectively. Further analyses did not reveal dose–response for trends in frequency of NSAID use or interactions with sex, UVR, eye and hair color, and skin complexion. In this large nationwide study, NSAID use was not associated with melanoma risk.

**Prevention Relevance:** NSAIDs have been associated with both reduced and increased melanoma risk. However, few studies have examined the role of UVR or personal sun-sensitivity on these associations. Our findings strengthen the evidence that NSAID use is not associated with melanoma risk, even in sun-sensitive subgroups.

## Introduction

Cutaneous melanoma is one of the most aggressive and lethal forms of skin cancer, with incidence rates increasing over the last several decades in the United States (1) and Europe (2). Potential contributory factors include aging populations, improved screening and earlier diagnosis, and exposure to ultraviolet radiation (UVR) (3). UVR may play roles in melanomagenesis by inducing DNA damage (4), and causing oxidative stress and inflammation (5). Mechanisms supporting a protective role for NSAIDs on melanoma risk include suppressing UVR-induced DNA damage and inflammation (6), blocking cyclooxygenase 2 (COX-2) (7), and inhibition of activation of nuclear factor-kappa light enhancer of activated B cells (8). This mechanistic research has prompted a number of epidemiologic studies on NSAIDs and melanoma risk.

Findings from large cohort studies evaluating specified levels of NSAIDs or acetaminophen use have been inconsistent with

some showing increased (9, 10) or reduced risks (11) for use of aspirin or other NSAIDs, whereas other studies have reported null findings for aspirin (12), non-aspirin NSAIDs (9, 13), or acetaminophen (9, 11), and risk of melanoma. Recent meta-analyses of epidemiologic studies examining any use versus no use of NSAIDs during the past year have reported little evidence of an association between NSAIDs and melanoma risk with overall pooled estimates just below the null value of 1.00 (14–16). These meta-analyses noted heterogeneity in previous studies which could not be explained by publication year, study design, study population, or other factors (sex or exposure assessment). Limitations of both meta-analysis and large cohort studies include a lack of information on ambient UVR or personal sun-sensitivity factors, with only one study (11) examining interactions between surrogates of sun exposure, NSAID use, and risk of melanoma.

The objective of this study is to address important gaps of studies to date in evaluating the association between NSAID use and first primary invasive cutaneous melanoma using data from the U.S. Radiologic Technologists (USRT). This study is the first cohort study to include subjects from nationwide residential locations. In addition, this investigation is one of the first to assess potential effect modification of the NSAID use and melanoma relationship among both women and men using quantitative measures of a wide range of ambient UVR and by personal sun-sensitivity factors including, eye and hair color, and skin complexion. The study also evaluated a broad and more comprehensive list of other known and suspected risk factors for melanoma than in previous publications.

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## Materials and methods

### Overview

The USRT is a nationwide cohort of 146,022 radiologic technologists who were certified by the American Registry of Radiological Technologists for 2+ years during 1926 to 1982. Detailed descriptions of the study design have been reported (17). In brief, self-administered questionnaires were mailed to cohort members. The second questionnaire (1994–1998) represents the baseline of this study because it collected information on NSAID use and important melanoma risk factors. All participants provided written informed consent. The study protocol has been approved by the institutional review boards of the NCI and the University of Minnesota, and was conducted in accordance with the ethical principles of the U.S. Common Rule.

### Study population and follow-up

The population for the current analysis included non-Hispanic whites who completed both the second and third questionnaires and did not report having a history of cancer (except keratinocyte carcinoma, KC) at baseline ( $N = 58,227$ ). We included only non-Hispanic whites due to a small number of participants in other race/ethnicity groups ( $N = 4,174$  participants;  $n$  cases = 3). In addition, we excluded participants without any residence-based ambient UVR information ( $N = 1,574$  participants;  $n$  cases = 17). Participants were followed until the earlier of first primary cancer diagnosis (except KC), including invasive cutaneous melanoma, or completion of their latest questionnaire (either the third or fourth).

### Case ascertainment

Our primary analysis evaluated self-reported invasive melanomas ( $N = 634$ ), which were ascertained from either the third or fourth questionnaires. We sought to validate a sample of the self-reported invasive melanomas using pathology reports, confirmatory medical records, or linkage with 43 population-based U.S. state/regional cancer registries (18). Either medical or registry records were successfully obtained and validated for 357 participants (56.3%) with self-reported melanoma. A previous study comparing cancer incidence in the USRT to the general population using cancer registry data from 1983 to 1998, aimed to confirm self-reported cancers by obtaining medical records from the diagnosing physician or hospital (19). They showed a high positive predictive value of pathology and medical records (86%) for melanoma (included both *in situ* and invasive cancers) that was calculated as follows:  $[147 \text{ self-reported cancers affirmed (same cancer that was reported)}/171 \text{ records obtained}] \times 100$ . In our study, the remaining 277 for whom confirmation could not be obtained were also included in the analysis because their inclusion did not substantially change the results.

### Exposure assessment

Use of NSAIDs and acetaminophen were ascertained from the second questionnaire (baseline), which also collected information on skin complexion, eye color, hair color at age

15, Gaelic/Celtic ancestry, previous KC diagnosis, family history of melanoma (first degree relative), smoking and drinking status, coffee consumption, body mass index, education, marital status, and cumulative absorbed occupational radiation dose to the skin of the head and neck (mGy). 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 (e.g., Anacin, Bufferin, Midol, Alka-Seltzer), other anti-inflammatory drugs (Ibuprofen, Motrin, Naprosyn, Advil), and acetaminophen (Tylenol). Possible responses in each drug category were none, <1, 1–4, 5–14, 15–21, or 22+ days per month. To enhance statistical power, we used four-group variables (none, <1, 1–4, or  $\geq 5$  days per month) for the main analysis, and three-group variables (none and <1, 1–4, or  $\geq 5$  days per month) in the analysis of effect modification. To address the potential for confounding by indication, we include analyses for acetaminophen use.

Ambient UVR was assigned by linking geocoded residential locations, based on self-reported residential history information collected from the third questionnaire to satellite based ambient UVR data from the NASA’s TOMS database (20). This database provides estimates of cloud-adjusted daily noontime ambient UVR of 305 nm, which is part of the UVB spectrum and is related to erythema response to the skin. Despite small fluctuations during 11-year solar cycles, variations of satellite-based annual estimates of UVR over the United States were relatively little since the start of measurements in the late 1970s. To generate stable estimates, daily noontime UVR values were averaged over 1982 to 1992 for each location. Then, weighted average daily lifetime ambient UVR values were generated (annual and July, separately) accounting for a subject’s number of years in each age period.

### Statistical analysis

To examine the association of NSAID use and first primary invasive cutaneous melanoma, we used Poisson regression to calculate rate ratios (RR) and 95% likelihood-based confidence intervals (CI). To perform these analyses, we created an event-time table of person-years and melanoma cases based on the following stratification factors: any and frequency of NSAID, aspirin/other NSAIDs, and acetaminophen use, attained age (<50, 50–<55, 55–<60, 60–<65, 65–<70, 70+), birth cohort (<1941, 1941–1945, 1946–1950, 1951–1955, 1956+), education, marital status, body mass index, physical activity, smoking and drinking status, skin complexion (medium/dark, fair, unknown/missing), eye color (hazel/brown/black, blue/green/grey, unknown/missing), hair color at age 15 (brown/black, blonde/red/auburn, unknown/missing), Gaelic/Celtic ancestry, ever KC diagnosis, family history of melanoma, prescription diuretic use, questionnaire response pattern, cumulative absorbed occupational radiation dose to the skin of the head and neck, and ambient UVR exposure quartile. Factors listed above were considered putative confounders because they may be associated with use of NSAIDs and acetaminophen and melanoma risk but are not considered on the causal

pathway. We included a *priori*, attained age, sex, birth year, and lifetime average annual ambient UVR because they are strong risk factors for melanoma or have been used in previous studies. We also considered including other potential confounders, but results were not meaningfully changed after their inclusion in the model. To investigate whether the associations between NSAIDs, acetaminophen use, and melanoma vary by sex, ambient UVR, and personal sun sensitivity factors, we calculated RR (95% CI) and conducted likelihood-ratio tests for multiplicative interaction between NSAIDs use and melanoma risk by sex, ambient UVR (by median; low: <28.2 vs. high: ≥28.2 J/m<sup>2</sup>), eye color (hazel/brown/black vs. blue/green/grey), natural hair color at age 15 (brown/black vs. blonde/red/auburn), and skin complexion (medium/dark vs. fair).

We conducted sensitivity analyses. To examine whether results differed between self-reported and medically confirmed cases, we restricted analyses to validated melanoma cases (*N* = 357). We examined associations restricted to attained age <60 years. We also used ambient UVR in July and analyzed different categorizations of medication use. All analyses were conducted using Epicure (Risk Sciences International Inc.).

**Data availability**

The data that support the findings of this study are available from the corresponding author upon request.

**Results**

The study population included 58,227 non-Hispanic white participants who did not report having cancer (except for KC) at baseline. Over a median follow-up time of 16.4 years, 1.09% of eligible participants had an incident primary melanoma (*n* = 634). Crude incidence rates of melanoma were higher in men, and participants with older attained age, blue/green/grey eye color, blonde/red/auburn natural hair color at age 15, fair skin complexion, and higher UVR quartiles (Table 1).

No significant association of melanoma was observed for any use of NSAIDs (RR, 0.87; 95% CI, 0.71–1.09; Table 2). The relative risks of melanoma for the highest categories of aspirin and other NSAID use (≥5 times per month vs. none) were 0.93 (95% CI, 0.74–1.16) and 1.02 (95% CI, 0.83–1.25), respectively. No dose–response patterns emerged when analyses were conducted for frequency of aspirin or other NSAID use. Use of acetaminophen was also not associated with melanoma risk.

The associations between NSAID use and melanoma were not modified by sex, average lifetime annual ambient UVR, eye color, natural hair color at age 15, or skin complexion (Supplementary Tables S1–S5). After stratifying by these factors, most associations for the main effects of NSAIDs, acetaminophen, and melanoma risk remained nonsignificant.

Sensitivity analyses using confirmed melanoma cases (Supplementary Table S6) and restricting to attained age <60 years, both did not reveal any statistically significant associations. Analyses which used the most detailed available categorization of medication frequency and considered none or none and less than 1 days per month as the reference group also did not reveal

**Table 1.** Distribution of baseline characteristics of 58,277 non-Hispanic white participants in the U.S. Radiologic Technologists Study.

Characteristic	Person-years <sup>a</sup>	No. with melanoma	Crude rate (per 10 <sup>5</sup> person-years)	95% CI
All	971,470	634	65.3	(60.3–70.5)
Sex				
Men	188,886	190	100.6	(87.0–116)
Women	782,583	444	56.7	(51.6–62.2)
Attained age, years				
<50	344,426	153	44.4	(37.8–51.8)
50–<55	201,238	126	62.6	(52.3–74.2)
55–<60	171,075	124	72.5	(60.5–86.0)
60–<65	116,226	98	84.3	(68.7–102)
65–<70	70,617	68	96.3	(75.2–121)
70+	67,888	65	95.7	(74.3–121)
Eye color				
Blue/green/grey	445,465	339	76.1	(68.3–84.5)
Hazel/brown/black	514,784	288	55.9	(49.7–62.7)
Unknown/missing	11,220	7	62.4	(26.8–121)
Natural hair color at age 15 <sup>b</sup>				
Blonde/red/auburn	207,309	205	98.9	(86.0–113)
Brown/black	754,146	426	56.5	(51.3–62.0)
Unknown/missing	10,014	3	30.0	(7.5–77.7)
Skin complexion				
Fair	479,802	393	81.9	(74.1–90.3)
Medium/dark	485,721	240	49.4	(43.4–55.9)
Unknown/missing	5,946	1	16.8	(1.0–74.0)
Average lifetime annual ambient UVR <sup>c</sup> , J/m <sup>2</sup>				
Quartile 1 (lowest)	245,947	141	57.3	(48.4–67.3)
Quartile 2	243,099	157	64.6	(55.0–75.2)
Quartile 3	242,968	153	63.0	(53.5–73.5)
Quartile 4 (highest)	239,455	183	76.4	(65.9–88.0)

Abbreviation: J/m<sup>2</sup>, joule per square meter.

<sup>a</sup>Median follow-up time = 16.4 years in all participants, and 8.2 years in 634 melanoma cases.

<sup>b</sup>Blonde/Red/Auburn included blonde and red or auburn; brown/black included light brown, dark brown/brunette and black.

<sup>c</sup>Quartile 1 < 24.8 J/m<sup>2</sup>, quartile 2 = 24.8–28.2 J/m<sup>2</sup>, quartile 3 = 28.2–36.8 J/m<sup>2</sup>, and quartile 4 > 36.8 J/m<sup>2</sup>.

significant associations between medication use and melanoma risk (Supplementary Table S7). Using ambient UVR exposure in July also did not reveal significant associations for NSAID use and melanoma. We also did not detect significant effect modification using confirmed melanoma cases.

**Discussion**

Our study assessed the relationship between NSAID use, acetaminophen use, and melanoma incidence in a large nationwide U.S. population. We included detailed information on a number of melanoma putative risk factors including lifetime ambient UVR exposure based on location of residence and personal sun sensitivity. We did not observe an association between frequency of self-reported baseline NSAID or

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**Table 2.** Use of nonsteroidal anti-inflammatory drugs, acetaminophen, and risk of melanoma among 58,227 non-Hispanic white participants in the U.S. Radiologic Technologists Study.

	Person-years	No. with cases <sup>a</sup>	RR <sup>b</sup>	95% CI
<b>NSAIDs</b>				
No	129,148	98	1 (ref.)	
Yes, any	799,011	510	0.87	(0.71-1.09)
<b>Aspirin, days per month</b>				
No	401,495	256	1 (ref.)	
<1	121,247	69	0.83	(0.63-1.07)
1-4	163,161	116	1.05	(0.84-1.30)
≥5	169,964	118	0.93	(0.74-1.16)
<b>Other NSAIDs (e.g., ibuprofen, naproxen), days per month</b>				
No	252,517	183	1 (ref.)	
<1	103,643	66	0.93	(0.70-1.23)
1-4	234,239	144	0.97	(0.78-1.21)
≥5	299,096	195	1.02	(0.83-1.25)
<b>Any acetaminophen</b>				
No	250,441	169	1 (ref.)	
Yes, any	619,109	389	1.03	(0.86-1.24)
<b>Acetaminophen, days per month</b>				
No	250,441	169	1 (ref.)	
<1	153,384	101	1.03	(0.80-1.32)
1-4	271,536	185	1.13	(0.92-1.40)
≥5	194,189	103	0.89	(0.69-1.13)

Note: For trend tests, categories of medication use frequency was coded ordinally with all *P* values >0.05.

<sup>a</sup>Numbers may be inconsistent because of missing values.

<sup>b</sup>Adjusted for attained age, sex, birth cohort (<1941, 1941-1945, 1946-1950, 1951-1955, 1956+), and quartile of lifetime average annual ambient UVR (ordinal).

acetaminophen use, and melanoma incidence. Although melanoma in the USRT was increased among men, those with highest ambient UVR and those with personal sun sensitivity, we observed little evidence of effect modification of the association of NSAIDs and acetaminophen with melanoma by these factors.

### Aspirin

Among NSAID types, aspirin specifically was associated with lower melanoma risks in three observational studies (11, 21, 22). However, our study did not find aspirin was associated with melanoma, which was consistent with other observational studies (13, 23), and one randomized controlled trial (24). Jeter and colleagues found an increased risk of melanoma among current and past aspirin users, but no dose-response effect in the Nurses' Health Study (9). Orrell and colleagues found chronic once-daily aspirin exposure was associated with an increased risk for melanoma (10). This study included patients with a minimum of 12 months of continuous once daily aspirin exposure based on prescription data. In contrast, our study ascertained exposure based on self-reported frequency of use that would be expected to reflect both prescription and over-the-counter use. Individuals using prescription once-daily aspirin possibly undergo more medical surveillance, which may lead to increased detection of melanoma.

### Other NSAIDs (e.g., ibuprofen, naproxen)

The lack of an association between other NSAIDs (e.g., ibuprofen, naproxen) use and melanoma risk in this study was consistent with two observational studies (9, 23). However, Johannesdottir and colleagues reported a reduced risk of melanoma for other nonselective NSAID use in a case-control study in Denmark (25). This study was conducted in locations with limited geographic variation, and did not have information on potential confounders including personal sun sensitivity and UVR exposure.

### Acetaminophen

Our null association between acetaminophen and melanoma was consistent with two cohort studies in U.S. non-Hispanic white women (9, 11), and in a case-control study among women (26). This null finding suggests that confounding by indication may not have played a significant role in this study because acetaminophen shares many of the same indications as NSAIDs in the general population, but acetaminophen does not inhibit COX-2, the suggested underlying mechanism.

### Strengths and limitations

Although information on exposure and outcome was based on self-report, this cohort of medical workers is likely to be more accurate in reporting their medication use and medical history than people in the general U.S. population. In addition, this study collected detailed information on a number of melanoma risk factors, including sun sensitivity factors and UVR that varied substantially by geographic region in this nationwide occupational cohort. However, personal sun exposure behaviors were not collected at baseline. Among the potential limitations, we did not find associations between NSAIDs and melanoma possibly because of low dosing levels for a potentially chemoprotective effect on melanoma risk in the general population. Previous observational studies that reported protective effects of NSAIDs had higher dose levels, longer duration of use, or daily use (12, 13, 24, 25). We did not have information on specific doses or classes of NSAIDs exposure in childhood and adolescence, which may be important exposure periods for melanoma. We also lacked information about the reason for NSAID use. Participants who take NSAIDs may be more likely to have a melanoma detected due to increased medical surveillance. However, effect estimates were not substantially changed after adjustment for skin cancer screening predictors such as older age, living with partner(s), light hair color, and fair skin tone.

### Conclusion

In this large geographically dispersed cohort, NSAID use was not associated with melanoma risk. Information on NSAID dose and duration, reasons for use, and a broad range of risk factors for melanoma could be collected in future prospective epidemiologic studies.

## Authors' Disclosures

No authors disclosure were reported.

## Authors' Contributions

**J.Z. Mai:** Conceptualization, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, methodology, writing—original draft, writing—review and editing. **C.M. Kitahara:** Resources, investigation, methodology, project administration, writing—review and editing. **M.R. Sargen:** Investigation, writing—review and editing. **M.P. Little:** Investigation, writing—review and editing. **B.H. Alexander:** Resources, investigation, methodology, project administration, writing—review and editing. **M.S. Linet:** Resources, validation, investigation, methodology, project administration, writing—review and editing. **M.A. Tucker:** Investigation, writing—review and editing. **E.K. Cahoon:** Conceptualization, resources, supervision, funding acquisition, validation, investigation, methodology, project administration, writing—review and editing.

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## Note

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