Cancer Causes Control (2012) 23:1451–1461
DOI 10.1007/s10552-012-0019-6

ORIGINAL PAPER

Non-steroidal anti-inflammatory drugs, acetaminophen, and risk of skin cancer in the Nurses' Health Study

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Received: 22 March 2012 / Accepted: 15 June 2012 / Published online: 5 July 2012

Abstract
Purpose Non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with lower risk of certain cancers, but data on the effect on skin cancer risk have been limited and contradictory. We prospectively examined whether use of NSAIDS or acetaminophen was associated with a lower risk of skin cancer in women.
Methods The 92,125 Caucasian women in the Nurses' Health Study provided information on aspirin use in 1980. Other NSAIDs and acetaminophen were added in 1990. Medication use, frequency, and quantity were reassessed on biennial questionnaires. Through 2008, we confirmed 658 melanoma cases, 1,337 squamous cell carcinoma (SCC) cases, and had 15,079 self-reports of basal cell carcinoma (BCC). We used COX proportional hazards models to compute relative risks (RR) adjusted for known skin cancer risk factors.
Results Neither aspirin nor non-aspirin NSAID use was associated with a lower risk of melanoma, SCC, or BCC, even for women with high quantity, frequency, or duration of use. Instead, we observed an increased risk of melanoma among current aspirin users (RR = 1.32, 95 % CI 1.03–1.70), though an increase of similar magnitude among past users and lack of a dose–response effect did not support a pharmacologic mechanism. We observed a mild reduction in SCC risk in current acetaminophen users (RR = 0.88, 95 % CI 0.75–1.02), with a linear decrease in risk with greater frequency of use ($p = 0.04$).
Conclusions Aspirin and other NSAIDs were not associated with a lower risk of melanoma, SCC, or BCC in women. Our large, prospective study does not support a chemoprotective effect of NSAIDs against skin cancers.

Keywords Skin cancer · Melanoma · Basal cell carcinoma · (Cutaneous) Squamous cell carcinoma · Aspirin · Acetaminophen · Non-steroidal anti-inflammatory medications (NSAIDs)

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Introduction

Skin cancer is a common malignancy. Non-melanoma skin cancers such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) occur so frequently that they are excluded from most cancer registries, whereas the incidence of melanoma in the United States has increased 15-fold in the last 70 years [1]. Cutaneous cancers cause considerable morbidity and, in the case of metastatic

melanoma, a high mortality burden. Although melanoma is curable in early stages, average survival for those with advanced disease is under 3 years, despite best efforts at therapy [2]. The major risk factor for skin cancers, sun exposure, has been targeted in prevention efforts. However, incidence continues to rise despite implementation of sun avoidance and protection programs in high-risk areas [3]. Additionally, melanoma can occur at locations that do not receive significant sun exposure. Due to the burden of these diseases and the limitations of behavioral interventions, chemoprevention has emerged as an area of investigation in melanoma and non-melanoma skin cancers.

Biologically, it is reasonable to suspect that non-steroidal anti-inflammatory drugs (NSAIDs) could affect the pathogenesis of skin cancers. Medications in this class have been shown to affect mechanisms of cellular damage at two points: they suppress the activity of MAPKs and can inhibit AP-1 directly as well [4]. Cyclooxygenase-2 (COX-2), a major target of NSAID therapy, is upregulated with activation of the MAPK pathway. In a study by Denkert et al., immunohistochemical staining showed that 93 % of melanomas expressed COX-2, and 68 % of melanomas had moderate to high expression [5]. Similarly, the COX-2 pathway has been implicated in non-melanoma skin cancers [6]. Topical diclofenac, an NSAID, is approved for use in the treatment of actinic keratoses, the precursor lesion for cutaneous SCC. In addition, polymorphisms of the COX-2 gene have been associated with increased risk of BCC [7].

Information regarding skin cancer risk and use of aspirin and other NSAIDs is limited and contradictory. Our prior analysis of data from a subset of the Genes, Environment, and Melanoma (GEM) study suggested that non-aspirin NSAIDs might be chemoprotective for melanoma [8]. Therefore, we conducted a prospective study to assess the hypothesis that NSAID use decreases the risk of developing skin cancer in women. We also assessed acetaminophen use as a control measure, since acetaminophen is used for a similar indication as NSAIDs and works through a different molecular mechanism.

Methods

Study population

The Nurses' Health Study (NHS) was established in 1976 when 121,700 female registered nurses in the US between the ages of 30 and 55 completed the initial questionnaire on their medical histories and health-related exposures. Follow-up questionnaires are sent every 2 years to collect updated exposure information (including medications), incident diagnoses of cancers, and other outcomes. A dietary assessment is included in alternate questionnaire cycles. Aspirin use was first assessed on the 1980 questionnaire, and non-aspirin NSAIDs and acetaminophen were added in 1990.

The study population was drawn from the 98,711 participants who provided information on aspirin use in 1980. Women were excluded if they reported a previous diagnosis of melanoma, SCC, BCC, or any other cancer ($n = 4{,}039$). Due to small numbers, non-Caucasians were also excluded ($n = 2{,}547$), leaving 92,125 women for analysis. Analyses of non-aspirin NSAIDs and acetaminophen included the 76,181 women from the study population who provided information on use of these medications in 1990. This investigation was approved by the Institutional Review Board of Brigham and Women's Hospital in Boston.

Identification of skin cancer cases

Participants reported diagnoses of melanoma, SCC, and BCC on the biennial questionnaires. Pathology records were reviewed for melanoma and SCC to confirm the diagnoses. Information from tumor registries was used when medical records could not be obtained. Within the study population, there were 1,778 reports of melanoma from 1980 to 2008, for which we were able to obtain 1,451 pathology records (82 %). Of these, 658 (45 %) were confirmed as invasive and included as cases in this study. Five hundred four (35 %) were found to be in situ melanomas and were excluded from this analysis. SCC was reported by 3,905 women, and we obtained pathology records for 2,701 (69 %). Of these, 1,337 (49.5 %) were confirmed as invasive and classified as a case. Eight hundred fifty-eight (32 %) were excluded as in situ disease. In situ cancers, mucosal cancers, and premalignant lesions were excluded from analysis, as these lesions may have a distinct pathophysiology from invasive cutaneous lesions. Medical records were not sought for BCC; all 15,079 self-reported diagnoses were included as cases. In a validation study, BCC was confirmed in 27 out of 28 medical records from self-reports in the NHS [9, 10].

Aspirin, other NSAIDs, and acetaminophen

At the initial 1980 assessment, participants were asked whether they used aspirin in most weeks, and if so, the exact number of years of use and the number of tablets consumed per week. On subsequent questionnaires, participants were asked whether they were a regular aspirin user over the past 2 years, and if so, the quantity was reported in pre-defined categories (1–2, 3–5, 6–14, $\geq$ 15 tablets per week). Frequency of use (1, 2–3, 4–5, 6–7 days per week) was added to the questionnaire in 1984.

Beginning in 2000, participants were also asked whether they took standard-dose (≥ 325 mg) or low-dose (≤ 100 mg) aspirin. The reported tablets per week of low-dose aspirin were converted into the equivalent quantity of standard-dose tablets for this analysis.

Frequency of use of non-aspirin NSAIDs and acetaminophen was first queried in 1990 and repeated on most questionnaires. Quantity of use for these medications was not assessed until 1998. Frequency and quantity were reported using the same pre-specified categories as those used for aspirin. Use of Cox-2 inhibitors was asked on the 2000–2006 questionnaires. These questionnaires have been used to assess aspirin and NSAID effects on a variety of oncologic and other medical outcomes [11–16] and are available for public viewing [17].

For the present study, we reclassified participants in each 2-year follow-up cycle by status, quantity and frequency of use for aspirin, non-aspirin NSAIDs, and acetaminophen. A participant was classified as a current user if she reported at least 1–2 tablets/week or 1 day/week of regular use for the last 2 years; a past user if she did not qualify as a current user but had been previously classified as such; or a never user if she had never been classified as a current user during cohort follow-up. When a participant failed to respond to a questionnaire, we used the medication information from the previous cycle. However, if the subsequent questionnaire was also missed, the aspirin, non-aspirin NSAID, and acetaminophen data remained missing until data were again provided by the participant. Duration of use was calculated for current and past users in each follow-up cycle as the total cumulative years of use. For aspirin, years of use before 1980 baseline was reported and included in the total. For non-aspirin NSAIDs and acetaminophen, participants were not asked to report use before the initial 1990 assessment; therefore, duration did not include earlier use.

Skin cancer risk factors

In 1982, participants were asked for their natural hair color (black, dark brown, light brown, blonde, red) and the number of lifetime severe or painful sunburns on their back/shoulders, lower limbs, face/arms, or all over (never, 1–2, 3–5, ≥ 6 burns at each location). The 1982 questionnaire also asked participants to report their skin reaction to 2 h in the sun on a sunny day after exposure on several previous occasions (none, some redness, burn, painful burn, or painful burn with blisters) and the kind of tan achieved after repeated sun exposures (none, light tan, average tan, deep tan) during childhood and adolescence. The number of moles ≥ 3 mm in diameter on the left arm (none, 1–2, 3–5, 6–9, 10–14, 15–20, ≥ 21 mol) was reported in 1986. Average annual ultraviolet (UV)-B flux [18, 19], a composite measure based on factors such as latitude, altitude, and cloud cover, was assigned in each follow-up cycle based upon current state of residence.

On every questionnaire, data were collected on menopausal status and use of postmenopausal hormones, body weight, and hours spent in recreational physical activity [20]. Height was reported in 1976. Family history of melanoma (parent or sibling) was reported on the 1982, 1992, 1996, and 2000 questionnaires. Diet was assessed every 4 years with a food frequency questionnaire [21, 22], and daily intakes of vitamin C from foods [23] and vitamin D from foods and supplements were calculated.

In 2006, participants were asked for the hours/week spent outdoors in direct sunlight in the middle of the day in summer months during high school and college and at ages 25–35, 36–59 and 60–65 years (<1, 2–5, 6–10, ≥11 h/week). Because lifetime sun exposure was assessed late in our follow-up period, we did not include it in our statistical models. However, in a cross-sectional analysis, none of these periods of sun exposure was associated with use of aspirin, non-aspirin NSAIDs, or acetaminophen and therefore would not be expected to confound an observed association between skin cancer and use of these medications.

Comorbid conditions that would affect use of aspirin, NSAIDs, and Tylenol were considered as additional covariates. However, preliminary analysis showed heart disease, stroke, ulcers, renal disease, and arthritis were not found to have a significant effect on melanoma risk in medication users; these variables were therefore not included in the multivariate models for melanoma or other tumor types (data not shown).

Statistical analyses

In analyses of aspirin use, each participant contributed person-time from the return date of the 1980 questionnaire and was censored at date of diagnosis, report of any cancer (except non-melanoma skin cancer in melanoma analyses), date of death, or the end of follow-up on June 1, 2008. The models for risk of melanoma were controlled for previous SCC and BCC, whereas in analyses of SCC and BCC, women were censored upon report of SCC, BCC, or melanoma diagnosis. Participants did not contribute person-time in follow-up cycles when they were missing information on aspirin use. A total of 92,125 women were followed through 2008, contributing approximately 2.0 million person-years (p-y) to melanoma analyses and 1.8 million p-y to the SCC and BCC analyses. In analyses of non-aspirin NSAID and acetaminophen use beginning in 1990, 76,181 women contributed 1.1 and 1.0 million p-y to the melanoma and SCC/BCC analyses, respectively.

The most current exposure and covariate data were used to allocate person-time to the appropriate category for each variable at the beginning of every cycle. For physical

activity, dietary intakes, and UV-B flux, we used a cumulative average of the current and all previous measures. We used Cox proportional hazards models to compute relative risks (RR) within categories of use of aspirin, non-aspirin NSAIDs, and acetaminophen. The models were conditioned on months of age and questionnaire cycle to account for age and time. Multivariable-adjusted RRs were calculated from models controlled simultaneously for all other potential skin cancer risk factors. In analyses with categorical variables of status, quantity, frequency, and duration of medication use, never users were the reference group in all models. To assess a dose–response effect, a p value for linear trend was determined by entering quantity, frequency, and duration of use into the model as a continuous value, excluding never users.

To determine whether the effect of aspirin, non-aspirin NSAIDs, or acetaminophen on skin cancer was different for women who were otherwise at low or high risk for disease, we reanalyzed the data stratified by a risk score. For melanoma, we used the risk score developed by Cho et al. [24], which was generated from a model based on age, hair color, number of severe sunburns over the lifetime, and number of moles on the left arm, and translated the score into a relative risk (RR) compared with women of the same age. We classified participants with an RR of <2 as low risk, an RR of 2–3.9 as medium risk, and an RR ≥ 4 as high risk. For SCC and BCC, we calculated a simple score based on the following six factors that were associated with increased risk in our models: tendency to burn after 2 h on a sunny day during childhood and adolescence; six or more severe burns over lifetime; six or more moles on left arm; blonde or red hair color; UV-B flux at residence $\geq$114 Robertson-Berger units; and activity $\geq$4 h/week. We classified participants with zero or one risk factor as low risk of SCC and BCC; two factors as medium risk; and three or more factors as high risk. For both the melanoma and SCC/BCC risk scores, the low, medium, and high categories were defined to ensure a sufficient number of cases in each stratum.

Results

The characteristics of medication users and non-users over the follow-up period are compared in Table 1. The median age of participants is greater for the non-aspirin NSAIDs and acetaminophen groups than for the aspirin group, as would be expected since the initial assessment was 10 years earlier for the aspirin analysis. Similarly, a larger proportion of subjects were postmenopausal in these groups than in the aspirin group. Despite this, an analysis stratifying participants by age did not alter the results overall, with the exception of revealing a significant interaction between age and duration of non-aspirin NSAID use. After adjusting for age, the characteristics of the subjects show little variation when classified by medication use status. One exception is body mass index (BMI), which was higher for current users of non-aspirin NSAIDs and acetaminophen than for never users. Of note, many medication users reported use of more than one type of analgesic concurrently (e.g., 46 % of current aspirin users reported current use of NSAIDs as well).

Aspirin use

Results of the analysis for aspirin are presented in Table 2. Risk of melanoma was significantly elevated for both past and current users compared with never users in the simple analysis adjusted for age and questionnaire cycle. Results were only mildly attenuated after adjustment for all risk factors (past use RR = 1.29, 95 % CI 0.98–1.71; current use RR = 1.32, 95 % CI 1.03–1.70). However, no dose response was observed for quantity ($p_{\text{trend}} = 0.61$), frequency ($p_{\text{trend}} = 0.21$), or duration ($p_{\text{trend}} = 0.44$) of aspirin use.

In the SCC analysis, current aspirin users did not have a reduced risk compared with never users (RR = 0.99, 95 % CI 0.83–1.19). Increasing quantity of tablets per week showed a marginally significant trend for mildly decreased risk of SCC ($p_{\text{trend}} = 0.05$), with a 2 % decrease in risk for each additional tablet/week. However, the results for frequency and duration of use did not support a dose–response relationship for this medication.

For the association between BCC and aspirin use, all risk ratios were close to unity. A significant decrease in risk of 2 % for every 10 years of aspirin use was shown ($p_{\text{trend}} = 0.02$).

Non-aspirin NSAID use

Results of analysis for this medication are reported in Table 3. Current use of non-aspirin NSAIDs was not associated with risk of melanoma (RR = 0.96, 95 % CI 0.76–1.20), SCC (RR = 0.94, 95 % CI 0.81–1.09), or BCC (RR = 1.01, 95 % CI 0.96–1.06) in the multivariable analyses. There was a suggestion of decreased risk with increasing quantity for melanoma (RR = 0.75, 95 % CI 0.49–1.15 for $\geq$ 6 vs. 1–2 tablets/week, $p_{\text{trend}} = 0.07$) and for SCC (RR = 0.72, 95 % CI 0.46–1.14 for $\geq$ 15 vs. 1–2 tablets/week, $p_{\text{trend}} = 0.12$); however, a dose–response effect was not shown for frequency or duration of use. In an analysis stratified for age, longer duration of use was beneficial for women over the age of 65, but not for younger women ($p_{\text{trend}} = 0.04$).

In a separate analysis of COX-2-specific inhibitors with a shorter follow-up period beginning in 2000, there was no

Table 1 Age and age-standardized characteristics of the study population of women by reported aspirin use (1980–2008) and by reported non-aspirin NSAID and acetaminophen use (1990–2008), Nurses' Health Study

	Aspirin			Non-aspirin NSAID			Acetaminophen		
	Never	Past	Current	Never	Past	Current	Never	Past	Current
	Mean								
Age, years	53.2	61.6	58.6	63.6	66.0	62.4	63.4	64.9	63.2
BMI, kg/m^2	25.3	26.3	25.9	25.6	26.9	27.2	26.0	26.7	26.9
Height, in	64.4	64.6	64.5	64.4	64.6	64.6	64.5	64.5	64.5
Vitamin C intake from foods, mg/day	139	136	138	148	146	146	148	146	145
Vitamin D intake from foods and supplements, μg/day	5.0	4.6	5.3	5.4	5.6	5.6	5.6	5.6	5.5
	Percent								
Painful burn after 2 h in sun[a]	13	14	14	12	14	14	13	13	14
Deep tan after repeated sun exposure[a]	21	22	22	21	22	21	21	21	21
Severe sunburns over lifetime ≥ 6	50	55	53	48	54	54	50	53	53
Blonde or red hair color	14	14	15	14	14	15	14	14	14
Family history of melanoma	7	8	7	7	8	8	7	8	8
Moles on left arm ≥ 6	3	4	4	3	4	4	4	4	4
Recreational activity ≥ 4 h/week	26	23	26	27	24	24	28	24	22
UV-B flux ≥ 114 R-B units[b]	31	28	29	31	32	33	33	31	31
Smoking, current	20	15	17	13	10	10	13	10	10
Postmenopausal	72	72	72	83	78	78	82	78	80
HRT, current use[c]	26	28	29	25	30	28	25	29	28
Aspirin, current use	na	na	na	52	52	46	55	49	44
Non-aspirin NSAID, current use	24	41	31	na	na	na	29	33	41
Acetaminophen, current use	30	38	28	27	30	38	na	na	na

[a] Skin reaction to sun during childhood and adolescence

[b] UV-B flux at state of residence, measured in Robertson-Berger units (count × 10^{-4})

[c] Use of hormone replacement therapy among postmenopausal women

association between current use and any of the skin cancer outcomes (RR [95 % CI] = 1.17 [0.79–1.74], 1.19 [0.92–1.61], and 1.05 [0.96–1.15] for melanoma, SCC, and BCC, respectively).

Acetaminophen use

Table 4 details the findings for acetaminophen. Risks of melanoma and BCC were unaffected by current use of acetaminophen (RR = 0.90 and 1.05, respectively). SCC rates were modestly decreased in current acetaminophen users (multivariable RR = 0.88 [95 % CI 0.75–1.02]), and this was supported by evidence of lower risk with more frequent and longer duration of use. Women who reported using acetaminophen 6–7 days/week had a 22 % reduction in risk (RR = 0.78, 95 % CI 0.59–1.02) with a significant linear trend in decreasing risk with increasing frequency ($p = 0.04$). Duration of use for 15 or more years was associated with a 37 % lower risk (RR = 0.63, 95 % CI 0.38–1.04), though no dose–response effect was apparent ($p_{trend} = 0.14$).

Stratified analyses

We examined associations between aspirin, non-aspirin NSAIDs, and acetaminophen and risk of melanoma, SCC, and BCC within strata of women who were at low, medium, and high risk for disease, but found no evidence that associations differed within these strata. Of note, we continued to observe an elevated risk of melanoma among current aspirin users in both low risk (RR = 1.35, 95 % CI 0.91–1.98) and high risk (RR = 1.20, 95 % CI 0.77–1.87) women, and a lower risk of SCC for women using acetaminophen 6–7 days/week in both the low risk (RR = 0.74, 95 % CI 0.49–1.11) and high risk (RR = 0.79, 95 % CI 0.47–1.33) categories.

Discussion

In this investigation, we did not find evidence to support our hypothesis that aspirin or non-aspirin NSAIDs can decrease the risk of melanoma or non-melanoma skin

Table 2 Risk of melanoma, cutaneous squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) by reported aspirin use in women in the Nurses' Health Study, 1980–2008

Aspirin use	Melanoma			SCC			BCC		
	Cases (P-Y)	Simple[a] RR (95 % CI)	Multivariable[b] RR (95 % CI)	Cases (P-Y)	Simple[a] RR (95 % CI)	Multivariable[b] RR (95 % CI)	Cases (P-Y)	Simple[a] RR (95 % CI)	Multivariable[b] RR (95 % CI)
Never[c]	83 (386)	1.00	1.00	143 (369)	1.00	1.00	2365 (369)	1.00	1.00
Past	199 (540)	1.36 (1.03–1.80)	1.29 (0.98–1.71)	459 (478)	1.00 (0.82–1.21)	0.98 (0.80–1.19)	4434 (478)	1.01 (0.96–1.07)	0.99 (0.94–1.04)
Current	376 (1084)	1.39 (1.08–1.78)	1.32 (1.03–1.70)	735 (991)	1.02 (0.85–1.22)	0.99 (0.83–1.19)	8280 (991)	1.01 (0.96–1.05)	0.98 (0.93–1.03)
Tablets/week									
1–2	193 (501)	1.53 (1.16–2.01)	1.45 (1.10–1.90)	386 (454)	1.11 (0.91–1.35)	1.08 (0.88–1.31)	3867 (454)	1.02 (0.96–1.07)	0.99 (0.94–1.04)
3–5	56 (204)	1.18 (0.83–1.66)	1.13 (0.79–1.59)	120 (189)	1.06 (0.83–1.36)	1.02 (0.80–1.30)	1499 (189)	1.00 (0.94–1.07)	0.97 (0.90–1.03)
6–14	86 (253)	1.31 (0.96–1.79)	1.25 (0.91–1.72)	164 (230)	0.88 (0.70–1.10)	0.86 (0.69–1.09)	1973 (230)	0.98 (0.92–1.04)	0.96 (0.90–1.02)
≥15	24 (66)	1.64 (1.03–2.59)	1.52 (0.96–2.40)	26 (62)	0.90 (0.59–1.37)	0.91 (0.59–1.38)	491 (62)	1.03 (0.94–1.14)	1.00 (0.91–1.10)
p for trend[d]		0.57	0.61		0.04	0.05		0.47	0.51
Days/week[e]									
1	95 (312)	1.32 (0.94–1.86)	1.29 (0.91–1.81)	142 (294)	1.04 (0.81–1.33)	1.01 (0.79–1.30)	2151 (294)	0.97 (0.91–1.04)	0.95 (0.89–1.02)
2–3	60 (147)	1.60 (1.10–2.31)	1.52 (1.05–2.20)	100 (134)	1.11 (0.85–1.44)	1.06 (0.81–1.38)	1116 (134)	1.00 (0.92–1.08)	0.96 (0.89–1.04)
4–5	30 (84)	1.24 (0.79–1.95)	1.14 (0.72–1.79)	68 (75)	1.05 (0.78–1.41)	1.00 (0.74–1.35)	657 (75)	0.95 (0.86–1.04)	0.90 (0.82–0.99)
6–7	140 (362)	1.15 (0.83–1.60)	1.08 (0.78–1.50)	395 (309)	1.03 (0.83–1.27)	1.01 (0.82–1.25)	3323 (309)	0.99 (0.93–1.06)	0.96 (0.90–1.02)
p for trend[d]		0.26	0.21		0.90	0.97		0.72	0.88
Years of use[f]									
<5	85 (269)	1.41 (1.03–1.92)	1.36 (0.99–1.86)	143 (253)	1.09 (0.86–1.37)	1.07 (0.84–1.35)	2027 (253)	1.03 (0.97–1.10)	1.02 (0.96–1.08)
5–9	96 (271)	1.42 (1.04–1.94)	1.36 (1.00–1.86)	204 (245)	1.09 (0.87–1.35)	1.07 (0.86–1.33)	2154 (245)	1.03 (0.96–1.09)	1.00 (0.94–1.07)
10–14	63 (175)	1.26 (0.90–1.78)	1.20 (0.85–1.69)	137 (155)	0.94 (0.74–1.20)	0.91 (0.71–1.16)	1399 (155)	0.99 (0.92–1.06)	0.96 (0.90–1.03)
15–19	34 (118)	0.96 (0.64–1.46)	0.90 (0.59–1.36)	108 (102)	0.95 (0.74–1.23)	0.91 (0.71–1.18)	1015 (102)	1.03 (0.95–1.11)	0.99 (0.92–1.07)
20–24	39 (105)	1.46 (0.98–2.15)	1.35 (0.91–2.00)	89 (95)	1.22 (0.93–1.60)	1.17 (0.89–1.54)	765 (95)	1.03 (0.94–1.12)	0.98 (0.90–1.07)
25–29	42 (81)	2.14 (1.46–3.14)	1.96 (1.33–2.89)	50 (74)	1.00 (0.72–1.39)	0.97 (0.70–1.34)	567 (74)	0.99 (0.91–1.09)	0.95 (0.87–1.05)
≥30	102 (266)	1.42 (1.05–1.93)	1.31 (0.97–1.79)	236 (237)	1.06 (0.86–1.32)	1.01 (0.82–1.25)	2162 (237)	0.98 (0.92–1.04)	0.93 (0.88–0.99)
p for trend[d]		0.22	0.44		0.60	0.89		0.18	0.02

RR relative risk, *CI* confidence interval, *P-Y* person years (in thousands)

[a] Simple models are adjusted for age and questionnaire cycle

[b] Multivariable models are conditioned on age, questionnaire cycle, reaction of skin to sun exposure, ability to tan, number of severe sunburns, number of moles on left arm, family history of melanoma, UV-B availability at state of residence, menopausal status and use of postmenopausal hormones, height, BMI, physical activity, smoking status, intake of vitamin C from foods, and intake of vitamin D from foods and supplements. Melanoma models were also adjusted for prevalent SCC and BCC

[c] Never report of aspirin use is the reference group for all other categories in the table

[d] Linear trend over quantity and frequency among current aspirin users and over duration among past and current users

[e] Follow-up did not begin until 1984 with the initial reported frequency of aspirin use

[f] Years of use is assessed among past and current aspirin users

Table 3 Risk of melanoma, cutaneous squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) by reported use of non-aspirin NSAIDs in women in the Nurses' Health Study, 1990–2008

Non-aspirin NSAID use	Melanoma			SCC			BCC		
	Cases (P-Y)	Simple[a] RR (95 % CI)	Multivariable[b] RR (95 % CI)	Cases (P-Y)	Simple[a] RR (95 % CI)	Multivariable[b] RR (95 % CI)	Cases (P-Y)	Simple[a] RR (95 % CI)	Multivariable[b] RR (95 % CI)
Never[c]	174 (477)	1.00	1.00	438 (418)	1.00	1.00	3886 (418)	1.00	1.00
Past	119 (276)	0.96 (0.75–1.23)	0.91 (0.71–1.17)	336 (232)	1.03 (0.88–1.19)	1.02 (0.88–1.19)	2557 (232)	1.08 (1.02–1.14)	1.04 (0.99–1.10)
Current	158 (390)	1.04 (0.83–1.29)	0.96 (0.76–1.20)	349 (340)	0.95 (0.82–1.10)	0.94 (0.81–1.09)	3190 (340)	1.06 (1.01–1.11)	1.01 (0.96–1.06)
Tablets/week[d]									
1–2	39[g] (73)	1.08 (0.74–1.58)	1.01 (0.68–1.49)	54 (32)	1.06 (0.79–1.43)	1.01 (0.75–1.37)	359 (32)	1.03 (0.92–1.16)	0.97 (0.86–1.09)
3–5				53 (28)	1.16 (0.86–1.56)	1.12 (0.83–1.52)	313 (28)	1.01 (0.89–1.14)	0.95 (0.84–1.07)
6–14	30[g] (73)	0.81 (0.53–1.23)	0.75 (0.49–1.15)	60 (43)	0.88 (0.66–1.17)	0.87 (0.65–1.17)	461 (43)	1.01 (0.91–1.12)	0.95 (0.85–1.05)
≥15				21 (19)	0.74 (0.47–1.15)	0.72 (0.46–1.14)	199 (19)	1.00 (0.86–1.16)	0.95 (0.82–1.10)
p for trend[e]		0.12	0.07		0.08	0.12		0.57	0.97
Days/week									
1	39 (109)	1.04 (0.73–1.49)	0.97 (0.67–1.38)	82 (97)	1.03 (0.81–1.30)	0.97 (0.76–1.23)	862 (97)	1.15 (1.06–1.23)	1.09 (1.01–1.17)
2–3	35 (86)	1.02 (0.70–1.47)	0.93 (0.64–1.36)	82 (75)	0.99 (0.77–1.25)	0.97 (0.76–1.24)	668 (75)	1.01 (0.93–1.10)	0.96 (0.88–1.05)
4–5	15 (35)	1.08 (0.63–1.83)	0.99 (0.58–1.70)	38 (31)	1.06 (0.76–1.49)	1.05 (0.75–1.47)	277 (31)	1.00 (0.83–1.13)	0.95 (0.84–1.07)
6–7	38 (98)	0.99 (0.69–1.40)	0.88 (0.61–1.27)	81 (85)	0.87 (0.68–1.10)	0.87 (0.68–1.11)	813 (85)	1.03 (0.95–1.11)	0.98 (0.91–1.06)
p for trend[e]		0.74	0.52		0.34	0.51		0.06	0.17
Years of use[f]									
<5	134 (341)	1.06 (0.84–1.33)	1.00 (0.79–1.26)	286 (299)	0.94 (0.81–1.09)	0.93 (0.80–1.08)	2773 (299)	1.05 (1.00–1.10)	1.02 (0.96–1.07)
5–9	93 (226)	0.93 (0.72–1.21)	0.86 (0.66–1.13)	238 (192)	0.98 (0.83–1.15)	0.98 (0.82–1.15)	2022 (192)	1.09 (1.03–1.16)	1.04 (0.93–1.11)
10–14	50[7] (98)	0.99 (0.71–1.40)	0.90 (0.64–1.28)	132 (68)	1.15 (0.93–1.41)	1.14 (0.92–1.42)	794 (68)	1.08 (0.99–1.17)	1.02 (0.95–1.12)
≥15				29 (13)	1.14 (0.76–1.69)	1.11 (0.74–1.66)	158 (13)	1.10 (0.93–1.30)	1.03 (0.87–1.22)
p for trend[e]		0.70	0.42		0.22	0.25		0.19	0.47

RR relative risk, *CI* confidence interval, *P-Y* person years (in thousands)

[a] Simple models are adjusted for age and questionnaire cycle

[b] Multivariable models are adjusted for age, questionnaire cycle, aspirin use, acetaminophen use, reaction of skin to sun exposure, ability to tan, number of severe sunburns, number of moles on left arm, family history of melanoma, UV availability at state of residence, menopausal status and use of postmenopausal hormones, height, BMI, physical activity, intake of vitamin C from foods, and intake of vitamin D from foods and supplements. Melanoma models were also adjusted for prevalent SCC and BCC

[c] Never report of non-aspirin NSAID use is the reference group for all other categories in the table

[d] Follow-up did not begin until 1998 with the initial reported quantity of use of non-aspirin NSAIDs

[e] Linear trend over quantity and frequency among current users of non-aspirin NSAIDs and over duration among past and current users

[f] Years of use is assessed among past and current users of non-aspirin NSAIDs

[g] Categories were combined when case counts were ten or fewer

Table 4 Risk of melanoma, cutaneous squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) by reported acetaminophen use in women in the Nurses' Health Study, 1990–2008

Acetaminophen use	Melanoma			SCC			BCC		
	Cases (P-Y)	Simple[a] RR (95 % CI)	Multivariable[b] RR (95 % CI)	Cases (P-Y)	Simple[a] RR (95 % CI)	Multivariable[b] RR (95 % CI)	Cases (P-Y)	Simple[a] RR (95 % CI)	Multivariable[b] RR (95 % CI)
Never[c]	176 (453)	1.00	1.00	428 (396)	1.00	1.00	3733 (396)	1.00	1.00
Past	142 (323)	0.96 (0.76–1.21)	0.97 (0.77–1.23)	385 (275)	1.05 (0.91–1.21)	1.07 (0.92–1.23)	2811 (275)	1.02 (0.97–1.07)	1.02 (0.96–1.07)
Current	133 (366)	0.91 (0.72–1.14)	0.90 (0.71–1.13)	310 (318)	0.86 (0.74–1.00)	0.88 (0.75–1.02)	3088 (318)	1.05 (1.00–1.11)	1.05 (1.00–1.10)
Tablets/week[d]									
1–2	22 (46)	0.84 (0.53–1.33)	0.81 (0.51–1.30)	63 (38)	0.95 (0.72–1.25)	0.94 (0.71–1.25)	469 (38)	1.07 (0.96–1.18)	1.07 (0.96–1.19)
3–5	17 (35)	0.87 (0.52–1.45)	0.85 (0.51–1.44)	58 (28)	1.10 (0.83–1.47)	1.11 (0.83–1.49)	338 (28)	1.00 (0.89–1.12)	0.99 (0.88–1.12)
6–14	31[g] (69)	0.81 (0.54–1.22)	0.79 (0.52–1.20)	51 (41)	0.66 (0.49–0.89)	0.68 (0.50–0.92)	560 (41)	1.14 (1.04–1.25)	1.13 (1.02–1.25)
≥15				25 (15)	0.87 (0.58–1.32)	0.92 (0.60–1.39)	164 (15)	0.90 (0.76–1.05)	0.89 (0.75–1.04)
p for trend[e]		0.90	0.90		0.18	0.30		0.26	0.40
Days/week									
1	43 (142)	0.87 (0.62–1.22)	0.87 (0.62–1.23)	116 (127)	1.09 (0.88–1.34)	1.10 (0.89–1.35)	1080 (127)	1.06 (0.99–1.14)	1.05 (0.98–1.12)
2–3	28 (90)	0.73 (0.49–1.10)	0.73 (0.48–1.09)	83 (77)	0.86 (0.68–1.09)	0.87 (0.68–1.11)	740 (77)	1.01 (0.93–1.09)	1.01 (0.93–1.09)
4–5	22 (38)	1.34 (0.86–2.10)	1.31 (0.83–2.06)	32 (32)	0.72 (0.50–1.04)	0.74 (0.52–1.07)	360 (32)	1.12 (1.01–1.25)	1.12 (1.01–1.25)
6–7	33 (70)	1.08 (0.74–1.57)	1.06 (0.72–1.56)	64 (59)	0.76 (0.58–0.99)	0.78 (0.59–1.02)	675 (59)	1.07 (0.99–1.17)	1.07 (0.98–1.17)
p for trend[e]		0.11	0.11		0.03	0.04		0.62	0.60
Years of Use[f]									
<5	130 (362)	0.95 (0.75–1.19)	0.95 (0.75–1.19)	319 (318)	0.97 (0.84–1.13)	1.00 (0.86–1.16)	2906 (318)	1.03 (0.98–1.08)	1.03 (0.98–1.08)
5–9	109 (245)	0.95 (0.74–1.22)	0.96 (0.74–1.24)	264 (209)	0.95 (0.81–1.12)	0.97 (0.83–1.14)	2198 (209)	1.06 (1.00–1.12)	1.06 (1.00–1.12)
10–14	36[g] (81)	0.80 (0.55–1.17)	0.81 (0.55–1.19)	95 (54)	0.92 (0.73–1.16)	0.95 (0.75–1.20)	633 (54)	1.00 (0.92–1.09)	1.00 (0.91–1.09)
≥15				17 (11)	0.63 (0.39–1.04)	0.63 (0.38–1.04)	162 (11)	1.12 (0.95–1.32)	1.10 (0.93–1.30)
p for trend[e]		0.51	0.51		0.09	0.14		0.34	0.35

RR relative risk, *CI* confidence interval, *P-Y* person years (in thousands)

[a] Simple models are adjusted for age and questionnaire cycle

[b] Multivariable models are adjusted for age, questionnaire cycle, use of aspirin and non-aspirin NSAIDs, reaction of skin to sun exposure, ability to tan, number of severe sunburns, number of moles on left arm, family history of melanoma, UV availability at state of residence, menopausal status and use of postmenopausal hormones, height, BMI, physical activity, intake of vitamin C from foods, and intake of vitamin D from foods and supplements. Melanoma models were also adjusted for prevalent SCC and BCC

[c] Never report of acetaminophen use is the reference group for all other categories in the table

[d] Follow-up did not begin until 1998 with the initial reported quantity of use of acetaminophen

[e] Linear trend over quantity and frequency among current acetaminophen users and over duration among past and current users

[f] Years of use is assessed among past and current acetaminophen users

[g] Categories were combined when case counts were ten or fewer

cancers. Rather, we observed an increased risk of melanoma among current aspirin users, though an increase of similar magnitude among past users and lack of evidence for a dose–response effect for quantity, frequency, or duration of use among current users detract from the plausibility of a pharmacologic mechanism.

Preclinical evidence indicates that NSAIDs are potential candidates for chemoprevention in skin cancers [25]. A primary target of ultraviolet radiation is a second-messenger system involving mitogen-activated protein kinases (MAPKs). The MAPK enzymes exhibit increased activity with the addition of UV radiation, increasing cell proliferation and differentiation and affecting apoptosis. The activation of the MAPKs results in unrestricted cell growth by means of activator protein 1 (AP-1). NSAIDs have been shown to affect these mechanisms of cellular damage at two points: they suppress the activity of MAPKs and can inhibit AP-1 directly as well [4]. Upregulation of MAPKs can also increase activity of cyclooxygenase-2 (COX-2), one of the primary targets of NSAIDs, and most melanomas have significant expression of this enzyme [5].

In addition to our prior analysis of NSAIDs and melanoma risk from the GEM study [8], five reports have addressed the chemopreventive potential of NSAIDs for melanoma in human subjects. In the only other prospective investigation, which was conducted in men and women in the Vitamins and Lifestyle (VITAL) study and included 349 incident cases of melanoma, risk of melanoma was not associated with either aspirin or non-aspirin NSAID use assessed retrospectively at baseline (HR = 1.10, 95 % CI = 0.76–1.58 for aspirin; HR = 1.22, 95 % CI = 0.75–1.99 for non-aspirin NSAIDs) [29]. Our findings supplement this result by assessing medication use every 2 years over a longer period of follow-up. Three case–control studies found a significant risk reduction of 43–55 % in melanoma for aspirin or non-aspirin NSAID users, but these results are open to doubt due to the potential for recall bias and lack of control for a full spectrum of other risk factors [26–28]. In the last of these five studies, which was conducted in melanoma patients, users of COX-2 inhibitors were significantly less likely to have a second primary melanoma, metastasis, or recurrence ($p = 0.03$) [30]. Although these results are interesting, individuals in a high-risk population may have a different predisposition to skin cancers, and the mechanisms for metastasis and recurrence differ from those of primary disease.

Several reports have evaluated the effects of aspirin and other NSAIDs on non-melanoma skin cancers and results have been inconsistent. Ours is the first reported prospective study in the general population. Retrospective results from three case–control studies reported non-significant odds ratios (OR) of 0.85 for BCC [7] and ORs between 0.07 and 1.32 for SCC, depending upon dose, frequency, and duration of use [31, 32]. Two studies were conducted in high-risk populations. In individuals with previous non-melanoma skin cancer, NSAID use in the year previous to a subsequent diagnosis was unassociated with BCC, whereas a non-significant 29 % lower risk of SCC was observed, though risk did not decline with greater frequency of use [33]. The other study in individuals with actinic keratoses found that recent initiators of NSAID use had significantly lower risks of first BBC or SCC, though risks were not reduced for continuous NSAID users [34]. Lastly, two clinical trials of celecoxib, a selective COX-2 inhibitor, have been conducted in individuals at high risk of non-melanoma skin cancers. In a trial conducted in subjects with basal cell nevus syndrome, development of new BCC was reduced by 50 % in celecoxib users with less severe disease [35], and in the other trial of this medication in individuals with multiple actinic keratoses, non-melanoma skin cancers were reduced by 59 % after 11 months of follow-up [36]. However, the pathophysiology of cancer in those with basal cell nevus syndrome or severe sun damage may differ substantially from that of the general population, and the short duration of follow-up in the actinic keratosis study may not be indicative of more extended benefit.

Although our study was designed around a hypothesis of a potential chemoprotective effect of NSAIDs, our data suggested a possible reduced risk of SCC for current users of acetaminophen, particularly for those with more frequent or longer duration of use. Epidemiologic and clinical data on the role of acetaminophen in the development of skin cancers are lacking. However, the effects of acetaminophen on melanoma investigated in vitro and in animal models do not support our results [37, 38]. These studies showed selective toxicity of acetaminophen against melanoma cells, which may be due to interactions with tyrosinase and increased formation of reactive oxygen species. Absence or alterations in tyrosinase, such as in certain types of albinism, have been shown to increase risk of both melanoma and non-melanoma skin cancers [39]. Given the lack of supporting mechanistic evidence, our observed association between acetaminophen use and decreased incidence of SCC may be an incidental finding without clinical significance.

The strengths of our study include the prospective design, large number of skin cancer cases, and reassessment of medication use over a long follow-up period. There are also several limitations. Our study included only Caucasian female nurses; therefore, the results may not be representative of the general population. However, these subjects would be expected to be more accurate in their reporting of medication use and diagnoses. Furthermore, sufficient data were not available to assess the full duration

of non-aspirin NSAID and acetaminophen use, as previous duration of use was not reported at the first assessment of these medications in 1990. It is possible that more extended use of these medications over time (more than 15 years) may have a significant effect. In addition, we were not able to confirm medication use with prescriptions. However, since most of these medications are commonly available over the counter, it is questionable whether this measure would increase the accuracy of reporting. Lastly, pathology review could not be done to confirm each reported case of BCC for practical reasons, and pathology reports could not be obtained for some reported melanomas and SCCs [9, 10].

In conclusion, we did not find a chemoprotective effect of aspirin or non-aspirin NSAIDs on risk of melanoma or non-melanoma skin cancers. Additional study is required to clarify our observation of a decreased risk of SCC with frequent acetaminophen use.

Acknowledgments We are indebted to the participants in the NHS for their dedication to this study. We thank the following state cancer registries for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming. This research was supported by R03CA125821, P30CA023074, and P01CA87969 from the National Institutes of Health and a Career Development Award from the American Society for Clinical Oncology.

Conflict of interest The authors declare that they have no conflict of interest.

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