ORIGINAL ARTICLE

Can oral nonsteroidal antiinflammatory drugs play a role in the prevention of basal cell carcinoma? A systematic review and metaanalysis

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Background: Evidence for an association between aspirin or other nonsteroidal antiinflammatory drug (NSAID) use and basal cell carcinoma (BCC) has been inconsistent.

Objective: We conducted a systematic review and metaanalysis to assess the effect of oral NSAIDs on BCC.

Methods: PubMed, Web of Science, and Embase databases were searched up to December 3, 2014. A random effects model metaanalysis was used to calculate summary estimates of the effects of aspirin, nonaspirin NSAIDs, or any (aspirin or nonaspirin) NSAID use in patients with BCC.

Results: The summary estimates from 11 studies (1 randomized controlled trial, 5 cohort studies, and 5 case control studies) found a 10% risk reduction of BCC among those using any NSAID (relative risk [RR], 0.90 [95% confidence interval {CI}, 0.84-0.97]). A similar but not statistically significant inverse association was observed for nonaspirin NSAIDs (RR, 0.93 [95% CI, 0.86-1.02]), while aspirin use was more weakly associated (RR, 0.95 [95% CI, 0.91-1.00]). The strongest inverse associations were noted among those with either a history of skin cancers or a high prevalence of actinic keratoses.

Limitations: Dose-effect estimates could not be calculated because the available data were too heterogeneous to pool.

Conclusion: The intake of NSAIDs may help prevent BCC, particularly in high-risk populations. A large randomized controlled trial is required to confirm these findings. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2015.08.034.)

Key words: aspirin; basal cell carcinoma; metaanalysis; NSAIDs; skin cancer; systematic review.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cancer in white populations, and its incidence has continued to rise over the past few decades.[1] Although BCC rarely metastasizes and is associated with very low mortality, it causes significant health care and financial burdens to the community,[2] and hence effective preventive strategies are needed. To

Abbreviations used:

BCC:	basal cell carcinoma
CI:	confidence interval
COX:	cyclooxygenase
NSAID:	nonsteroidal antiinflammatory drug
OR:	odds ratio
RCT:	randomized controlled trial

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Supported by Program Grant 552429 from the National Health and Medical Research Council of Australia (Dr Olsen) and a postdoctoral fellowship of The University of Queensland (Dr Pandeya).

Conflicts of interest: None declared.

Accepted for publication August 15, 2015.

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Published online September 30, 2015.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.08.034

date, few chemopreventive medications for BCC have been identified.[3]

Evidence is accumulating that nonsteroidal anti-inflammatory drugs (NSAIDs) have the potential to decrease the risks of several types of cancer,[4,5] including some keratinocyte skin cancer.[6,7] Whilst a recent systematic review and metaanalysis reported no preventive effect of NSAID use on BCC,[8] a more recent one reported marginal protective effects of aspirin on skin cancer.[9] Regular NSAID use significantly reduced the risk of keratinocyte cancers, defined subtype BCC and squamous cell carcinoma (SCC), in women with a history of melanoma or keratinocyte cancers, but not among women with no history of melanoma or keratinocyte cancers.[10]

CAPSULE SUMMARY

- The evidence of the effect of nonsteroidal antiinflammatory drugs on basal cell carcinoma is inconsistent.
- This metaanalysis shows that any nonsteroidal antiinflammatory drug use significantly reduces the risk of basal cell carcinoma by 10%, but the effects of either aspirin or nonaspirin nonsteroidal antiinflammatory drugs alone are not significant.
- Collectively, oral nonsteroidal antiinflammatory drugs have the potential to reduce the risk of basal cell carcinoma, particularly among high-risk populations.

The aim of this study was to systematically review relevant published epidemiologic studies and synthesize all evidence on the association between oral intake of aspirin or nonaspirin NSAIDs and the risk of BCC.

METHODS

Search strategy

This review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as a guideline. We searched the PubMed, Web of Science, and EMBASE databases using the specific terms "nsaids," "aspirin," "cyclooxygenase," "basal cell carcinoma," "nonmelanoma," "non-melanoma," "case-control," "cohort," "trial," and "incidence." Language restrictions were not applied. A single reviewer identified potentially relevant studies published before December 2014 (Appendix A; available at http://www.jaad.org). Titles and abstracts of all identified articles were reviewed; laboratory-based or therapeutic studies, reviews, and duplicate publications were excluded and full texts of the remaining articles were obtained. The reference lists of reviews and retrieved articles, "related citations" in PubMed, and "times cited" in Web of Science from relevant articles were searched for additional relevant studies. Reasons for excluding studies were recorded.

Inclusion criteria

Case control, cohort, or intervention studies examining the oral intake of aspirin or nonaspirin NSAIDs in relation to the risk of BCC were included. To be eligible, studies must have reported relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs), or provided sufficient data to permit these calculations.

Data extraction and quality assessment

Data extracted from the relevant studies included first author, publication year, and other study characteristics, such as study location, study population, design and duration, sample size, individuals with and without BCC, exposure to NSAIDs, and sex distribution. Extracted exposure information included the type of NSAID used (ie, aspirin, nonaspirin NSAIDs, any NSAIDs, or a specific NSAID), exposure assessment method (ie, self-report or pharmacy database), BCC diagnosis method (ie, pathology, self-report, or registry), effect estimates with 95% CIs, and confounding factors accounted for in analyses.

Studies were classified by geographic location (ie, North America or Europe), source population (ie, general population, "high risk"—with a history of skin cancer or high prevalence [>10] of actinic keratoses [AKs]), sex distribution (ie, predominantly [>75%] male, predominantly female, or mixed), exposure assessment (ie, prescription database or self-report), diagnosis method (ie, histology, cancer registry, self-report, or not mentioned), and types of antiinflammatory drugs assessed (ie, NSAIDs including aspirin, NSAIDs excluding aspirin, or aspirin only).

Study quality was evaluated using a scoring system designed with reference to the following guidelines: Meta-analysis Of Observational Studies in Epidemiology (MOOSE),[11] Quality Assessment Tool for Systematic reviews of Observational studies (QATSO),[12] and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[13] Cohort studies or randomized controlled trials (RCTs) were allocated 2 points, population-based case control studies 1 point, exposure assessed on pill counts received 2 points, personal recall 1 point, and pharmacy database assessments scored 0 points. Studies adjusted for

only age and sex scored 1 point, those additionally adjusted for a measure of skin pigmentation received 2, and those that also adjusted for a measure of sun exposure received 3 points. A total score of 4 to 6 was considered high quality and a total of 1 to 3 was considered low to moderate quality.

Statistical analysis

A random effects metaanalysis model was used to obtain the pooled estimate separately for aspirin, nonaspirin NSAIDs, and any NSAIDs.[14] The Cochrane Q test for heterogeneity was used to test for heterogeneity among studies.[15] The I^2 value was calculated to estimate the degree of heterogeneity due to between-study variability.[16] A funnel plot[17] was constructed and the Egger regression asymmetry test[18] was applied to examine potential publication bias. Sensitivity analyses were conducted, removing 1 study at a time to examine the influence on the pooled estimate.

For studies where risk estimates were reported for various doses but not for ever-use, the effect of ever-use was estimated by combining the estimates of different doses using Relative Risk Estimation software (P N Lee Statistics & Computing Ltd, Sutton, UK).[19] When studies reported separate effect estimates for nonselective NSAIDs and selective cyclooxygenase-2 (COX-2) inhibitors for nonaspirin NSAID use, the estimates of nonselective NSAIDs were pooled due to sample size. Similarly, when studies did not report an effect estimate for any NSAID use but reported separate effect estimates for aspirin and nonaspirin NSAID use in the same case population, we used estimates involving the larger sample size for any NSAID use rather than combine to avoid double-counting people who used both aspirin and nonaspirin NSAIDs.

Subgroup and sensitivity analysis

Analyses were performed to assess the consistency of the association between aspirin or nonaspirin NSAIDs and BCC within certain prespecified subgroups: study design (cohort vs case control), study location (Europe vs North America), study population (general vs high risk), sex (predominantly male vs predominantly female vs both sexes), exposure measure (prescription database vs self-report), diagnosis method (pathological vs others), and quality assessment (low vs high). We performed a sensitivity analysis including the study by Wysong et al[10] that reported on the risk of keratinocyte cancers combined rather than for BCC alone (as a large proportion of these cancers were likely to have been BCCs). Statistical analyses were performed with STATA software (version 13.0; StataCorp LP, College Station, TX). All *P* values were 2-tailed.

RESULTS

Study selection and study characteristics

Our search identified 231 articles (Fig 1); 51 duplicates were removed. The titles and abstracts of the remaining 180 articles were reviewed, and 16[6,7,10,20-32] were identified for full review. Five articles not meeting the inclusion criteria were excluded for the following reasons: estimated risk of keratinocyte cancers combined was not for BCC alone[10]; estimated ORs using individuals with nonaggressive BCC as controls[29]; no specific effect estimate reported for NSAIDs[32]; population comprised of individuals with basal cell nevus syndrome[30]; and the risk of regular aspirin use being compared with shorter duration users.[27] Therefore, 11 studies were eligible for inclusion in the metaanalyses (Tables I and II), and all were published in English. Of these, 1 was a RCT,[6] 5 were cohort studies,[7,20-23] and 5 were case control studies.[24-26,28,31] Six studies presented independent effect estimates for aspirin use, nonaspirin NSAID use, and any NSAID use; 1 presented estimates for aspirin and nonaspirin NSAIDs but not any NSAIDs; 1 provided estimates for nonaspirin NSAIDs (celecoxib) use only; and the remaining 3 studies provided estimates for any NSAID only.

Quality assessment

Six of the 11 studies were considered to be of high quality[6,20-23,26]; the remaining 5 were of low to moderate quality.[7,24,25,28,31]

Use of aspirin

Four cohort[7,20,21,23] and 3 case control[24,26,28] studies provided estimates for the association between aspirin use and BCC (Table II). One case control study reported separate estimates for low- and high-dose aspirin that could not be combined, so both were included in the metaanalysis.[24] The adjusted effect estimates for the use of aspirin ranged from 0.64 to 0.98 in cohort studies and from 0.81 to 0.99 in case control studies, with only 1[7] reporting a significant inverse association between aspirin use and BCC. The pooled effect of use of aspirin compared with no use had a RR of 0.95 (95% CI, 0.91-1.00) with significant heterogeneity (I^2 = 55% [*P* = .028]; Fig 2). There was no difference in the pooled estimate according to various study characteristics (ie, study type, geographic location, sex, exposure assessment, diagnosis method, and study quality), except that estimates were lower for studies of high-risk populations than for the general population (Table III). A sensitivity analysis including the study by Wysong et al[10] did not change the pooled estimates materially. There was evidence

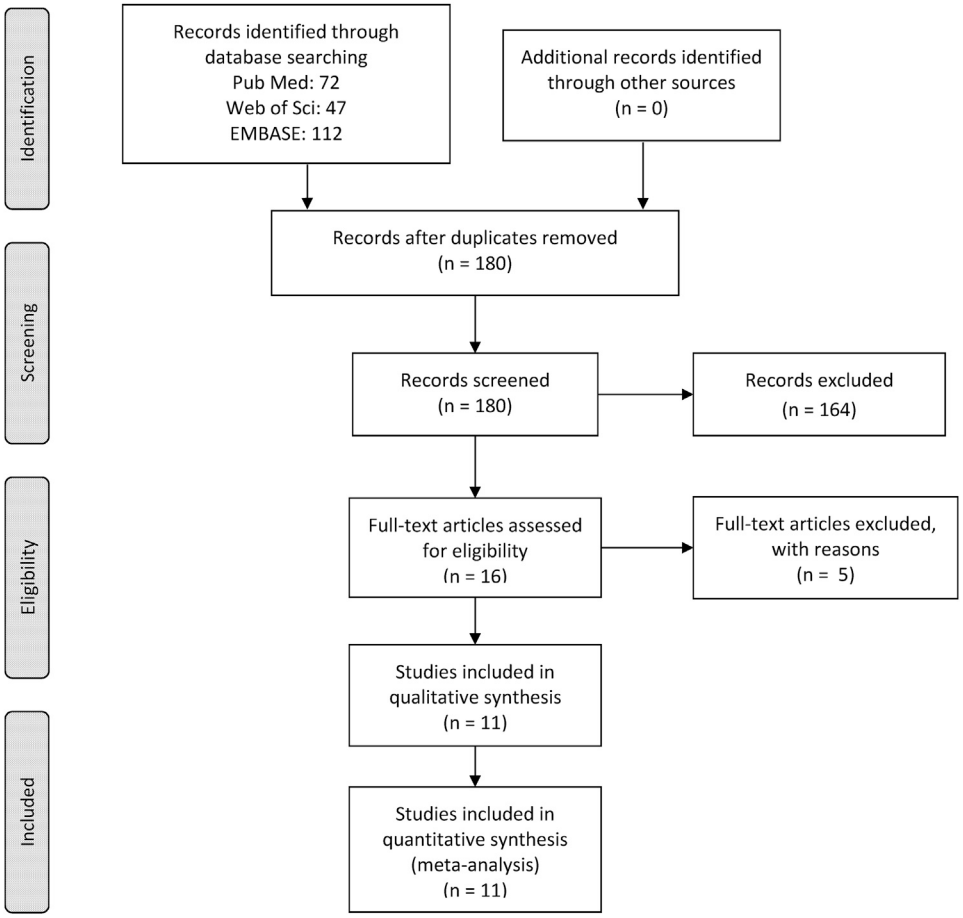

Fig 1. Flow diagram of study selection for metaanalysis of the effect of aspirin or nonaspirin nonsteroidal antiinflammatory drugs on basal cell carcinoma (search date: December 3, 2014).

of significant publication bias (Begg $P = .046$; Egger $P = .012$).

Use of nonaspirin NSAIDs

Eight studies (1 RCT,[6] 4 cohort studies,[7,20,21,23] and 3 case control studies[24,26,28]) presented estimates for the association between nonaspirin NSAID use and BCC (Table II). Of these, 2 assessed nonselective NSAIDs,[7,24] 1 limited the use to propionic acid NSAIDs,[26] and the RCT evaluated the use of celecoxib.[6] The RCT, 1 cohort study, and 1 case control study reported a significant inverse association with BCC.[6,7,24] The adjusted RRs for nonaspirin NSAID use ranged from 0.40 (95% CI, 0.18-0.93) in the RCT, to 0.60 to 1.06 in the cohort studies, to 0.91 to 1.51 in the case control studies. The pooled effect estimate was 0.93 (95% CI, 0.86-1.02), with significant heterogeneity ($I^2 = 83\%$ [$P < .001$]; Fig 3). The pooled estimates did not differ by study characteristics, although associations were stronger and statistically significant among studies with either predominantly male participants or high-risk populations (Table III). A sensitivity analysis including the study by Wysong et al[10] did not change the pooled estimates materially. There was no evidence of publication bias (Begg $P = .711$: Egger $P = .089$).

Use of any (aspirin or nonaspirin) NSAIDs

Eleven studies presented adjusted estimates of the association between use of any NSAIDs and BCC (Table II). The RRs ranged from 0.40 (RCT), to 0.51 to 1.04 and 0.91 to 1.25 in cohort and case control studies, respectively. The pooled estimate was 0.90 (95% CI, 0.84-0.97), with significant heterogeneity ($I^2 = 85\%$ [$P < .001$]; Fig 4). There was no evidence of publication bias (Begg $P = .304$; Egger $P = .089$). Subgroup analyses revealed a stronger significant inverse association between any NSAID use and BCC among studies of populations at high risk of BCC. North American studies reported comparatively greater risk reduction than European studies (Table III). Although there were 2 studies with overlapping study populations,[24,31] excluding the smaller study[31] made no difference to the results. A sensitivity

Table I. Characteristics of the 11 studies included in the metaanalysis of aspirin and nonaspirin nonsteroidal antiinflammatory drug use and the risk of basal cell carcinoma

First author (year)	Study location	Study design	Study duration	Study population description	Sex (male %)	Diagnosis method	Exposure assessment	Exposure definition
Elmets (2010)	US	RCT	2001-2006	Participants with 10-40 AKs and a previous histologic diagnosis of ≥1 AK and/or keratinocyte carcinoma; high risk for BCC	82	Biopsy specimen	Pill counts at each visit	>80% of pills (celecoxib 200 mg twice daily) during 9-mo period
Jeter (2012)	US	Cohort	1980-2008	Nurses' Health Study; female registered nurses 30-55 years of age	0	Self-report	Questionnaire	Past or current use in most weeks
Nunes (2011)	US	Cohort	1998-2004	Veterans Affairs Topical Tretinoin Chemoprevention Trial (≥2 keratinocyte carcinomas on the face or ears within the 5 years before enrollment; high risk for BCC	98	Biopsy specimen	Pharmacy database	≥1 prescription
Cahoon (2012)	US	Cohort	1983-2005	Health survey of radiologic technologist; radiologic technologists between 1926 and 1982	20	Questionnaire and medical record	Questionnaire	Any use during the past year
Clouser (2009)	US	Cohort	1984-1988	SKICAP-AK Trial (a history of ≥10 AKs; high risk for BCC)	68	Biopsy specimen	Questionnaire	>1 time per week during the follow-up period
Grau (2006)	US	Cohort	1983-1989	Skin Cancer Prevention Study (≥1 histologically confirmed BCC or SCC after January 1, 1980; high risk for BCC)	40	Biopsy specimen	Questionnaire	≥1 positive answer in 3 questionnaires (current use)

Continued

Table I. Cont'd

First author (year)	Study location	Study design	Study duration	Study population description	Sex (male %)	Diagnosis method	Exposure assessment	Exposure definition
Reinau (2014)	UK	Population-based case control	1995-2013	Clinical Practice Research Datalink	50	Primary care database	Prescription database	≥1 prescription
Johannesdottir (2012)	Denmark	Population-based case control	1991-2008	Cases: Danish Cancer Registry; controls: Danish Civil Registration System	45	Database based on morphology and histology	Prescription database	Total of >2 prescriptions during the entire study period
Torti (2011)	US	Population-based case control	1997-2000	Cases: dermatologist and pathology laboratories; controls: residents list in New Hampshire	56	Dermatologist and pathology laboratories	Interview	≥4 times a week for at least 1 month
Vogel (2007)	Denmark	Population-based case control	1993-1997	Diet, cancer, and health; individuals 50-64 years of age born in Denmark with no previous cancer diagnosis	35	Danish Cancer Registry	Questionnaire	≥2 pills per month during 1 year
Milan (2003)	Finland	Population-based case control	1975-1981	Finnish Adult Twin Cohort; same sex twins 24-89 years of age	45	Cancer registry and histologic	Questionnaire	Ever used

AK, Actinic keratosis; *BCC*, basal cell carcinoma; *SKICAP-AK*, Retinoid Skin Cancer Prevention-Actinic Keratosis.

Table II. Summary of published results on aspirin and nonaspirin nonsteroidal antiinflammatory drug use and risk of basal cell carcinoma

First author (year)	Cases	Cohort size/controls	Type of drug(s) analyzed	Adjusted factors
RCT				
Elmets (2010)	N/A*	240	Nonaspirin NSAIDs	Age, sex, Fitzpatrick skin type, AK history at screening, skin cancer history, and log-transformed patient time on study
Cohort studies				
Jeter (2012)	Aspirin: 15,079; nonaspirin NSAIDs: 9633	Aspirin: 92,125; nonaspirin NSAIDs: 76,181	Aspirin and nonaspirin NSAIDs	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, UVB light availability in 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; aspirin is also adjusted for smoking status; nonaspirin NSAIDs are also adjusted for use of aspirin and acetaminophen
Nunes (2011)	150	1051	Aspirin, nonaspirin NSAIDs, and any NSAID	Age, number of previous BCCs, number of previous SCCs, and Charlson comorbidity index
Cahoon (2012)	2291	56,964	Aspirin, nonaspirin NSAIDs, and any NSAID	Age, sex, and solar UV exposure quartile calculated from summer erythemal UV values weighted by time outdoors
Clouser (2009)	188	1402	Aspirin, nonaspirin NSAIDs, and any NSAID	Treatment, age, and sex
Grau (2006)	702	1019	Any NSAID	Age, sex, center, risk set time, number of skin cancers before study entry, skin type, and total number of questionnaires completed
Case control studies				
Reinau (2014)	65,398	65,398	Aspirin, nonaspirin NSAIDs, and any NSAID	BMI, smoking status, alcohol status, ischemic stroke/ transient ischemic attack, ischemic heart disease, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, psoriasis, systemic glucocorticoids, other

Continued

Table II. Cont'd

First author (year)	Cases	Cohort size/controls	Type of drug(s) analyzed	Adjusted factors
				immunosuppressants, photosensitizing or phototoxic drugs, and the number of general practitioner visits in the year before the index date
Johannesdottir (2012)	12,864	128,609	Aspirin, nonaspirin NSAIDs, and any NSAID	Charlson comorbidity index score, use of systemic glucocorticoids, cytostatic or immunosuppressive medications, and drugs with pigmenting adverse effects
Torti (2011)	487	462	Aspirin, nonaspirin NSAIDs, and any NSAID	Age, sex, number of cigarettes smoked per day, skin type, lifelong number of painful sunburns, and lifelong cumulative number of hours of sun exposure
Vogel (2007)	304	315	Any NSAID	Age and sex
Milan (2003)	232	232	Any NSAID	No adjustment

AK, Actinic keratosis; *BCC*, basal cell carcinoma; *BMI*, body mass index; *N/A*, not applicable; *NSAID*, nonsteroidal antiinflammatory drug; *RCT*, randomized controlled trial; *SCC*, squamous cell carcinoma; *UV*, ultraviolet; *UVB*, ultraviolet B.
*Mean number of tumors per patient is presented instead of number of incidence.

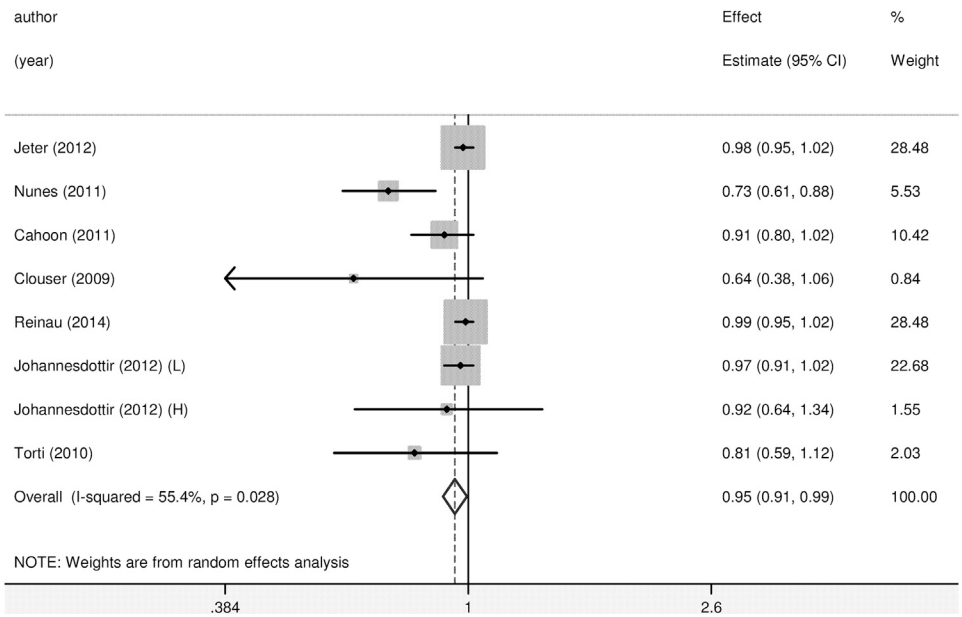

Fig 2. Forest plot of the association (relative risk) between aspirin use and basal cell carcinoma (denoted by first author and publication year).

analysis including the study by Wysong et al[10] did not change the pooled estimates materially.

Dose–response analyses

Ten studies evaluated a dose-specific relationship between either aspirin or nonaspirin NSAIDs and BCC[6,7,20-24,26,28]; however varying aspects of dose, such as frequency of use, drug dose, and duration by intensity were used, and among those reporting frequencies or duration, varying categories for the risk estimates were used, hence it was not possible to calculate pooled dose–response effects.

Table III. Metaanalysis results using a random effects model: Risk of basal cell carcinoma associated with aspirin/nonaspirin nonsteroidal antiinflammatory drug use

	Aspirin use				Nonaspirin NSAID use				Any use of aspirin/nonaspirin NSAIDS			
	No. of studies	RR (95% CI)	I^2 (%)	*P* value	No. of studies	RR (95% CI)	I^2 (%)	*P* value	No. of studies	RR (95% CI)	I^2 (%)	*P* value
All studies	7	0.95 (0.91-1.00)	55%	.028	8	0.93 (0.86-1.02)	84%	.000	11	0.90 (0.84-0.97)	85%	< .001
Study type												
Cohort	4	0.87 (0.75-1.00)	77%	.004	4	0.89 (0.75-1.07)	87%	.000	5	0.80 (0.64-1.00)	93%	< .001
Case control	3	0.98 (0.95-1.01)	0%	.597	3	0.94 (0.89-0.99)	49%	.141	5	0.99 (0.97-1.01)	0%	.459
Study location												
Europe	2	0.98 (0.96-1.01)	0%	.786	2	0.94 (0.89-0.99)	62%	.104	4	0.99 (0.96-1.01)	7%	.366
North America	5	0.86 (0.75-0.98)	72%	.007	6	0.88 (0.73-1.06)	83%	.000	7	0.79 (0.65-0.96)	91%	< .001
Population studied												
General	5	0.98 (0.96-1.00)	0%	.650	5	0.99 (0.92-1.06)	80%	.000	7	0.99 (0.97-1.01)	0%	.581
High risk*	2	0.72 (0.61-0.85)	0%	.621	3	0.64 (0.53-0.77)	0%	.496	4	0.61 (0.41-0.92)	88%	< .001
Sex												
Predominantly male (>75%)	1	0.73 (0.61-0.88)	NA	NA	2	0.61 (0.42-0.88)	26%	.245	3	0.64 (0.35-1.18)	77%	.013
Predominantly female (<25%)	2	0.97 (0.91-1.02)	24%	.251	2	1.04 (1.00-1.09)	0%	.730	3	0.99 (0.95-1.02)	0%	.603
Mixed	4	0.98 (0.94-1.02)	14%	.323	4	0.93 (0.87-1.00)	52%	.098	6	0.96 (0.91-1.01)	58%	.038
Exposure assessment												
Pharmacy database	3	0.94 (0.86-1.02)	71%	.015	3	0.88 (0.79-0.98)	86%	.000	3	0.84 (0.72-0.97)	96%	< .001
Self-report	4	0.93 (0.84-1.02)	43%	.156	4	1.04 (0.96-1.13)	33%	.212	7	0.95 (0.88-1.03)	37%	.131
Diagnosis method												
Histology only	5	0.92 (0.84-1.00)	65%	.013	6	0.86 (0.77-0.96)	78%	.000	9	0.85 (0.76-0.94)	87%	< .001
Self-report	2	0.97 (0.91-1.02)	24%	.251	2	1.04 (1.00-1.09)	0%	.730	2	0.99 (0.95-1.02)	0%	.337
Quality assessment												
High	4	0.93 (0.84-1.02)	43%	.156	5	1.01 (0.89-1.15)	59%	.046	6	0.93 (0.83-1.04)	62%	.021
Low	3	0.94 (0.86-1.02)	71%	.015	4	0.88 (0.79-0.98)	86%	.001	5	0.86 (0.76-0.98)	92%	< .001
Sensitivity analysis including Wysong et al (2014)	8	0.96 (0.92-0.99)	50%	.044	9	0.94 (0.88-1.01)	81%	.000	12	0.92 (0.86-0.97)	83%	< .001

CI, Confidence interval; *NA*, not applicable; *NSAID*, nonsteroidal antiinflammatory drug; *RR*, relative risk.
*All participants who are considered to be in high-risk populations (ie, history of skin cancer or high prevalence [>10] of actinic keratoses).

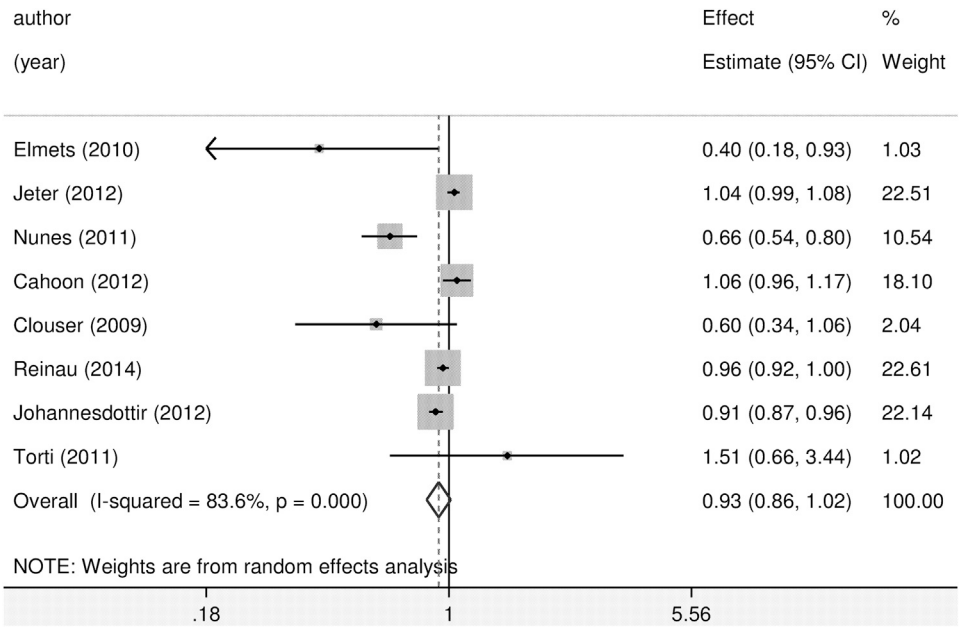

Fig 3. Forest plot of the association (relative risk) between nonaspirin nonsteroidal antiinflammatory drug use and basal cell carcinoma (denoted by first author and publication year).

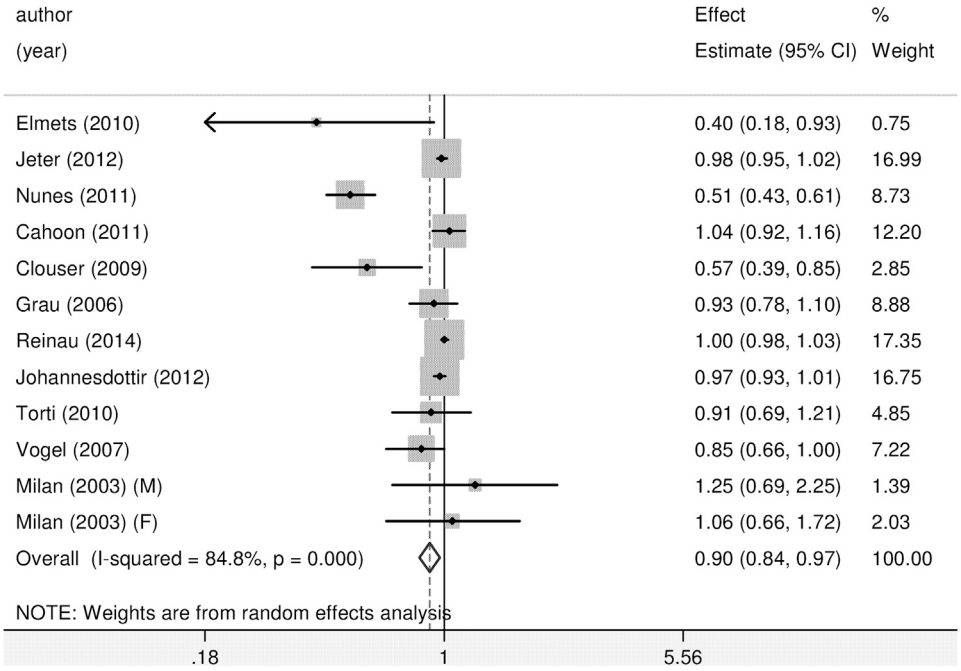

Fig 4. Forest plot of the association between any aspirin or nonaspirin nonsteroidal antiinflammatory drug use and basal cell carcinoma (denoted by first author and publication year).

DISCUSSION

Our meta analysis found a significant (10%) reduction in the risk of BCC among the users of any NSAID (aspirin or nonaspirin) overall, noting that the estimate included study populations at high risk of skin cancer. Compared to nonusers, a 5% risk reduction for BCC with aspirin use and an approximate 7% risk reduction with nonaspirin NSAID use were also observed; however, contributing studies were few, and statistical significance was not achieved. For all 3 NSAID subgroups, there was significant heterogeneity between studies in the

effect estimates derived from high-risk populations compared to the general population, with greater reductions among high-risk populations (with no heterogeneity in the risk estimates), suggesting that NSAIDs deserve attention as potential chemopreventive agents in such targeted groups. A lack of uniformity in reporting dose effect estimates prevented the estimation of dose-dependent associations between NSAID use and BCC. Our results add more detailed evidence to 2 previous metaanalyses, one of which concluded that there were no chemopreventive effects of NSAIDs on BCC (and did not explore heterogeneity), and the other limited exposure to aspirin, reporting a marginal protective effect on BCC.[8,9]

Our meta analysis had several strengths. The included studies were identified by a broad search using multiple databases with a manual review, were not limited by language, and detailed sensitivity analyses were performed to examine heterogeneity according to study characteristics. Compared with previous metaanalyses,[8,9] we added 4 additional studies for any NSAID use,[7,25,27,28,31] 6 additional studies than the first metaanalysis and 3 additional than the second for aspirin use,[6,7,23,25,27,28,31] and 6 studies for nonaspirin NSAID use.[6,7,20,24,26,28] Our finding of a stronger reduction in BCC risk with NSAIDs use among high-risk populations is broadly supported by a recent report showing that the regular use of NSAIDs significantly reduced the risk of BCC and SCC combined in women with a history of melanoma, BCC, or SCC but not among women without a history of melanoma, BCC, or SCC.[10] Limitations reflected limitations of included studies based on preexisting databases—namely, the lack of information about study participants' ultraviolet exposure, skin type, and actual NSAID use.[33] NSAIDs are common over the counter medications, and the use of nonprescription NSAIDs were necessarily ignored in studies using prescription database records. Similarly, studies based on self-reported use had the potential for misclassification of nonrepetitive NSAID use due to poor recall,[34] and those relying on self-report of BCC potentially misclassified the study outcome. Most studies included in the metaanalysis did not measure details of the timing of NSAID use in relation to skin cancer diagnosis and were therefore not informative about the most efficacious period of NSAID use for skin cancer chemoprevention. Finally, reasons for NSAID intake were also often unknown yet may have been linked to BCC risk. For example, patients with rheumatoid arthritis have an abnormal immune response and they may be restricted in outdoor activity, either of which may modify their risk of keratinocyte skin cancers independent of NSAID use.[35]

The hypothesized mechanism for the protection NSAIDs provide against skin cancer is their inhibition of inflammatory cytokines, such as COX-2 and its product prostaglandin E_2 that promote skin carcinogenesis.[36,37] In human skin, the expression of COX-2 was increased in BCC tumor samples, although to a lesser extent than in SCC and AK samples.[38] This may explain the weaker inverse association of NSAIDs with BCC compared to SCC (pooled RR, 0.82 [95% CI, 0.71-0.94]).[39] It suggests that carcinogenesis of BCC occurs less through a pathway of COX-2 inhibition than SCC, or that COX-2 is involved in the early stage of BCC carcinogenesis. In the present analysis, all nonaspirin NSAIDs were regarded as similar even though different NSAIDs have different kinetics and dynamics.[40] Moreover, NSAIDs are also commonly known to be photosensitizing, which could increase the vulnerability of the skin to ultraviolet light–induced damage and lead to the development of BCC.[41] Further categorization of nonaspirin NSAIDs by their photosensitizing potential could further elucidate potential mechanisms of action underlying the observed associations of NSAID use and BCC.

In conclusion, a synthesis of the existing published data suggests that overall, oral aspirin or nonaspirin NSAID intake may reduce the risk of BCC. In particular, there is strong indication of potential secondary prevention of BCC in populations at a priori high risk of skin cancer. The effect size is modest, however, and should be viewed in the context of other mechanisms to prevent these cancers, such as reducing excessive sun exposure. Additional research with more detailed exposure information in terms of dose and timing of NSAID use, and statistical adjustment of potential confounders—particularly exposure to ultraviolet light—is required for confirmation.

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APPENDIX A. SEARCH STRATEGY USED TO FIND RELEVANT STUDIES

Searches were conducted using the PubMed, Web of Science, and Embase databases, limited to articles published before December 2014 (the last searched date was December 3, 2014). The publication language was not limited to English. Search strategies were tailored using PubMed. Search terms were applied together with text terms, such as aspirin instead of acetylsalicylic acid. PubMed and Embase were searched with MeSH terms, but Web of Science does not use MeSH terms. PubMed search terms were as follows:

1. **To identify relevant outcomes (BCC):** ("basal cell carcinoma"[All Fields] OR "non-melanoma"[All Fields] OR nonmelanoma[All Fields])
2. **To identify relevant exposures (NSAIDS):** (("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) OR ("anti-inflammatory agents, non-steroidal" [Pharmacological Action] OR "anti-inflammatory agents, non-steroidal"[MeSH Terms] OR ("anti-inflammatory"[All Fields] AND "agents"[All Fields] AND "non-steroidal"[All Fields]) OR "non-steroidal anti-inflammatory agents"[All Fields] OR "nsaids"[All Fields]) OR ("prostaglandin-endoperoxide synthases"[MeSH Terms] OR ("prostaglandin-endoperoxide"[All Fields] AND "synthases"[All Fields]) OR "prostaglandin-endoperoxide synthases"[All Fields] OR "cyclooxygenase"[All Fields]))
3. **To limit to epidemiologic studies:** (case-control[All Fields] OR cohort[All Fields] OR ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms]))

Parts 1, 2, and 3 were combined using 'AND' to search PubMed.