ARTICLE

Chemoprevention of Nonmelanoma Skin Cancer With Celecoxib: A Randomized, Double-Blind, Placebo-Controlled Trial

Craig A. Elmets, Jaye L. Viner, Alice P. Pentland, Wendy Cantrell, Hui-Yi Lin, Howard Bailey, Sewon Kang, Kenneth G. Linden, Michael Heffernan, Madeleine Duvic, Ellen Richmond, Boni E. Elewski, Asad Umar, Walter Bell, Gary B. Gordon

Manuscript received January 7, 2010; revised September 13, 2010; accepted October 8, 2010.

Correspondence to: Craig A. Elmets, MD, Department of Dermatology, 1530 3rd Ave South, EFH 414, University of Alabama at Birmingham, Birmingham, AL 35294 (e-mail: celmets@uab.edu).

Background Preclinical studies indicate that the enzyme cyclooxygenase 2 plays an important role in ultraviolet-induced skin cancers. We evaluated the efficacy and safety of celecoxib, a cyclooxygenase 2 inhibitor, as a chemopreventive agent for actinic keratoses, the premalignant precursor of nonmelanoma skin cancers, and for nonmelanoma skin cancers, including cutaneous squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs).

Methods A double-blind placebo-controlled randomized trial involving 240 subjects aged 37–87 years with 10–40 actinic keratoses was conducted at eight US academic medical centers. Patients were randomly assigned to receive 200 mg of celecoxib or placebo administered orally twice daily for 9 months. Subjects were evaluated at 3, 6, 9 (ie, completion of treatment), and 11 months after randomization. The primary endpoint was the number of new actinic keratoses at the 9-month visit as a percentage of the number at the time of randomization. In an intent-to-treat analysis, the incidence of actinic keratoses was compared between the two groups using t tests. In exploratory analyses, we evaluated the number of nonmelanoma skin cancers combined and SCCs and BCCs separately per patient at 11 months after randomization using Poisson regression, after adjustment for patient characteristics and time on study. The numbers of adverse events in the two treatment arms were compared using χ^2 or Fisher exact tests. All statistical tests were two-sided.

Results There was no difference in the incidence of actinic keratoses between the two groups at 9 months after randomization. However, at 11 months after randomization, there were fewer nonmelanoma skin cancers in the celecoxib arm than in the placebo arm (mean cumulative tumor number per patient 0.14 vs 0.35; rate ratio [RR] = .43, 95% confidence interval [CI] = 0.24 to 0.75; P = .003). After adjusting for age, sex, Fitzpatrick skin type, history of actinic keratosis at randomization, nonmelanoma skin cancer history, and patient time on study, the number of nonmelanoma skin cancers was lower in the celecoxib arm than in the placebo arm (RR = 0.41, 95% CI = 0.23 to 0.72, P = .002) as were the numbers of BCCs (RR = 0.40, 95% CI = 0.18 to 0.93, P = .032) and SCCs (RR = 0.42, 95% CI = 0.19 to 0.93, P = .032). Serious and cardiovascular adverse events were similar in the two groups.

Conclusions Celecoxib may be effective for prevention of SCCs and BCCs in individuals who have extensive actinic damage and are at high risk for development of nonmelanoma skin cancers.

J Natl Cancer Inst 2010;102:1835–1844

Cutaneous squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs), classified together as nonmelanoma skin cancers, are the most common malignancies in the United States (1). Although it is uncommon for these cancers to metastasize, they are responsible for considerable morbidity and represent a substantial economic burden to the health-care system. The direct cost of treatment for nonmelanoma skin cancers in the United States has been estimated to exceed $1.4 billion annually (2). The incidence of nonmelanoma skin cancers, unlike that of many other malignancies,

has been increasing (3,4), and these cancers are beginning to occur more frequently in younger people (5).

Because most cutaneous SCCs and BCCs are thought to be caused by excessive exposure to ultraviolet (UV) radiation (6–8), there has been a concerted effort by various health-care organizations to educate the public about the hazards of overexposure to the sun and artificial UV light sources. Actions that have been advocated include the use of protective clothing and hats, avoidance of outdoor activities during peak hours of sun exposure,

construction of permanent shade structures in outdoor areas, and the liberal and frequent application of sunscreens (9,10). However, sunscreens may not completely protect against SCCs, and there is limited evidence that they reduce the incidence of BCCs (11). Thus, attempts have been made to identify alternative forms of chemoprevention for sunlight-induced skin cancers.

A number of chemopreventive agents for nonmelanoma skin cancer have been examined, including retinoids (12), oral difluoro-methylornithine (13), topically applied DNA repair enzymes (14), and low-fat diets (15,16). In addition, evidence from experimental and epidemiological studies suggests that cyclooxygenase 2, an enzyme involved in prostaglandin synthesis, may be involved in the pathogenesis of nonmelanoma skin cancers (17–24). On the basis of evidence that cyclooxygenase 2 may be involved in UV-induced nonmelanoma skin cancers (17–22), we conducted a clinical trial to examine whether oral administration of celecoxib, a nonsteroidal anti-inflammatory drug (NSAID) that is an inhibitor of cyclooxygenase 2, would be an effective chemopreventive agent in individuals who had evidence of substantial UV damage and therefore were at increased risk for development of additional actinic kera-

toses and/or nonmelanoma skin cancers. Based on the evidence from animal models that treatment with celecoxib inhibits the development of UV-induced premalignant skin papillomas, which are thought to correspond to actinic keratoses in humans, and results of immunohistochemical studies in humans indicating that COX-2 is expressed in actinic keratoses (17–22), the primary endpoint of the trial was the number of new actinic keratoses at month 9 after randomization as a percentage of those at randomization. Patients were treated with celecoxib or placebo for 9 months and followed up for an additional 2 months. In exploratory analyses, we also evaluated the number of nonmelanoma skin cancers over the same period.

Participants and Methods

Study Design
We conducted a randomized, double-blind, placebo-controlled phase II–III clinical trial to assess whether oral administration of celecoxib reduces the incidence of actinic keratoses, BCCs, and cutaneous SCCs in individuals who were at high risk for these lesions (25,26). Patients were considered to be at high risk based on the reports from other studies which showed that individuals with large numbers of actinic keratoses and Fitzpatrick sun reactive skin types I, II, or III are at increased risk of developing nonmelanoma skin cancers. The clinical trial was registered at clinicaltrials.gov (NCT0027976). Eight study sites in the United States participated: the University of Alabama at Birmingham (Birmingham, AL); the University of Rochester School of Medicine and Dentistry (Rochester, NY); the University of Wisconsin–Madison (Madison, WI); the University of Michigan (Ann Arbor, MI); the University of California, Irvine (Irvine, CA); Washington University School of Medicine (St Louis, MO); the University of Texas M.D. Anderson Cancer Center (Houston, TX); and Northwestern University (Chicago, IL). The study began on January 18, 2001, and completed on November 3, 2006, at which time the Food and Drug Administration (FDA) requested termination of this trial after preliminary data from another trial (27) showed an association between another cyclooxygenase 2 inhibitor and cardiovascular adverse events. The protocol was approved by the institutional review board at each participating site, and all participants gave written informed consent. The trial was a cooperative effort of the participating sites, the National Cancer Institute (NCI), and Pfizer, Inc (New York, NY) (the manufacturer of celecoxib [Celebrex]) through a clinical trials agreement with the NCI's Division of Cancer Prevention.

Study Population
Individuals were eligible to participate if they were at least 18 years old and had a Fitzpatrick sun reactive skin type of I, II, or III. All subjects were required to have 10–40 actinic keratoses on the upper extremities, neck, face, and scalp at the time of entry into the study, and a previous histological diagnosis of at least one actinic keratosis and/or nonmelanoma skin cancer. On the basis of these inclusion criteria, subjects were considered to be at high risk for nonmelanoma skin cancers (25,26). Individuals with more than 40 actinic keratoses were excluded because of technical difficulties involved in mapping that many lesions. Subjects were not allowed to take

NSAIDs or doses of aspirin more than 81 mg/day at any time during the study and in the 30 days before randomization or use any topical medications during the study with the exception of emollients and sunscreens, which were allowed and recommended.

Exclusion criteria included having a known photosensitivity disorder; use of topical corticosteroids, alpha-hydroxyacids, or retinoids within 14 days before random assignment; use of oral or intravenous corticosteroids for more than two consecutive weeks during the 6 months before randomization; use of inhaled corticosteroids for more than 4 weeks during the 6 months before randomization and/or the use of nasally inhaled cortico-steroids in the month before randomization; use of psoralens, cryotherapy to target skin lesions, immunotherapy, retinoids, or radiation therapy within 30 days of randomization; or laser resurfacing, dermabrasion, or chemical peels within 60 days before randomization. Subjects were excluded if they had been treated with topical 5-fluorouracil within 3 months of randomization or with other forms of topical chemotherapy or local radiotherapy to the areas being studied within 6 months of randomization.

Study Treatment

Participants were screened for inclusion and exclusion criteria and the number of actinic keratoses. Two weeks later, they were randomly assigned to receive 200 mg of celecoxib or placebo orally twice daily. Randomization was performed by a block randomization procedure that was stratified for each center in blocks of four treatment assignments. Study medications were administered through month 9 after randomization, at which time they were discontinued, and the subjects were followed up for two additional months. Subjects were evaluated for chemopreventive efficacy and safety at months 3, 6, 9, and 11 after randomization. At each visit, actinic keratoses were counted on the upper extremities, neck, face, and scalp. A clear plastic template was placed over each anatomical site on which actinic keratoses were counted and the location of each actinic keratosis was recorded by a study investigator on the plastic template. Separate plastic templates were used at each visit, and the person who recorded the lesions had no knowledge of or access to earlier results for that subject. At the end of the study, we compared the location of actinic keratoses on the plastic template map from months 3, 6, 9, and 11 with the one prepared at randomization to identify the number of new, persistent, and regressed actinic keratoses. On clinical examination, lesions that appeared as discrete scaling or keratotic patches, often with erythema and a sandpaper-like scale, were considered actinic keratoses. Lesions that did not have these clinical characteristics of an actinic keratosis were not recorded on the plastic maps. At randomization, 32 lesions suspected of being actinic keratoses were biopsied and analyzed histologically, of which 28 (88%) were confirmed to be actinic keratoses, an accuracy rate that is consistent with other reports in the literature (28–32). Actinic keratoses were not treated at baseline or during the entire duration of the study. Lesions suspected of being BCC or SCC were biopsied, examined histologically, and, if found to be skin cancers by histopathologic examination, were managed by surgical removal. Adverse events were graded according to the NCI Common Toxicity Criteria (33).

Statistical Analysis

The sample size calculation was based on information from previous studies that examined the effects of sunscreens on the incidence of actinic keratoses (28,34); those studies used Poisson models to model the number of new actinic keratoses as the percentage of the number at randomization for both users and nonusers of sunscreen. With 120 subjects per treatment arm and assuming a 20% dropout rate, a simulation modeling based on 1000 replications showed that this study had approximately 95% power at a two-sided statistical significance level of .05 to detect a 40% relative reduction in the number of new actinic keratoses at the final visit (month 9 visit) as the percentage of randomization in the celecoxib-treated group compared with the placebo group.

Analyses were performed on the per-protocol and the intention-to-treat populations for all subjects who were randomly assigned to a study arm and who had at least one follow-up visit after baseline. Compliance with study medications was monitored by pill counts at each visit. Subjects who had taken more than 80% of their pills were considered to be compliant, a compliance figure that is consistent with that used in another clinical chemoprevention trial of NSAIDs in BCC (35). In addition, subjects who failed to present for clinic follow-up on two consecutive visits were withdrawn from the study. Patients' baseline characteristics were compared for the two treatment arms (celecoxib vs placebo) using the t test for continuous variables and the χ^2 or Fisher exact test for categorical variables. We used the same univariate analytical methods to compare the baseline characteristics for subjects who completed and withdrew from the study, stratified by treatment arm.

The two treatment arms were compared for the mean values of the following measures using t tests: the total number of actinic keratoses at randomization, the total number of actinic keratoses at the completion of therapy (ie, month 9), the number of new actinic keratoses at the completion of therapy, the ratio of new actinic keratoses at the completion of therapy to the number of actinic keratoses at randomization, and the ratio of the total number of actinic keratoses at the completion of therapy to the number at randomization. The effect of celecoxib on the ratio of new actinic keratoses at the completion of therapy to the number of actinic keratoses at randomization was also evaluated using a Poisson regression model that controlled for age, sex (male/female), sunscreen use (yes/no), and Fitzpatrick skin type (I, II, or III) (25,26).

The mean cumulative number of nonmelanoma skin cancers, BCCs, and SCCs per patient at months 3, 6, 9, and 11 (or at the time of withdrawal) and their 95% confidence intervals (CIs) were calculated based on the Poisson distribution. The difference between study arms in the mean cumulative number of tumors at each visit (or at the time of withdrawal) was evaluated using Poisson regression, adjusting for patient on-study time. The celecoxib treatment effect was also evaluated after adjusting for age, sex (male/female), Fitzpatrick skin type (I, II, or III), actinic keratosis history at randomization (yes/no), skin cancer history at baseline (yes/no), and time on study.

The safety analysis included all randomly assigned patients who took at least one dose of study medicine. The numbers of adverse events in the two treatments arms were compared using χ^2 or Fisher exact tests. All statistical analyses (including univariate tests and

Poisson regressions) were performed using SAS version 9.0 software (SAS Institute, Cary, NC). A P value less than .05 was considered statistically significant. All statistical tests were two-sided.

Results

Between January 18, 2001, and November 3, 2006, 240 patients were randomly assigned to treatment with celecoxib 200 mg twice daily or placebo. There were 122 participants in the celecoxib group and 118 in the placebo group (Table 1). Participants ranged in age from 37.5 years to 87.6 years at enrollment. Specifically, the mean age of the participants was 65.2 years (SD = 10.2 years), all participants had evidence of extensive actinic damage and a Fitzpatrick skin type of I, II, or III, and the average number of previous skin cancers was 2.3 (SD = 4.2). Of the 240 individuals who entered the study, 183 completed it, including 87 (71%) of those randomly assigned to celecoxib and 96 (81%) of those randomly assigned to placebo (Figure 1). The reasons participants withdrew from the trial are shown in Figure 1. The major differences between the celecoxib and placebo groups in reasons for participant withdrawal were withdrawal of consent (seven vs one participant, respectively) and termination of the study by the FDA (12 vs six participants, respectively). The main reason participants gave for withdrawing consent was the prohibition on taking pain medications for arthritis. The FDA terminated the study early after preliminary data from another study showed an association between another cyclooxygenase 2 inhibitor (27) and an increased risk of cardiovascular adverse events because of concerns that the increased risk might extend to celecoxib, the cyclooxygenase 2 inhibitor used in this study. At the time that this study was terminated, there were more subjects in the celecoxib arm of the study than in the placebo arm (12 vs six participants, respectively).

Efficacy of Treatment

We performed separate analyses to examine whether treatment with celecoxib influenced the number of actinic keratoses after 3, 6, and 9 months of therapy and at 2 months following the completion of therapy (ie, month 11). Specifically, we assessed the total number of actinic keratoses, the number of new actinic keratoses, and the ratio of total lesions to the number at baseline for the body as a whole and for the upper extremities, neck, face, and scalp individually. For each of these analyses, there was no difference in any of these measures between the celecoxib and placebo arms at month 9 (Table 2) or month 11 (data not shown) after randomization. After controlling for age, sex, sunscreen use, and Fitzpatrick skin type using Poisson regression, the ratio of new lesions to the number at randomization did not differ statistically significantly between the celecoxib and placebo groups (P = .69). A total of 29.3% of the actinic keratoses in both treatment groups regressed spontaneously, consistent with other reports (36,37).

Table 1. Baseline characteristics of participants at screening

Characteristic	Celecoxib group (n = 122)	Placebo group (n = 118)	P*
Age, y			
Mean (SD)	65.6 (9.9)	64.9 (10.4)	.57
Median (range)	66.4 (39.2–85.5)	65.8 (37.5–87.6)	
Sex, No. (%)			
Male	102 (84)	95 (81)	.53
Female	20 (16)	23 (19)	
Race, No. (%)			
White	121 (99)	118 (100)	1.00
Other	1 (1)	0 (0)	
Fitzpatrick skin type, No. (%)			
I	18 (15)	20 (17)	.82
II	73 (60)	66 (56)	
III	31 (25)	32 (27)	
Number of actinic keratoses at screening			
Mean (SD)	24.2 (9.2)	23.6 (8.4)	.58
Median (range)	23.0 (10–46)	23.0 (11–41)	
History of skin cancer, No. (%)			
Yes	79 (65)	70 (59)	.39
No	43 (35)	48 (41)	
Total number of skin cancer diagnoses per patient before screening, No. (%)			
0	43 (35)	48 (41)	.56
1	27 (22)	19 (16)	
2	18 (15)	21 (18)	
>2	34 (28)	30 (25)	
Mean (SD)	2.0 (2.5)	2.4 (5.1)	.42
Median (range)	1.0 (0–13)	1.0 (0–35)	
Medical history of cardiovascular abnormalities,† No. (%)	67 (46)	47 (36)	.11
Medical history of gastrointestinal abnormalities,‡ No. (%)	76 (51)	54 (40)	.07

* Based on two-sided t tests for continuous variables and two-sided χ^2 test or Fisher exact tests for categorical variables.

† One patient in the placebo group had missing data.

‡ Two patients in the placebo group had missing data.

The effect of treatment on the number of nonmelanoma skin cancers was evaluated by using Poisson regression and adjusting for patient time on study (Table 3). By month 11 after randomization (or at early study withdrawal), the mean number of nonmelanoma skin cancers per patient was statistically significantly less in participants who received celecoxib than in participants who received placebo (0.14 vs 0.35; rate ratio [RR] = 0.43, 95% CI = 0.24 to 0.75, P = .003), representing a 60% reduction in the mean number of nonmelanoma skin cancers. A decrease in nonmelanoma skin cancers was also observed at month 9 after randomization (Table 3). A difference in the number of nonmelanoma skin cancers between the two treatment groups was clearly evident by month 9 and was sustained for the rest of the time that the subjects were on the trial. In addition, we observed no rebound in the rate of development of nonmelanoma skin cancers in the celecoxib arm during the 2 months after subjects stopped taking celecoxib (Table 3). An inhibitory effect of celecoxib on nonmelanoma skin cancer development was also observed when cutaneous SCCs and BCCs were evaluated separately. By month 11 after randomization, the mean number of BCCs per patient in the celecoxib group was 0.07 (95% CI = 0.03 to 0.13) compared with 0.16 (95% CI = 0.1 to 0.25) in the placebo group (RR = 0.44; 95% CI = 0.19 to 0.99; P = .049) (Table 3). By month 11 after randomization, the mean number of SCCs per patient was 0.07 (95% CI = 0.04 to 0.14) in the celecoxib group compared with 0.19 (95% CI = 0.12 to 0.28) in the placebo group (RR = 0.42; 95% CI = 0.19 to 0.92; P = .03) (Table 3).

The celecoxib treatment effect on skin cancer remained statistically significant after adjusting for age, sex, Fitzpatrick skin type, actinic keratosis history at screening, skin cancer history, and log-transformed patient time on study. The adjusted rate ratios for the celecoxib arm compared with the placebo arm were 0.41 (95% CI = 0.23 to 0.72, P = .002) for nonmelanoma skin cancers, 0.40 (95% CI = 0.18 to 0.93, P = .032) for BCCs, and 0.42 (95% CI = 0.19 to 0.93, P = .032) for cutaneous SCCs. In subgroup analyses according to Fitzpatrick skin type (I, II, or III) and stratified by history of skin cancers and median number of actinic keratoses (≤23 vs >23), we observed no statistically significant consistent difference between treatment arms with respect to nonmelanoma skin cancers, BCC, or SCC among subgroups (Supplementary Table 1, available online), possibly reflecting the small number of subjects in several of the subgroups.
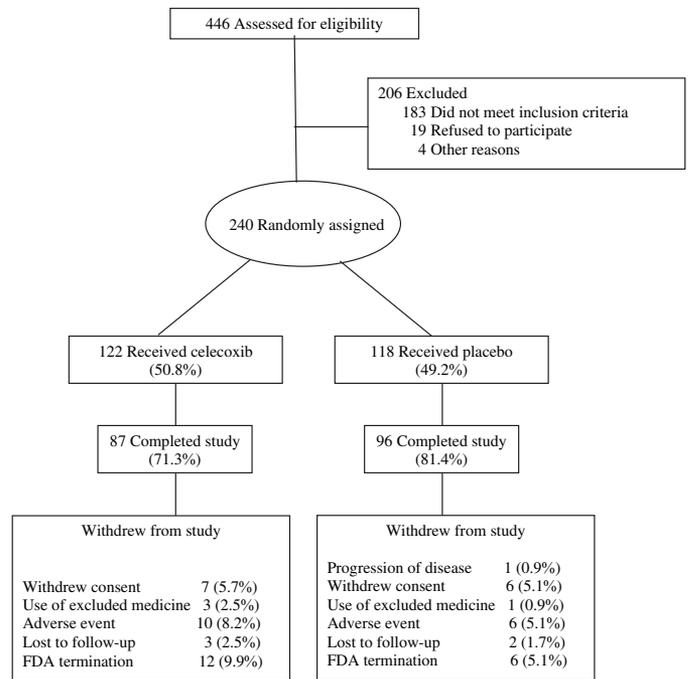
Figure 1. Study design and participant status by treatment arm. FDA = Food and Drug Administration.

There was no statistically significant difference between those who remained in the study and those who withdrew with regard to any of the demographic or clinical characteristics (Table 4).

Four patients in the placebo group had three or more nonmelanoma skin cancers compared with none in the celecoxib group (data not shown). One melanoma was diagnosed in the celecoxib group and none were diagnosed in the placebo group.

Safety

Eighty-four percent of celecoxib-treated subjects reported at least one adverse event compared with 85% of control subjects (P = .95) (Table 5). The most common adverse events were infections and infestations, followed by gastrointestinal, musculoskeletal, and skin disorders and hypertension (a frequent side effect of NSAIDs) (Supplementary Table 2, available online). The adverse effects that were more common in the celecoxib group than in the placebo group were those that are commonly attributed to cyclooxygenase

Table 2. Effect of celecoxib on actinic keratoses at month 9*

Outcome variable	Celecoxib group	Placebo group	*P*
Mean number of actinic keratoses per patient (95% CI)			
At randomization	22.7 (21.1 to 24.3†)	22.2 (20.6 to 23.8)	.67
At the completion of therapy	17.9 (16.2 to 19.6)	18.1 (15.0 to 21.2)	.95
Mean number of new actinic keratoses per patient that had developed by the completion of therapy (95% CI)	8.5 (6.9 to 10.1)	9.6 (7.4 to 11.8)	.43
Ratio of total lesions per patient at completion to randomization lesions (95% CI)	0.81 (0.71 to 0.91)	0.78 (0.69 to 0.87)	.66
Ratio of new lesions per patient at completion to lesions at randomization (95% CI)	0.40 (0.32 to 0.48)	0.41 (0.35 to 0.47)	.84

* CI = confidence interval.

† Two-sided *t* test.

Table 3. Mean number of nonmelanoma skin cancers, BCCs, and SCCs at each visit*

Type of lesion	Study arm	N	Mean number of tumors per patient (95% CI)†	Rate ratio‡ (95% CI)	P§
Month 3 visit					
Nonmelanoma skin cancer	Celecoxib	122	0.02 (0.01 to 0.08)	0.6 (0.14 to 2.49)	.478
	Placebo	118	0.04 (0.02 to 0.1)		
BCC	Celecoxib	122	0	–	–
	Placebo	118	0.03 (0.01 to 0.08)		
SCC	Celecoxib	122	0.025 (0.008 to 0.076)	1.49 (0.25 to 8.92)	.662
	Placebo	118	0.017 (0.004 to 0.068)		
Month 6 visit					
Nonmelanoma skin cancer	Celecoxib	122	0.09 (0.05 to 0.16)	0.56 (0.27 to 1.16)	.119
	Placebo	118	0.17 (0.11 to 0.26)		
BCC	Celecoxib	122	0.03 (0.01 to 0.09)	0.41 (0.13 to 1.29)	.127
	Placebo	118	0.08 (0.05 to 0.16)		
SCC	Celecoxib	122	0.06 (0.03 to 0.12)	0.71 (0.27 to 1.86)	.485
	Placebo	118	0.08 (0.05 to 0.16)		
Month 9 visit					
Nonmelanoma skin cancer	Celecoxib	122	0.12 (0.07 to 0.2)	0.48 (0.26 to 0.88)	.018
	Placebo	118	0.27 (0.19 to 0.38)		
BCC	Celecoxib	122	0.07 (0.03 to 0.13)	0.68 (0.28 to 1.66)	.398
	Placebo	118	0.1 (0.06 to 0.18)		
SCC	Celecoxib	122	0.06 (0.03 to 0.12)	0.36 (0.15 to 0.84)	.019
	Placebo	118	0.17 (0.11 to 0.26)		
Month 11 visit					
Nonmelanoma skin cancer	Celecoxib	122	0.14 (0.09 to 0.22)	0.43 (0.24 to 0.75)	.003
	Placebo	118	0.35 (0.26 to 0.47)		
BCC	Celecoxib	122	0.07 (0.03 to 0.13)	0.44 (0.19 to 0.99)	.049
	Placebo	118	0.16 (0.1 to 0.25)		
SCC	Celecoxib	122	0.07 (0.04 to 0.14)	0.42 (0.19 to 0.92)	.03
	Placebo	118	0.19 (0.12 to 0.28)		

* At each visit or at time of early study withdrawal. BCC = basal cell carcinoma; SCC = squamous cell carcinoma; CI = confidence interval; – = not applicable.

† The 95% confidence interval is based on Poisson distribution.

‡ Poisson regression adjusted for patient time on study.

§ Based on the Wald test in the Poisson regression models (two-sided).

inhibitors, that is, gastrointestinal disorders, skin rashes, hypertension, and hemorrhage. Serious events occurred in 16 subjects, nine of whom received celecoxib and seven of whom received placebo. This difference was not statistically significant. There were no deaths in either group.

Because cyclooxygenase 2 inhibitors have been reported (27) to increase the risk of serious cardiovascular adverse events (ie, myocardial infarction, stroke, congestive heart failure, or cardiovascular deaths), we examined the occurrence of cardiovascular adverse events in greater detail (Table 5 and Supplementary Table 2, available online). A similar number of individuals experienced cardiovascular adverse events in the two treatment groups. There were nine adverse cardiovascular events in seven subjects treated with celecoxib compared with six adverse events in five subjects in the placebo group. The number of subjects in the two treatment arms who experienced a cardiovascular event was not statistically significantly different.

Discussion

We found that compared with placebo, the cyclooxygenase 2 inhibitor celecoxib administered for 9 months was highly effective in preventing nonmelanoma skin cancers in subjects who had large

numbers of actinic keratoses, some of whom had already developed one or more skin cancers, and thus were at high risk for these neoplasms (25,26). Our findings validate preclinical data that were the premise for the entry of celecoxib into clinical testing (17,19,20,22). However, this analysis of nonmelanoma skin cancers should be considered exploratory because it was not the primary endpoint of the randomized trial.

This study was initiated because of preclinical evidence suggesting that cyclooxygenase 2 is involved in the pathogenesis of sunlight-induced skin cancers (17–21). Specifically, expression of this enzyme is increased in the epidermis following UV exposure, and cyclooxygenase 2 can be detected in actinic keratoses and SCCs (17,19,22). In BCCs, cyclooxygenase 2 has been found in tumor islands and in the stroma surrounding the tumor islands (17). Moreover, cyclooxygenase 2 inhibitors have been successful at preventing UV-induced skin cancers in mouse models (17–21). There is also evidence from epidemiological studies that NSAIDs, which inhibit cyclooxygenases, are associated with a decreased risk of cutaneous SCCs. For example, in a case–control study conducted in Australia, subjects who had taken large doses of NSAIDs on a regular basis were less likely than subjects who had used NSAIDs infrequently or not at all to have had a cutaneous SCC (23). Another study (24) reported that among individuals

Table 4. Baseline characteristics of patients who completed and withdrew from the study by treatment arm*

Characteristic	Celecoxib group			Placebo group		
	Withdrew (n = 35)	**Completed (n = 87)**	**P**	**Withdrew (n = 22)**	**Completed (n = 96)**	**P**
Age, y						
Mean (SD)	67.0 (11.1)	65.0 (9.5)	.32	65.7 (9.0)	64.7 (10.7)	.68
Median (range)	68.4 (45.1–84.2)	65.9 (39.2–85.5)		64.1 (50.0–87.6)	66.5 (37.5–83.9)	
Sex, No. (%)						
Male	30 (86)	72 (83)	.69	19 (86)	76 (79)	.56
Female	5 (14)	15 (17)		3 (14)	20 (21)	
Race, No. (%)						
White	35 (100)	86 (99)	1.00	22 (100)	96 (100)	–
Other	0	1 (1)		0	0	
Fitzpatrick skin type, No. (%)				4 (18)	16 (17)	.98
I	8 (23)	10 (11)	.25	12 (55)	54 (56)	
II	20 (57)	53 (61)		6 (27)	26 (27)	
III	7 (20)	24 (28)				
No. of actinic keratoses at screening						
Mean (SD)	23.8 (8.4)	24.4 (9.5)	.74	24.1 (8.6)	23.5 (8.4)	0.75
Median (range)	22 (10–41)	23 (10–46)		24 (12–38)	23 (11–41)	
History of skin cancer, No. (%)						
Yes	24 (69)	55 (63)	.58	16 (73)	54 (56)	.16
No	11 (31)	32 (37)		6 (27)	42 (44)	
Total number of skin cancer diagnoses per patient before screening, No. (%)						
0	11 (31)	32 (37)	.86	6 (27)	42 (44)	.17
1	9 (26)	18 (21)		7 (32)	12 (12)	
2	6 (17)	12 (14)		4 (18)	17 (18)	
>2	9 (26)	25 (29)		5 (23)	25 (26)	
Mean (SD)	2.0 (2.6)	2.0 (2.4)	.92	1.6 (1.8)	2.6 (5.6)	.16
Median (range)	1 (0–13)	1 (0–11)		1 (0–7)	1 (0–35)	

* P values from t tests for continuous variables and χ^2 tests or Fisher exact tests for categorical variables. All statistical tests were two-sided. – = not applicable.

with a history of nonmelanoma skin cancers, those who were NSAID users had a reduced risk of nonmelanoma skin cancers, in particular SCCs, compared with nonusers. However, the protective effect of NSAIDs on nonmelanoma skin cancer was less striking in another study (38). In that study, in a cohort of high-risk patients, subjects who used NSAIDs for less than the study duration developed fewer BCCs and SCCs than subjects who used NSAIDs for the entire length of the study (38). However, another retrospective case–control study (39) did not observe a statistically significant reduction in SCCs among individuals who reported taking any NSAID, ibuprofen, or nonaspirin NSAIDs. Similar conclusions were reached when pharmacy databases were examined for prescriptions for NSAID that were filled among patients with SCCs (39).

To our knowledge, no agents have been approved by either the FDA or governmental regulatory agents in other countries for the prevention of skin cancer. However, previous studies (11,40) that were based in Australia, where the skin cancer rates are the highest in the world, and conducted in the general population have convincingly demonstrated that sunscreens are effective chemopreventive agents for actinic keratoses and cutaneous SCCs. They showed that the regular use of an SPF15 sunscreen for more than 5 years inhibited SCCs by approximately 35%, whereas the data for BCCs were limited (11,40). Despite the widespread use of sunscreens for skin cancer prevention, appreciable numbers of these malignancies still occur. The findings of this study, which showed that the celecoxib-treated individuals developed fewer nonmelanoma skin cancers than placebo-treated individuals, suggest that cyclooxygenase inhibitors may provide an additional benefit to sunscreens in the prevention of nonmelanoma skin cancers.

There has been substantial interest in the use of cyclooxygenase inhibitors for the prevention of other types of cancer besides nonmelanoma skin cancers. For example, celecoxib has been shown in clinical trials to inhibit the formation of sporadic colorectal adenomas and adenomas in familial adenomatous polyposis (41–43). Our results extend those findings to a second target organ system (ie, the skin) and to tumors caused by a different etiologic agent (ie, chronic UV exposure). In a recent study (35) that examined NSAID use in subjects with basal cell nevus syndrome, which

Table 5. Adverse events in participants who received celecoxib or placebo

Type of adverse event	Celecoxib group	Placebo group	P*
Any adverse event, No. of participants (%)			
0	19 (16)	18 (15)	.95
≥1	103 (84)	100 (85)	
Serious adverse event, No. of participants (%)			
No	113 (93)	111 (94)	.65
Yes	9 (7)	7 (6)	
Cardiovascular adverse event, No. of participants (%)			
No	115 (94)	113 (96)	.59
Yes	7 (6)	5 (4)	

* Two-sided χ^2 test.

predisposes individuals to develop large numbers of BCCs because of a genetic defect in the patched 1 gene (*PTCH1*) of the sonic hedgehog signal transduction pathway, among patients with fewer than 15 BCCs at study entry, those who received celecoxib for 24 months developed statistically significantly fewer new BCCs than those treated with placebo.

Other agents have been evaluated for the chemoprevention of nonmelanoma skin cancer. Oral retinoid (44–46) and topical application of the DNA repair enzyme T4 endonuclease V in liposomes (14) have both been shown to have chemopreventive activity against nonmelanoma skin cancers in patients with predisposing conditions, but neither has been tested in the general population. It is interesting that low-fat diets have also been reported to reduce the number of actinic keratoses and nonmelanoma skin cancers in clinical trials (16,47). However, compliance with such a restrictive diet could prove challenging for individuals placed on the diet. Thus, there is clearly a need for new interventions that prevent these common malignancies.

Celecoxib was effective at reducing the incidence of cutaneous SCC but did not prevent its precursor, actinic keratosis. This finding was unexpected because results of preclinical studies on the prevention of SCC in mouse models suggested that celecoxib would reduce premalignant actinic keratoses as well as nonmelanoma skin cancers (17,19–22). This preferential effect of celecoxib against later stages of tumor development is consistent with findings of colorectal adenoma trials that tested celecoxib or aspirin (42,48,49). Although the precise mechanism for these unexpected results is not known, we envision three potential mechanisms by which celecoxib could inhibit the progression of premalignant keratinocytes to invasive malignancies. First, cyclooxygenase 2 is required for the synthesis of prostaglandin E2, which stimulates the proliferation of malignant cells (50,51). Celecoxib could thus have an antiproliferative effect, possibly by promoting apoptosis. The antiproliferative effect has been invoked to explain the regression of colorectal adenomas in a placebo-controlled trial of celecoxib in patients with familial adenomatous polyposis (52,53). Second, myeloid suppressor cells, which promote invasion and angiogenesis of human BCC cells (54), require cyclooxygenase 2 for production of the immunosuppressive molecule arginase-1 (55). Celecoxib might render these cells less active and thereby inhibit the development of cutaneous SCCs and BCCs. Finally, celecoxib could suppress the epithelial–mesenchymal transition, a process through which malignant cells weaken intercellular adhesions, thereby enhancing their motility and allowing them to penetrate into surrounding tissues. In lung carcinogenesis, it has been proposed that cyclooxygenase 2 is intimately involved in this process (56).

The chemopreventive effect of celecoxib occurred rapidly. The numbers of new nonmelanoma skin cancers in the two treatment arms began to diverge within 3 months of the initiation of therapy for BCCs and within 6 months of the initiation of therapy for SCCs. This is not the first time that a chemopreventive agent has been shown to work this quickly to prevent BCCs: Kraemer et al. (45) observed an inhibitory effect on skin cancer development in xeroderma pigmentosum patients within 3 months of administering oral isotretinoin, and, a recurrence of nonmelanoma skin cancers within 3 months after oral isotretinoin was stopped. In this study, nonmelanoma skin cancers did not recur during the 2-month follow-up period. However, the follow-up was short, and future studies will need to ascertain the durability of the response after cyclooxygenase inhibitors are discontinued.

Any beneficial effects of cyclooxygenase 2 inhibitors must be balanced against the adverse events associated with this class of compounds. Long-term use of rofecoxib (57) and of celecoxib (58) has been reported to increase the risk of serious cardiovascular events. The risk of serious cardiovascular events appears to depend on the dose and duration of exposure, and in six randomized trials it was greatest in patients who had the highest risk of cardiovascular disease at baseline (59). In this study, there was no statistically significant difference in the number of cardiovascular adverse events between participants who received celecoxib and those who received placebo. However, participants in this study took celecoxib for only 9 months, whereas increases in serious cardiovascular adverse events with the cyclooxygenase 2 inhibitor rofecoxib were not observed until patients had taken it for 1 or more years (57).

The dose selected for this study—200 mg twice daily—is the same as that used to treat arthritis (60). It would be interesting to examine whether lower doses of celecoxib, an intermittent dosing regimen, or combination regimens are as effective as the dose used in this study but with fewer toxic effects. Alternatively, it is possible that chemoprevention of skin cancer could be achieved by topical application of a cyclooxygenase 2 inhibitor or a nonspecific cyclooxygenase inhibitor (61).

The original intent of this trial was to examine the effect of celecoxib on actinic keratoses. Thus, one limitation of this study is that the effect of celecoxib on nonmelanoma skin cancers was not a primary or secondary endpoint. Therefore, additional studies will need to be conducted in which the effect of cyclooxygenase inhibitors on nonmelanoma skin cancer development is the primary endpoint to confirm this observation. A second limitation is that all of the participants in this study had extensive actinic damage. It is unclear whether celecoxib would have the same effect in subjects with less actinic damage.

In conclusion, this study demonstrates that the cyclooxygenase 2 inhibitor celecoxib is an effective chemopreventive agent for nonmelanoma skin cancer in patients who are at high risk for the disease. It is possible that a combination of medications that include sunscreens as well as cyclooxygenase inhibitors and/or other chemopreventive agents could be taken on a regular basis by individuals at risk for development of nonmelanoma skin cancers to reduce the incidence of this exceptionally common malignancy.

References

1. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol.* 2010;146(3):283–287.
2. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004: a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol.* 2006;55(3):490–500.
3. Athas W, Hunt W, Key C. Changes in nonmelanoma skin cancer incidence between 1977-1978 and 1998-1999 in Northcentral New Mexico. *Cancer Epidemiol Biomarkers Prev.* 2003;12(10):1105–1108.
4. Miller D, Weinstock M. Non-melanoma skin cancer in the United States: Incidence. *J Am Acad Dermatol.* 1994;30(5, pt 1):774–778.
5. Christenson LJ, Borrowman TA, Vachon CM, et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. *JAMA.* 2005;294(6):681–690.

6. Karagas MR, Greenberg ER. Unresolved issues in the epidermiology of basal cell and squamous cell skin cancer. In: Mukhtar H, eds. *Skin Cancer: Mechanisms and Human Relevance*.Boca Raton, FL: CRC Press; 1995:79–86.

7. Rigel DS. Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. *J Am Acad Dermatol*. 2008;58(5) (suppl 2):S129–S132.

8. Weinstock MA. Epidemiology of nonmelanoma skin cancer: clinical issues, definitions, and classification. *J Invest Dermatol*. 1994;102(6):4S–5S.

9. American Academy of Dermatology. *Sunscreens/Sunblocks*. Schaumburg, IL: American Academy o Dermatology. www.aad.org/public/publications/pamplets/sun_sunscreens.html. Accessed October 25, 2010.

10. American Cancer Society. *Skin Cancer Facts*.www.cancer.org/Cancer/CancerCauses/SunandUVExposure/skin-cancer-facts. Accessed October 25, 2010.

11. Green A, Williams G, Neale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet*. 1999;354(9180):723–729.

12. Tangrea JA, Edwards BK, Taylor PR, et al. Long-term therapy with low-dose isotretinoin for prevention of basal cell carcinoma: a multicenter clinical trial. *J Natl Cancer Inst*. 1992;84(5):328–332.

13. Bailey HH, Kim K, Verma AK, et al. A randomized, double-blind, placebo-controlled phase 3 skin cancer prevention study of {alpha}-difluoromethylornithine in subjects with previous history of skin cancer. *Cancer Prev Res (Phila Pa)*. 2010;3(1):35–47.

14. Yarosh D, Klein J, O'Connor A, et al. Effect of topically applied T4 endonuclease V in liposomes on skin cancer in xeroderma pigmentosum: a randomised study. *Lancet*. 2001;357(9260):926–929.

15. Black HS, Herd JA, Goldberg LH, et al. Effect of a low-fat diet on the incidence of actinic keratosis. *N Engl J Med*. 1994;330(18):1272–1275.

16. Black HS, Thornby JI, Wolf JE Jr., et al. Evidence that a low-fat diet reduces the occurrence of non-melanoma skin cancer. *Int J Cancer*. 1995;62(2):165–169.

17. An KP, Athar M, Tang X, et al. Cyclooxygenase-2 expression in murine and human nonmelanoma skin cancers: implications for therapeutic approaches. *Photochem Photobiol*. 2002;76(1):73–80.

18. Einspahr JG, Bowden GT, Alberts DS, et al. Cross-validation of murine UV signal transduction pathways in human skin. *Photochem Photobiol*. 2008;84(2):463–476.

19. Fischer S, Lo H, Gordon G, et al. Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor, and indomethacin against ultraviolet light-induced skin carcinogenesis. *Mol Carcinog*. 1999;25(4):231–240.

20. Pentland A, Schoggins J, Scott G, et al. Reduction of UV-induced skin tumors in hairless mice by selective COX-2 inhibition. *Carcinogenesis*. 1999;20(10):1939–1944.

21. Rundhaug JE, Mikulec C, Pavone A, et al. A role for cyclooxygenase-2 in ultraviolet light-induced skin carcinogenesis. *Mol Carcinog*. 2007;46(8):692–698.

22. Buckman SY, Gresham A, Hale P, et al. COX-2 expression is induced by UVB exposure in human skin: implications for the development of skin cancer. *Carcinogenesis*. 1998;19(5):723–729.

23. Butler GJ, Neale R, Green AC, et al. Nonsteroidal anti-inflammatory drugs and the risk of actinic keratoses and squamous cell cancers of the skin. *J Am Acad Dermatol*. 2005;53(6):966–972.

24. Grau MV, Baron JA, Langholz B, et al. Effect of NSAIDs on the recurrence of nonmelanoma skin cancer. *Int J Cancer*. 2006;119(3):682–686.

25. Foote JA, Harris RB, Giuliano AR, et al. Predictors for cutaneous basal- and squamous-cell carcinoma among actinically damaged adults. *Int J Cancer*. 2001;95(1):7–11.

26. Karagas MR, Stukel TA, Greenberg ER, et al. Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. Skin Cancer Prevention Study Group. *JAMA*. 1992;267(24):3305–3310.

27. Kerr DJ, Dunn JA, Langman MJ, et al. Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. *N Engl J Med*. 2007;357(4):360–369.

28. Thompson SC, Jolley D, Marks R. Reduction of Solar Keratoses by Regular Sunscreen Use. *N Engl J Med*. 1993;329(16):1147–1151.

29. Frost CA, Green AC. Epidemiology of solar keratoses. *Br J Dermatol*. 1994;151(4):455–464.

30. Ponsford MW, Goodman G, Marks R. The prevalence and accuracy of diagnosis of non-melanotic skin cancer in Victoria. *Australas J Dermatol*. 1983;24(2):79–82.

31. Frost CA, Green AC, Williams GM. The prevalence and determinants of solar keratoses at a subtropical latitude (Queensland, Australia). *Br J Dermatol*. 1998;139(6):1033–1039.

32. Weinstock MA, Bingham SF, Cole GW, et al. Reliability of counting actinic keratoses before and after brief consensus discussion: the VA topical tretinoin chemoprevention (VATTC) trial. *Arch Dermatol*. 2001;137(8):1055–1058.

33. National Cancer Institute. *Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE)*. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed October 25, 2010.

34. Naylor MF, Boyd A, Smith DW, et al. High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol*. 1995;131(2):170–175.

35. Tang JY, Aszterbaum M, Athar M, et al. Basal cell carcinoma chemoprevention with nonsteroidal anti-inflammatory drugs in genetically predisposed PTCH1+/- humans and mice. *Cancer Prev Res (Phila Pa)*. 2010;3(1):25–34.

36. Frost C, Williams G, Green A. High incidence and regression rates of solar keratoses in a Queensland community. *J Invest Dermatol*. 2000;115(2):273–277.

37. Harvey I, Frankel S, Marks R, et al. Non-melanoma skin cancer and solar keratoses, I: Methods and descriptive results of the South Wales Skin Cancer Study. *Br J Cancer*. 1996;74(8):1302–1307.

38. Clouser MC, Roe DJ, Foote JA, et al. Effect of non-steroidal anti-inflammatory drugs on non-melanoma skin cancer incidence in the SKICAP-AK trial. *Pharmacoepidemiol Drug Saf*. 2009;18(4):276–283.

39. Asgari MM, Chren M-M, Warton EM, et al. Association between nonsteroidal anti-inflammatory drug Use and cutaneous squamous cell carcinoma. *Arch Dermatol*. 2010;146(4):388–395.

40. van der Pols JC, Williams GM, Pandeya N, et al. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. *Cancer Epidemiol Biomarkers Prev*. 2006;15(12):2546–2548.

41. Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med*. 2006;355(9):885–895.

42. Bertagnolli MM, Eagle CJ, Zauber AG, et al. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med*. 2006;355(9):873–884.

43. Steinbach G, Lynch PM, Phillips RKS, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med*. 2000;342(26):1946–1952.

44. Chen K, Craig JC, Shumack S. Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. *Br J Dermatol*. 2005;152(3):518–523.

45. Kraemer K, DiGiovanna J, Moshell A, et al. Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. *N Engl J Med*. 1988;318(25):1633–1637.

46. Levine N, Moon T, Cartmel B, et al. Trial of retinol and isotretinoin in skin cancer prevention: a randomized, double-blind, controlled trial. Southwest Skin Cancer Prevention Study Group. *Cancer Epidemiol Biomarkers Prev*. 1997;6(11):957–961.

47. Black HS, Herd JA, Goldberg LH, et al. Effect of a low-fat diet on the incidence of actinic keratosis. *N Engl J Med*. 1994;330(18):1272–1275.

48. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med*. 2003;348(10):891–899.

49. Cho NL, Redston M, Zauber AG, et al. Aberrant crypt foci in the adenoma prevention with celecoxib trial. *Cancer Prev Res*. 2008;1(1):21–31.

50. Ansari KM, Rundhaug JE, Fischer SM. Multiple signaling pathways are responsible for prostaglandin E2-induced murine keratinocyte proliferation. *Mol Cancer Res*. 2008;6(6):1003–1016.

51. Rundhaug JE, Pavone A, Kim E, et al. The effect of cyclooxygenase-2 overexpression on skin carcinogenesis is context dependent. *Mol Carcinog*. 2007;46(12):981–992.

52. Sinicrope FA, Half E, Morris JS, et al. Cell proliferation and apoptotic indices predict adenoma regression in a placebo-controlled trial of

celecoxib in familial adenomatous polyposis patients. *Cancer Epidemiol Biomarkers Prevent.* 2004;13(6):920–927.

53. Stratton MS, Alberts DS. Current application of selective COX-2 inhibitors in cancer prevention and treatment. *Oncology (Williston Park).* 2002;16(5) (suppl 4):37–51.

54. Tjiu J-W, Chen J-S, Shun C-T, et al. Tumor-associated macrophage-induced invasion and angiogenesis of human basal cell carcinoma cells by cyclooxygenase-2 induction. *J Invest Dermatol.* 2009;129(4):1016–1025.

55. Rodriguez PC, Hernandez CP, Quiceno D, et al. Arginase I in myeloid suppressor cells is induced by COX-2 in lung carcinoma. *J Exp Med.* 2005;202(7):931–939.

56. Lee JM, Yanagawa J, Peebles KA, et al. Inflammation in lung carcinogenesis: new targets for lung cancer chemoprevention and treatment. *Crit Rev Oncol Hematol.* 2008;66(3):208–217.

57. Kerr DJ, Dunn JA, Langman MJ, et al. Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. *N Engl J Med.* 2007;357(4):360–369.

58. Solomon SD, McMurray JJV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med.* 2005;352(11):1071–1080.

59. Solomon SD, Wittes J, Finn PV, et al. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis. *Circulation.* 2008;117(16):2104–2113.

60. Pfizer Inc. *Celecoxib [package insert].* New York, NY; 2009.

61. Nelson C, Rigel D, Smith S, et al. Phase IV, open-label assessment of the treatment of actinic keratosis with 3.0% diclofenac sodium topical gel (Solaraze). *J Drugs Dermatol.* 2004;3(4):401–407.

Funding

Notes

Affiliations of authors: Moffitt Cancer Center and Research Institute, Tampa, FL (H-YL); Formerly of Department of Dermatology, Skin Diseases Research Center and the Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL (H-YL); Department of Dermatology, Skin Diseases Research Center and the Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL (CAE, WC, BEE); Veteran Affairs Medical Center, Birmingham, AL (CAE); Department of Pathology, Skin Diseases Research Center and the Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL (WB); MedImmune, Inc, Gaithersburg, MD (JLV); Formerly of Division of Cancer Prevention, National Cancer Institute, Bethesda, MD (JLV); Division of Cancer Prevention, National Cancer Institute, Bethesda, MD (ER, AU); Department of Dermatology, University of Rochester School of Medicine and Dentistry, Rochester, NY (APP), Department of Medicine, University of Wisconsin–Madison, Madison, WI (HB); Johns Hopkins University, Baltimore, MD (SK); Formerly of Department of Dermatology, University of Michigan, Ann Arbor, MI (SK); Department of Dermatology, University of California, Irvine, CA (KGL); Wright State University, Dayton, OH (MH); Formerly of Department of Medicine, Washington University School of Medicine, St Louis, MO (MH); Department of Dermatology, University of Texas M.D. Anderson Cancer Center, Houston, TX (MD); Abbott Laboratories, Abbott Park, IL (GBG); Formerly of Oncology/Immunodeficiency Research and Development, G.D. Searle, Skokie, IL (GBG).