Risk of basal cell carcinoma in a randomized clinical trial of aspirin and folic acid for the prevention of colorectal adenomas*

M.N. Passarelli,1 E.L. Barry,1 D. Zhang,2 P. Gangar,3 J.R. Rees,1 R.S. Bresalier,4 G. McKeown-Eyssen,5 M.R. Karagas1 and J.A. Baron1,2

1Department of Epidemiology, Geisel School of Medicine at Dartmouth, Hanover, NH, U.S.A.
2Department of Epidemiology, University of North Carolina, Chapel Hill, NC, U.S.A.
3Department of Pediatrics, University of Arizona, Tucson, AZ, U.S.A.
4Department of Gastroenterology, Hepatology, and Nutrition, University of Texas MD Anderson Cancer Center, Houston, TX, U.S.A.
5Epidemiology Division, Dalla Lana School of Public Health, University of Toronto, ON, Canada

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Summary

Background Aspirin may reduce the risk of several types of cancer.

Objectives To evaluate if folic acid is associated with risk of basal cell carcinoma (BCC).

Methods BCC incidence was evaluated in a randomized, double-blind, placebo-controlled clinical trial of aspirin (81 mg daily or 325 mg daily for ~3 years) and/or folic acid (1 mg daily for ~6 years) for the prevention of colorectal adenomas among 1121 participants with a previous adenoma. BCC was confirmed by blinded review of pathology reports.

Results One hundred and four of 958 non-Hispanic white participants were diagnosed with BCC over a median follow-up of 13.5 years. Cumulative incidence of BCC was 12% [95% confidence interval (CI) 7–17] for placebo, 16% (95% CI 11–21) for 81 mg aspirin daily and 15% (95% CI 10–20) for 325 mg aspirin daily [hazard ratio (HR) for any aspirin 1.45 (95% CI 0.93–2.26); HR for 81 mg daily 1.57 (95% CI 0.96–2.56); HR for 325 mg daily 1.33 (95% CI 0.80–2.20)]. BCC risk was higher with aspirin use in those without previous skin cancer but lower with aspirin use in those with previous skin cancer (Pinteraction = 0.02 for 81 mg aspirin daily; Pinteraction = 0.03 for 325 mg aspirin daily). Folic acid supplementation was unrelated to BCC incidence (HR 0.85; 95% CI 0.57–1.27).

Conclusions Neither aspirin nor folic acid treatment had a statistically significant effect on risk of BCC. Subgroup analysis suggested that chemopreventive effects of nonsteroidal anti-inflammatory drugs may be specific to those at high risk for BCC.

What’s already known about this topic?

- Clinical trials have found that short-term oral celecoxib may reduce the risk of basal cell carcinoma (BCC) in those with multiple actinic keratoses or basal cell nevus syndrome.
- Observational studies have reported no association or a modest decrease in the risk of developing BCC or cutaneous squamous cell carcinoma with use of aspirin or other nonsteroidal anti-inflammatory drugs.
- Dietary consumption of folic acid does not appear to be linked to BCC.
More than 1 million cases of basal cell carcinoma (BCC) are diagnosed annually in the U.S.A.\(^1\) Exposure to ultraviolet (UV) radiation is the primary risk factor for common skin cancers such as BCC.\(^1\) Aspirin (acetylsalicylic acid) and other commonly used nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of certain cancers,\(^6\) with consistent evidence across observational and randomized studies for malignancies of the large intestine, stomach and oesophagus.\(^4\) For BCC, some studies reported reduced risk among aspirin users, but others found no association.\(^5\) The topical NSAID diclofenac effectively treats actinic keratosis (AK), precursors for cutaneous squamous cell carcinomas (SCC),\(^6\) and a randomized clinical trial among individuals with numerous AKs found that the oral cyclooxygenase (COX)-2 inhibitor celecoxib reduced the short-term risk of BCC by 60%.\(^7\) Folic acid plays an essential role in DNA synthesis and repair, and folate deficiency is a hypothesized risk factor for cancer.\(^8\) Few studies have specifically evaluated folic acid exposure and BCC risk. Large prospective cohort studies observed that high dietary folate intake was associated with a modest increase in risk of BCC, but not SCC.\(^9,10\) The Aspirin/Folate Polyp Prevention Study provided an opportunity to investigate both aspirin and folic acid use and the incidence of BCC in a randomized, double-blind, placebo-controlled study.

### Materials and methods

#### Study design

Details of the study design and primary findings of the Aspirin/Folate Polyp Prevention Study have been previously published.\(^11,12\) From July 1994 to March 1998, patients aged 21–80 years recently diagnosed with colorectal adenomas were enrolled to evaluate the efficacy of aspirin, folic acid or both to prevent future adenomas. The phase III study had a 3 × 2 factorial design, comparing 81 mg aspirin daily and 325 mg aspirin daily with placebo and 1 mg folic acid daily with placebo. Participants were recruited from medical centres affiliated with Dartmouth-Hitchcock Medical Center (Lebanon, NH, U.S.A.); University of North Carolina (Chapel Hill, NC, U.S.A.); University of Southern California (Los Angeles, CA, U.S.A.); University of Colorado (Denver, CO, U.S.A.); Henry Ford Health System (Detroit, MI, U.S.A.); University of Toronto (Toronto, ON, Canada); University of Iowa (Iowa City, IA, U.S.A.); Cleveland Clinic Foundation (Cleveland, OH, U.S.A.); and University of Minnesota (Minneapolis, MN, U.S.A.).

Exclusion criteria included a history of invasive colorectal cancer, familial polyposis, inflammatory bowel disease (IBD) and conditions treated or worsened with aspirin or folate, such as anaemia, vitamin B12 deficiency, arthritis and atherosclerotic cardiovascular disease. After a 3-month placebo run-in period, 1121 participants taking ≥ 80% of allocated pills underwent blocked randomization stratified by centre, sex and age (Fig. S1; see Supporting Information). A baseline questionnaire ascertained demographics and medical history, including previous diagnosis of melanoma and nonmelanoma skin cancer, but did not distinguish subtypes. Institutional review boards at the nine participating clinical centres approved study protocols; all participants provided written informed consent. The study was registered at ClinicalTrials.gov (NCT00272324).

#### Follow-up and outcome ascertainment

Treatment with aspirin/placebo ended after a surveillance colonoscopy anticipated 3 years after a baseline colonoscopy. To assess longer exposure to folic acid, participants were invited to continue folic acid/placebo for an additional 3- or 5-year colonoscopy interval before 1 October 2004.\(^12\) Observational follow-up continued after the end of the active treatment periods. Questionnaires were completed every 4 months during the treatment phase to assess adherence to study pills, use of prescription and over-the-counter medications, nutritional supplements and the occurrence of medical events. A similar questionnaire was completed annually during observational follow-up until withdrawal or 31 December 2006. A final questionnaire was completed between 1 February 2010 and 31 May 2012 in order to update medication use and medical events since the previous contact. Blinded study physicians reviewed clinical records to verify reported events. BCC or SCC histology was confirmed from pathology reports. Anatomical location of lesions was ascertained from pathology or clinical records.

#### Statistical analyses

Time to first BCC diagnosis was calculated from date of randomization and censored at date of death or last contact. Cumulative incidence was estimated with the Kaplan–Meier method, and hazard ratios (HRs) estimated from proportional

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**What does this study add?**

- In the Aspirin/Folate Polyp Prevention Study, a randomized, double-blind, placebo-controlled clinical trial, neither aspirin (81 mg daily or 325 mg daily for approximately 3 years) nor folic acid (1 mg daily for approximately 6 years) resulted in a statistically significant alteration in the risk of first primary BCC after randomization.
- Subgroup analysis revealed that the treatment effect for aspirin differed for those with and without a history of skin cancer.
hazards regression with adjustment for the randomization stratification variables (centre, sex and age). Given the low prevalence of skin cancer in nonwhite populations, we excluded all study participants that self-reported a race/ethnicity other than non-Hispanic white. All analyses were performed according to the intention-to-treat approach.

Effect modification of the aspirin effect by folic acid treatment (and vice versa) was assessed by including an interaction term in regression models. A subgroup analysis was conducted to address potential effect modification by geographical location of study centre as a proxy for overall UV exposure [distinguishing study centres in Iowa, Michigan, Minnesota, New Hampshire, Ohio and Ontario from study centres in California, Colorado and North Carolina (areas with generally more UV exposure)]. A similar analysis assessed effect modification by previous history of any skin cancer (including any diagnoses prior to baseline of BCC, SCC, melanoma or other malignancies of the skin). SCC was included as a secondary end point, but, owing to small numbers, subgroup analyses were not considered for SCC. The proportional hazards assumption was assessed by testing for the statistical significance of interaction terms with log-transformed time since randomization. Two-sided \( P \)-values \( \leq 0.05 \) were considered to be statistically significant. All analyses were performed using R version 3.3.0.

**Results**

**Randomization, follow-up and outcomes**

The original study included 1121 participants randomized to aspirin or placebo, including a total of 100 participants who had been randomized to aspirin or placebo prior to the time of folic acid randomization. After the exclusion of 163 participants who were not non-Hispanic white, and thus at very low risk for skin cancer, a total of 958 participants were included in analyses for aspirin (329 assigned to 81 mg aspirin daily; 322 assigned to 325 mg aspirin daily; 307 assigned to placebo) and 874 were included in analyses for folic acid (443 assigned to 1 mg folic acid daily; 431 assigned to placebo). The distribution of participant characteristics was similar across treatment arms at baseline (Table 1). The average age of the participants was 57 years and 64% were men. The majority (74%) were enrolled from study centres in the northern U.S.A. or Canada. A total of 47 (4.9%) reported a previous diagnosis of BCC, SCC, melanoma or other skin cancer.

During the first year of follow-up, 94% of participants reported taking at least 85% of aspirin tablets and 74% reported no use of nonprotocol aspirin or NSAIDs outwith the study (4% using for > 4 days a month). Adherence to folic acid or placebo was similar. Of the 958 randomized participants included in this analysis, 874 (91.2%) completed a planned surveillance colonoscopy approximately 3 years after the baseline colonoscopy; of these, 637 (72.9%) continued folic acid/placebo treatment and 237 (27.1%) discontinued study pills but agreed to be followed observationally for study end points. The median time on aspirin or placebo was 2.6 years and the median time on folic acid or placebo was 6.0 years. During a median follow-up of 13.5 years after randomization, 104 (10.8%) participants were diagnosed with BCC (24 during the aspirin treatment period and 80 afterward). The majority of BCC lesions were found on the head or neck (Table S1; see Supporting Information). A total of 31 patients were diagnosed with SCC (four during the aspirin treatment period and 27 afterward).

### Table 1 Baseline characteristics of non-Hispanic white participants in the Aspirin/Folate Polyp Prevention Study

| Characteristic at baseline | Aspirin treatment assignment | Folic acid treatment assignment* |
|----------------------------|------------------------------|---------------------------------|
|                            | Aspirin placebo (n = 307)    | Aspirin 81 mg daily (n = 329)    | Aspirin 325 mg daily (n = 322)    | Folic acid placebo (n = 431) | Folic acid 1 mg daily (n = 443) |
| Mean ± SD age (years)      | 57.5 ± 10.0                  | 57.1 ± 9.7                      | 58.0 ± 9.3                       | 57.7 ± 9.3                   | 57.4 ± 9.8                      |
| Men                        | 190 (61.9)                   | 214 (65.0)                      | 206 (64.0)                       | 277 (64.3)                   | 282 (63.7)                      |
| Mean ± SD BMI (kg m⁻²)     | 27.2 ± 4.3                   | 27.3 ± 4.5                      | 27.3 ± 4.3                       | 27.3 ± 4.3                   | 27.4 ± 4.6                      |
| Current cigarette smoker   | 40 (13.1)                    | 43 (13.1)                       | 47 (14.6)                        | 57 (13.3)                    | 59 (13.3)                       |
| Aspirin useb               | 28 (9.1)                     | 35 (10.6)                       | 27 (8.4)                         | 53 (12.3)                    | 35 (7.9)                        |
| Nonaspirin NSAID use       | 19 (6.2)                     | 22 (6.7)                        | 24 (7.5)                         | 27 (6.3)                     | 35 (7.9)                        |
| Mean ± SD plasma folate (ng mL⁻¹) | 10.5 ± 8.1                  | 10.7 ± 8.2                      | 10.5 ± 7.1                       | 10.8 ± 7.7                   | 10.8 ± 8.1                      |
| High UV study centreetc    | 77 (25.1)                    | 89 (27.1)                       | 83 (25.8)                        | 108 (25.1)                   | 117 (26.4)                      |
| History of skin cancerd    | 12 (3.9)                     | 18 (5.5)                        | 17 (5.3)                         | 22 (5.1)                     | 21 (4.7)                        |

Data are n (%) unless otherwise indicated. Two participants were missing data for body mass index (BMI), three participants were missing data for smoking status and 106 participants were missing data for plasma folate. NSAID, nonsteroidal anti-inflammatory drug; UV, ultraviolet. *Excludes 84 participants randomized to aspirin/placebo only. †Defined as use for > 4 days per month, on average, over the past year. ‡High-UV study centres located in California, Colorado and North Carolina. Low-UV study centres located in Iowa, Michigan, Minnesota, New Hampshire, Ohio and Ontario. §Self-reported personal history of basal cell carcinoma, squamous cell carcinoma, melanoma or other skin cancer.
Aspirin treatment

The 15-year cumulative incidence of BCC was 12% [95% confidence interval (CI) 7–17] for placebo, 16% (95% CI 11–21) for 81 mg aspirin daily and 15% (95% CI 10–20) for 325 mg aspirin daily (Fig. 1). Relative to placebo, participants assigned any dose of aspirin were more likely to develop BCC (HR 1.45; 95% CI 0.96–2.56) for 81 mg aspirin daily; HR 1.33 (95% CI 0.80–2.20) for 325 mg aspirin daily). For SCC, the 15-year cumulative incidence was 4% (95% CI 1–7) for placebo, 4% (95% CI 2–6) for 81 mg aspirin daily and 6% (95% CI 2–9) for 325 mg aspirin daily. HRs for SCC were in the same direction as for BCC, but were also not statistically significant (Table S2; see Supporting Information).

There was evidence that the aspirin treatment effect on BCC risk depended on whether participants had a history of skin cancer (Table 2; Pinteraction = 0.02 for 81 mg aspirin daily vs. placebo; Pinteraction = 0.03 for 325 mg aspirin daily vs. placebo). For the 911 participants who reported no history of skin cancer at baseline, BCC risk was higher with aspirin treatment throughout the follow-up (P = 0.04 for 81 mg aspirin daily vs. placebo; P = 0.11 for 325 mg aspirin daily vs. placebo). However, for the 47 participants who did report a history of skin cancer, BCC risk was lower with aspirin treatment (P = 0.15 for 80 mg aspirin daily vs. placebo; P = 0.09 for 325 mg aspirin daily vs. placebo). Although the cumulative incidence of BCC during the study was higher in participants recruited from medical centres in regions with more daily sunshine exposure, the aspirin treatment effect did not appear to be modified by geography. There was also no evidence of interaction between aspirin and folic acid treatment.

Participants began using aspirin and other NSAIDs frequently after the intervention period, but this did not vary substantially by treatment assignment (Table S3; see Supporting Information). Estimates for randomized aspirin treatment assignment changed very little when additionally adjusted for self-reported use of nonprotocol aspirin and NSAIDs (> 4 days per month) as a time-varying variable over all available follow-up, including after the treatment period [HR for 81 mg aspirin daily 1.57 (95% CI 0.96–2.56; P = 0.07); HR for 325 mg aspirin daily 1.33 (95% CI 0.81–2.20; P = 0.27)]. Across all analyses, we concluded that modelling proportional hazards over time was appropriate. Results were also similar using data from the full study of 1121 participants without excluding the 163 individuals who reported a race/ethnicity other than non-Hispanic white (data not shown).

![Fig 1. Kaplan–Meier estimates of the cumulative incidence of basal cell carcinoma (BCC) according to (a) randomized aspirin treatment assignment and (b) randomized folic acid treatment assignment in the Aspirin/Folate Polyp Prevention Study.](https://example.com/fig1.png)
### Table 2

| Study Centre | At baseline | Placebo | Aspirin 81 mg daily | Aspirin 325 mg daily | HR (95% CI) |
|--------------|-------------|---------|-------------------|-------------------|-----------|
| Low UV       | 16/83 (19.3) | 20/239 (8.4) | 15/80 (19.0) | 31/305 (10.2) | 0.87 (0.57–1.36) |
| High UV      | 17/230 (7.4) | 14/19 (7.4)  | 14/19 (7.4)  | 14/19 (7.4)  | 1.00 (0.57–1.77) |

**Discussion**

The 15-year cumulative incidence of BCC was 15% (95% CI 11–19) for placebo and 13 (95% CI 9–16) for 1 mg folic acid daily. Folic acid supplementation at 1 mg daily was not associated with risk of BCC (Fig. 1), and was consistent across geography and history of skin cancer (Table 3). In total, 47 participants were diagnosed with BCC during the folic acid treatment period and 57 were diagnosed afterward. The folic acid treatment effect was also not statistically significant for risk of first primary SCC after randomization (Table S2; see Supporting Information).

**Folic acid treatment**

In the Aspirin/Folate Polyp Prevention Study, daily use of low- or high-dose aspirin did not decrease the overall risk of BCC. Instead, there was an unexpected nonsignificant suggestion of an increased risk. Only in the small subgroup of participants with a history of skin cancer did aspirin treatment appear to reduce risk of BCC, consistent with the magnitude and direction of treatment effects observed in a previous clinical trial of oral celecoxib in individuals with multiple AKs. Small numbers of SCCs precluded detailed analysis, but the overall direction and magnitude of the effect for low- and high-dose aspirin did not seem substantially different for SCC than BCC. In addition, we did not observe a statistically significant treatment effect for folic acid supplementation at 1 mg daily for about 6 years.

How aspirin affects skin responses to UV radiation is not fully understood. Observation of a delay in cutaneous erythema from UV light with aspirin treatment was made 50 years ago, but recent phototoxic reactions have also been attributed to certain anti-inflammatory agents. Cutaneous adverse reactions to aspirin are rare and often acute; a type II hypersensitivity in those with chronic idiopathic urticaria is recognized. Preclinical studies point to an important role for COX-2 in the development of UV-induced skin cancers. COX-2 expression has antiapoptotic and proliferatory effects on keratinocytes, and is overexpressed in AKs, BCCs and SCCs. Treatment of UV-exposed hairless mice with celecoxib and nonselective indomethacin, both in oral and topical preparations, reduces the occurrence of cutaneous tumours, but whether COX-2 inhibition is effective as primary or secondary preventive remains unclear as many studies have focused on new lesions in mice with at least one previous tumour.

Two placebo-controlled randomized clinical trials have evaluated oral celecoxib therapy for prevention of keratinocyte carcinoma in high-risk individuals. Elmets et al. found that 200 mg celecoxib for 9 months reduced the incidence of BCC by 56% in 11 months relative to placebo in a study of 240 individuals with ≥ 10 AKs. Of note, this study was designed to evaluate actinic lesions as primary end points, and celecoxib had no effect on the regression of prevalent AKs or on the incidence of new AKs. A trial of 200 mg celecoxib twice daily
Aspirin, folic acid and risk of basal cell carcinoma, M.N. Passarelli

 Among members of Kaiser Permanente Northern California in the same direction as our findings. A case

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 tionnaire response to NSAID therapy that may depend on skin characteris-

 tics. A case–control study found that the odds ratio for SCC increased with increasing levels of arachidonic acid in red blood cell membranes among those who did not report current use NSAIDs. There were noted differences in the dose–response relationship in models that did, and did not, adjust for previous history of AKs. A phase II study involving 90-day treatment of forearm skin with topical difluoromethylornithine (DFMO) in combination with topical diclofenac found that actinic damage to skin cells measured by karyometry unexpectedly increased combination with topical diclofenac found that actinic damage to skin cells measured by karyometry unexpectedly increased

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carcinoma, particularly in the luminal gastrointestinal tract. Observational studies of the association of aspirin or NSAID use with risk of BCC and SCC have generally reported either no association or a modest decrease in risk.5,25 Our findings of an inverse association only among those with a history of skin cancer,16 and, consequently, many preclinical and clinical studies have focused on celecoxib rather than aspirin, which is not COX-2 selective.24

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 Among members of Kaiser Permanente Northern California identified a 38% increase in SCC risk for those who used aspirin once a week for > 1 year relative to less frequent and never users, but this was not statistically significant (adjusted relative risk 1.38; 95% CI 0.96–1.97).27

 The factorial design of the Aspirin/Folate Polyp Prevention Study permitted an evaluation of whether aspirin and folic acid treatment interact, and we did not find evidence of this interaction. In addition, there was no suggestion that the treat-

 ment effects differed by geography, which may offer some characterization of the participant’s cumulative sun exposure.

 We also considered the potential of interaction with previous history of skin cancer, given that previous clinical trials of NSAIDs have focused on populations with numerous precancerous lesions, that observational studies have reported inverse associations with NSAID use specific to individuals at high risk for skin cancer, and that studies of BCC incidence often do not exclude participants with BCC history because recurrence of the condition is relatively common. Our observation of modification of the aspirin treatment effect by baseline history of any type of skin cancer, if confirmed in other populations, suggests that aspirin may play a role in BCC susceptibility in some individuals, while potentially preventing BCC in others.

 Molecular mechanisms whereby aspirin could have opposing effects on keratinocyte proliferation depending on the baseline level of actinic damage remains unclear. Findings from previous clinical studies in humans underscore a complex cutaneous response to NSAID therapy that may depend on skin characteristics. A case–control study found that the odds ratio for SCC increased with increasing levels of arachidonic acid in red blood cell membranes among those who did not report current use NSAIDs. There were noted differences in the dose–response relationship in models that did, and did not, adjust for previous history of AKs.28 A phase II study involving 90-day treatment of forearm skin with topical difluoromethylornithine (DFMO) in combination with topical diclofenac found that actinic damage to skin cells measured by karyometry unexpectedly increased for DFMO alone, diclofenac alone and DFMO with diclofenac.29

 Interestingly, the motivation for testing the addition of DFMO to NSAIDs for treatment of skin was based primarily on evidence from chemoprevention studies conducted among those with colorectal adenomas.30

 In addition to aspirin, our study also investigated daily supplementation with 1 mg folic acid. Total folic levels in the human dermis and epidermis are known to correlate with circulating concentrations,31 and UV exposure can degrade folic
acid present in blood and skin cells. Preclinical and clinical evidence of whether folic acid supplementation alters skin cancer risk is limited. A meta-analysis of randomized studies of folic acid supplementation showed no clear effect on cancer risk across multiple cancer types, but did not include non-melanoma skin cancer.6 Our study suggests no association between folic acid supplementation at 1 mg daily for about 6 years and risk of first primary BCC or SCC after randomization.

Strengths of the Aspirin/Folate Polyp Prevention Study include its randomized design, which helped control confounding by baseline factors and prevented bias from self-report of medication use. The long follow-up period provided sufficient time to evaluate delayed effects of the study treatments. Adherence was excellent, and drop-out rate was low and unrelated to treatment. Patients with IBD, who may be at increased risk of BCC from immunosuppressive therapy with thiopurines, were ineligible. The cumulative incidence of BCC over the follow-up period was consistent with age-specific nationwide estimates.

The study also has limitations. The Aspirin/Folate Polyp Prevention Study was not originally designed to examine skin cancer, and did not collect information on sun exposure history, skin type or pre-existing AKs. However, based on the randomized design it is expected that these factors would be balanced according to treatment assignment. We believe that it is unlikely that participants in the aspirin treatment arms would have been subject to more intense sun exposure or skin cancer screening after the study treatment period than those in the placebo arm, but we cannot directly test this assumption. Although all occurrences of BCC and SCC during the follow-up period were verified by pathology reports, history of skin cancer at baseline was based on self-report, not validated, and not specified by subtype.

Participants were followed-up for several years beyond the 3-year aspirin treatment period, and over time the balanced distribution of potential confounding variables created by randomization could have been lost. In particular, aspirin use occurring after the end of the study treatment period may have affected our findings, but because self-reported use over several years following the end of the treatment period did not substantially differ by treatment assignment, any influence of uncontrolled use over an extended follow-up period may be modest. Although we did not observe an aspirin dose–response relationship for BCC incidence, which would have provided additional support for a causal mechanism, it should be noted that there was also no evidence of a dose–response for the chemopreventive effects of aspirin on the primary colorectal adenoma end points in this trial.

Evidence of a potentially increased risk of BCC over long-term follow-up for those without a personal history of skin cancer was unexpected and warrants further investigation. Subgroup analyses should always be interpreted with caution, and we acknowledge that secondary analyses of a completed clinical trial should be considered exploratory. Larger clinical trials designed to evaluate BCC incidence will likely have improved statistical power relative to our study. However, our results may inform the planning of future clinical trials of NSAID treatment for skin cancer prevention with broader inclusion criteria than the previous studies that have focused on patients with multiple AKs. As there is limited previous evidence from randomized studies of NSAID use with long-term skin cancer outcomes, further research is needed to determine whether daily use of these drugs can have opposing effects in those at low and high risk of developing skin cancer.

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Aspirin, folic acid and risk of basal cell carcinoma, M.N. Passarelli et al.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Fig S1. Flow of participants in aspirin/placebo arms of the Aspirin/Folate PolyP Prevention Study.

Table S1 Counts of non-Hispanic white participants diagnosed with basal cell carcinoma and/or cutaneous squamous cell carcinoma during the Aspirin/Folate PolyP Prevention Study.

Table S2 Hazard ratios of cutaneous squamous cell carcinoma for aspirin and folic acid treatment assignment.

Table S3 Self-reported use of non-protocol aspirin and non-steroidal anti-inflammatory drugs according to study year.