Analgesic and nonsteroidal anti-inflammatory use in relation to nonmelanoma skin cancer: A population-based case-control study

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Background: Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are potentially chemopreventive.

Objective: We examined the relation between NSAID use and nonmelanoma skin cancer in a population-based case-control study.

Methods: NSAID and analgesic use was analyzed in 1484 participants: 535 with squamous cell carcinoma (SCC), 487 with basal cell carcinoma (BCC), and 462 control subjects.

Results: Use of NSAIDs, particularly aspirin, was associated with a reduced odds ratio (OR) of SCC, especially tumors positive for p53 (OR 0.29; 95% confidence interval 0.11-0.79) or with *PTCH* loss of heterozygosity (OR 0.35; 95% confidence interval 0.13-0.96). Although not considered a NSAID, decreased ORs of both basal cell carcinoma and SCC were observed in relation to use of paracetamol (acetaminophen). Risk of BCC was unrelated to NSAID use.

Limitations: Self-reported drug use was a limitation.

Conclusions: This study supports the hypothesis that NSAIDs, aspirin in particular, may reduce risk of SCC and may affect specific molecular subtypes of SCC. (J Am Acad Dermatol 2011;65:304-12.)

Key words: basal cell carcinoma; case-control study; nonmelanoma skin cancer; nonsteroidal anti-inflammatory drug; p53; PTCH; squamous cell carcinoma.

Nonmelanoma skin cancer (NMSC) is the most common form of cancer in the United States with more than 1 million skin cancers diagnosed annually. Between 40% and 50% of Americans who live to age 65 years will have NMSC at least once.[1] The major environmental risk factor for the development of NMSC is ultraviolet radiation (UVR) exposure.[2] In addition to UVR, risk factors for NMSC include exposure to ionizing radiation, arsenic, or organic chemicals; human papillomavirus infection; and immunosuppression.[2]

Two important tumor suppressor genes in the pathogenesis of NMSC are *TP53* and *PTCH*. *PTCH* is the human homolog of the *Drosophila* tumor suppressor gene, Patched, and encodes a receptor that mediates Hedgehog signaling,[3] a key pathway in the

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Conflicts of interest: None declared.

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regulation of cell growth and differentiation and tumorigenesis. PTCH represses Hedgehog target gene expression through its interaction with Smoothened, and this repression is relieved when Sonic Hedgehog binds *PTCH*, or after *PTCH* has been inactivated through mutation. Inactivating mutations in *PTCH* result in constitutive activation of Hedgehog signaling and are a common event in sporadic basal cell carcinoma (BCC).[4] Mutations in *PTCH* are associated with Gorlin syndrome, a rare autosomal dominant hereditary nevoid BCC syndrome.[5] Although less commonly recognized, *PTCH* is also frequently mutated in squamous cell carcinoma (SCC). In a previous report, we demonstrated a high prevalence of any *PTCH* loss of heterozygocity (LOH) in both BCC (75.5%) and SCC (60.8%) tumors although BCCs were more likely to contain LOH than SCCs ($P < .009$).[6]

CAPSULE SUMMARY

- Reported use of aspirin was associated with a reduced risk of squamous cell carcinoma in a large population-based case-control study.
- The association between squamous cell carcinoma and aspirin use was seen primarily in molecular subtypes positive for p53 or with *PTCH* loss of heterozygosity.
- In contrast, use of nonsteroidal anti-inflammatory drugs was unrelated to risk of basal cell carcinoma.

TP53 is the most frequently mutated gene in human cancer,[7] and is mutated in both SCC and BCC.[8] The p53 protein regulates signaling pathways involved in cell division and apoptosis, and serves as a sensor of cytotoxic stress. Mutations in *TP53* occur early in the progression of SCC, and may facilitate genomic instability and subsequent acquisition of additional genetic mutations.[9]

In addition to mutations in these tumor suppressor genes, another genetic event associated with NMSC is overexpression of cyclo-oxygenase (*COX*)*2* (now designated prostaglandin-endoperoxide synthase 2). *COX2* is involved in the synthetic pathway of prostaglandins. The *COX2* isoenzyme induces antiapoptotic, proangiogenic, and other tumorigenic pathways.[10] Although *COX2* is not overexpressed in BCC, it is in 40% of SCC tumors.[11] This has led to the suggestion that nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, that inhibit *COX2* may be useful in the treatment or prevention of SCC. Consistent with this hypothesis, in mouse carcinogenesis models, both systemic and topical application of NSAIDs inhibited the formation of SCC, and specifically UVR-induced lesions.[12,13] A number of clinical trials have demonstrated regression of actinic keratoses in response to the topical NSAID, diclofenac (a potent *COX2* inhibitor).[14-16]

Although both animal models and small clinical trials suggest a protective effect of NSAIDs on NMSC, there are limited epidemiologic data. A nested case-control study of SCC from Australia (n = 86 cases and 187 controls) found a dramatically reduced risk among long-term NSAID users (ie, odds ratio [OR] = 0.37 for use ≥ 2 times/wk and OR = 0.07 for use ≥ 8 times/wk for ≥ 5 years) compared with nonusers.[17] An analysis of NSAID use in 1402 participants in a retinoid skin cancer prevention trial (SKICAP-AK) in Arizona indicated reduced hazard ratios (HRs) for both BCC (HR 0.43; 95% confidence interval [CI] 0.25-0.83) and SCC (HR 0.49; 95% CI 0.28-0.87) among participants who were new users of NSAIDs, but not among continuous users.[18] Similarly, data from a prevention trial found evidence of a decreased risk of subsequent SCC occurrences in patients with NMSC who used NSAIDs in the year before diagnosis (OR 0.71; 95% CI 0.48-1.04).[19]

To test whether NSAIDs might exert a chemopreventive effect on NMSC development, we assessed NSAID and analgesic use in a population-based case-control study of 1484 participants. We explored potential associations between BCC and SCC tumors separately, and for SCC tumors, by specific histologic findings (adjacent actinic keratoses) and anatomic location. We also examined whether any relation between NSAIDs and SCC tumors was associated with molecular alterations in *TP53* or *PTCH*.

METHODS

Study group

To identify cases for our study, we enlisted the collaboration of dermatologists and pathology laboratories throughout New Hampshire and bordering regions. We selected a random sample of incident BCC cases (for efficiency) and all cases of incident invasive SCC diagnosed from July 1, 1997, through March 31, 2000. The sample of BCC cases was drawn concomitantly with the SCC cases (at a ratio of about 1:1). These BCC cases were selected to represent the entire diagnosis group for anatomic site, age, and sex. Eligible patients included New Hampshire residents who were age 25 to 74 years at the time of diagnosis, spoke English, and had a listed telephone number. A small percentage (<1%) were excluded because of physician refusal to contact. We identified 1403 potentially eligible participants. Of these, we