Objective: To determine whether ongoing use of a cyclooxygenase (COX) inhibitor is associated with a reduction in mortality and disease recurrence after head and neck cancer treatment.

Design: Retrospective case-control study.

Patients: A total of 325 potential subjects with head and neck squamous cell carcinoma were identified using an electronic patient database.

Main Outcome Measure: The rate of COX inhibitor use among patients who had died or whose disease had recurred (cases) was compared with the rate of use among survivors or those without recurrence (controls). The comparison was controlled for tumor site, tumor stage, treatment received, age, sex, race, smoking, and alcohol use.

Results: The 325 patients were compared by logistic regressions, with recurrence rate and survival status as the dependent variables. There was no difference in COX inhibitor exposure between patients with recurrence and those with no recurrence (P = .42) or between survivors and those who died of disease (P = .66). The median survival of COX inhibitor users, however, was 96 months, compared with 47 months in nonusers. The only independent variable with a significant impact on recurrence and survival was tumor stage at the time of diagnosis.

Conclusions: Although preliminary in vitro studies suggest an antitumor effect of COX inhibitors in head and neck cancer, this study found no difference in head and neck cancer recurrence or survival in nonselective COX inhibitor users vs nonusers. A randomized, double-blinded controlled trial is needed to determine if COX inhibitors are an effective chemopreventive therapy in patients with head and neck cancer.

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Cancers of the head and neck are challenging to treat and often carry a poor prognosis despite aggressive surgical and oncologic therapy. Oral cyclooxygenase (COX) inhibitors (eg, aspirin; nonsteroidal anti-inflammatory drugs [NSAIDs]; and selective COX-2 inhibitors) have been shown to reduce disease recurrence and incidence rates in several types of carcinomas including colon and lung cancers. Moreover, there is an ever-expanding body of evidence that suggests COX enzymes are important in the malignant transformation of head and neck cancer. Oral cancers and premalignant lesions demonstrate increased expression of COX-2 enzyme compared with normal adjacent tissue. In addition, oral carcinomas with increased expression of COX-2 are more aggressive with higher rates of lymph node metastasis and postoperative recurrence compared with tumors that weakly express COX-2.

Expression of COX-2 confers radioresistance in head and neck cancer cell lines, which can be countered by the use of selective COX-2 inhibitors. The mechanism of action by which COX enzymes influence tumor development are not fully delineated but may be related to COX-induced up-regulation of prostaglandin E2 (PGE2). Increased levels of PGE2 in the local tumor environment promote angiogenesis, thwart anti-tumor immune responses, and may reduce programmed cell death within tumor cells. In addition, COX inhibitors inhibit the proliferation of oral cancer cell lines by reducing the production of PGE2.

Although in vitro studies support the antitumor effects of COX inhibitors in head and neck cancer cell lines, data supporting the use of these drugs in head and neck cancer clinical care are limited. The present study aimed to determine whether ongoing use of a COX inhibitor is associated with decreased mortality and disease recurrence after head and neck cancer treatment.
A retrospective case-control study was performed to test the null hypothesis of no difference in the rate of COX inhibitor use among patients with head and neck cancer recurrence and/or mortality (cases) compared with patients with head and neck cancer without recurrence and/or mortality (controls). The study was approved by the institutional review board of the Medical University of South Carolina and the Ralph H. Johnson VA Medical Center, Charleston, SC. All patients with a diagnosis of squamous cell carcinoma of the head and neck prior to 2003 were identified from the cancer registry of the Ralph H. Johnson VA Medical Center. The year 2003 was made the stop date to allow a minimum of 24 months of follow-up time for all survivors.

A total of 325 potential subjects were identified. Medical charts were reviewed to record the dependent and independent variables to be studied by logistic regression. Independent variables included age, sex, race, tumor site, tumor stage, treatment, tobacco use, alcohol use, COX inhibitor exposure, and COX inhibitor type. The dependent (outcome) variables of interest included patient survival status and disease recurrence. Survival status was defined as alive, dead of disease, or dead of other causes. Survival time was defined as the time in months from diagnosis to either death or last follow-up. Recurrence status was defined as either the presence or absence of disease recurrence (local, regional, or distant) at the time of last follow-up (minimum, 24 months). The independent variable (risk factor) of interest was the use of COX inhibitors. Patients were classified as COX inhibitor users if they had a standing order for daily COX inhibitor therapy in their outpatient pharmacy orders. Cyclooxygenase inhibitor use was classified as the use of aspirin, NSAIDs, selective COX-2 inhibitor, or a combination thereof. Additional independent variables recorded to control for differences between COX inhibitor users and nonusers included patient age, sex, tumor site, tumor stage, treatment received, and tobacco and alcohol use. Treatment was categorized as surgery only, irradiation only, chemoradiation, surgery with irradiation, combination of the 3, or no treatment. Tobacco and alcohol use were separately characterized as current, previous, or never. A Kaplan-Meier survival curve was generated to compare COX inhibitor users to nonusers with respect to survival status. Test results were considered significant at $P<.05$.

## RESULTS

A total of 325 subjects with head and neck squamous cell carcinoma were identified from the cancer registry. The sample consisted of 323 men and 2 women, with a mean age at diagnosis of 66 years (range, 42-92 years). Medication data were available for 319 subjects, of whom 232 (73%) were COX inhibitor users and 87 (27%) were nonusers. The COX inhibitor group included 44 baby aspirin users (14%), 93 NSAID users (29%), and 95 combination users (30%), and no selective COX inhibitor users.

Cancer sites included oral cavity in 74 patients (23%), oropharynx in 89 patients (27%), larynx/hypopharynx in 100 patients (31%), other sites (eg, sinonasal and temporal bone) in 30 patients (9%), and unclassified in 32 patients (10%). Cancer stage was I or II in 35% of cases, stage III in 14%, and stage IV in 51%. Treatment information was available for 277 subjects and consisted of surgery alone in 53 (19%) of cases, irradiation alone in 66 (24%), surgery and irradiation in 94 (34%), chemoradiation in 55 (20%), and no treatment in 9 (3%).

Recurrence data were available for 267 subjects, 131 (49%) of whom experienced recurrence at a mean follow-up time of 33 months. Survival data were available for 290 subjects, and the mortality rate in these patients was 49% (142 patients). Of those who died, head and neck cancer was the cause of death in 68% (97 patients).

Logistic regressions were performed for the dependent variables (1) recurrence and (2) survival (Table), while controlling for various independent variables. There was no difference in COX inhibitor exposure between patients with recurrence and those with no recurrence ($P = .88$) or between survivors and those who died of disease ($P = .34$). Tumor stage at the time of diagnosis was the only independent variable with a significant impact on recurrence ($P = .03$) and survival ($P = .05$).

Kaplan-Meier curves were generated to determine whether there was a difference in disease-free survival (Figure 1) and overall survival time between COX inhibitor users and nonusers (Figure 2). Although the curves suggest a trend of improved disease-free and overall survival in COX inhibitor users, these differences were nonsignificant. The median disease-free and overall survival times of COX inhibitor users were greater than those of nonusers in both cases. Likewise, there was no significant difference in overall survival by COX inhibitor type among COX users (Figure 3).

The mortality rate from head and neck squamous cell carcinoma has not changed in the last 25 years despite advances in therapy that have improved the quality of life and function in patients with head and neck cancer. The propensity for locoregional recurrence of head and neck cancer after aggressive treatment has generated interest in

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### Table. Comparison of Risk Factors Between Patients With and Without Recurrence and Between Survivors and Nonsurvivors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (SE) [95% CI]</th>
<th>Z Score</th>
<th>P Value (&gt;z)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparison Between Patients With and Without Recurrence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX inhibitor use</td>
<td>0.94 (0.39) [0.42-2.10]</td>
<td>−0.15</td>
<td>.88</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.02) [0.96-1.03]</td>
<td>−0.54</td>
<td>.59</td>
</tr>
<tr>
<td>Race</td>
<td>1.24 (0.44) [0.62-2.47]</td>
<td>0.60</td>
<td>.55</td>
</tr>
<tr>
<td>Tumor site</td>
<td>0.98 (0.19) [0.67-1.43]</td>
<td>−0.10</td>
<td>.92</td>
</tr>
<tr>
<td>Tumor stage</td>
<td>1.54 (0.30) [1.05-2.26]</td>
<td>2.20</td>
<td>.03</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.89 (0.14) [0.65-1.21]</td>
<td>−0.74</td>
<td>.46</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.22 (0.46) [0.58-2.55]</td>
<td>0.52</td>
<td>.60</td>
</tr>
<tr>
<td>Drinking</td>
<td>1.13 (0.42) [0.55-2.33]</td>
<td>0.33</td>
<td>.74</td>
</tr>
</tbody>
</table>

| **Comparison Between Survivors and Nonsurvivors** | | | |
| COX inhibitor use | 1.47 (0.60) [0.66-3.25] | 0.95 | .34 |
| Age | 0.99 (0.02) [0.96-1.03] | −0.55 | .58 |
| Race | 0.99 (0.35) [0.50-1.97] | −0.02 | .99 |
| Tumor site | 0.85 (0.16) [0.50-1.97] | −0.84 | .40 |
| Tumor stage | 1.46 (0.28) [1.00-2.13] | 1.97 | .05 |
| Treatment | 0.99 (0.15) [0.74-1.33] | 0.06 | .96 |
| Smoking | 1.24 (0.46) [0.60-2.57] | 0.59 | .56 |
| Drinking | 0.95 (0.34) [0.46-1.93] | −0.15 | .88 |

Abbreviations: CI, confidence interval; COX, cyclooxygenase.
Chemopreventive strategies to counteract the ongoing malignant transformation of genetically altered upper aerodigestive tract tissues. Chemopreventive agents include therapies designed to reduce the risk of recurrence or second primary tumors in high-risk populations.11 Cyclooxygenase inhibitors are among the most widely recommended and prescribed medications in the United States, with over 60 million prescriptions written each year.12 Large observational cohort studies provide strong epidemiological evidence that long-term use of nonselective COX inhibitors (eg, aspirin and NSAIDs) decreases the risk of colon, breast, lung, and prostate cancers.13 The risk reduction appears to increase with increasing dosages and duration of exposure. In addition, 2 randomized-controlled studies in patients with colonic polyps demonstrated a significant reduction in polyp recurrence in the patients taking aspirin.11 Non-specific COX inhibitors exert anti-inflammatory effects through nonspecific inhibition of COX enzymes. The blockade of the COX enzymes reduces the production of prostaglandins, including PGE2, which may play a role in increasing tumor vascularization, blocking tumor apoptosis, and reducing host immune surveillance.

Cyclooxygenase enzymes consist of 2 isoforms, COX-1 and COX-2. Cyclooxygenase-1 is found in many normal tissues and is involved in the synthesis of prostaglandins that protect the gastrointestinal and urinary tracts.14 As a result, long-term blockade of COX-1 increases the risk of gastrointestinal ulcer and renal failure. Interest in COX-2 as a target of chemoprevention resulted from the observation that COX-2 was predominately expressed in sites of tissue inflammation as well as many types of carcinomas, including those of the head and neck.4 However, the use of high-dose selective COX-2 inhibitors in clinical trials for the prevention of colonic polyps demonstrated an increased risk of acute cardiovascular events in selective COX-2 users compared with placebo.12 It is thought that COX-2 blockade can lead to a reduction in essential fatty acids that are involved in vasodilation and endothelial protection.15 This effect is more pronounced in rofecoxib (Vioxx; Merck & Co Inc, Whitehouse Station, NJ) compared with other selective COX-2 inhibitors and led to the discontinuance of this drug by Merck in late 2004. Nevertheless, preclinical studies of selective COX-2 inhibitors demonstrate a pronounced ability to inhibit tumor growth in head and neck cancer cell lines and animal models.9,16,17 Therefore, selective COX-2 inhibitors continue to hold promise as potential chemopreventive agents in head and neck cancer if safety issues regarding dosing and duration can be resolved.

The present study found no difference in survival and recurrence in patients with head and neck cancer who used nonselective COX inhibitors compared with nonusers. The data did show a statistically significant difference in recurrence and survival based on tumor stage at presentation, so the overall data can be assumed to be representative of patients with head and neck cancer in general. This study, however, demonstrated a longer median survival time in COX inhibitor users (96 months) compared with nonusers (47 months). In addition, there was a persistent nonsignificant trend toward better survival in the COX inhibitor user group during the midpoint of the survival curves. Therefore, the present study suggests that nonselective COX inhibitors provide a modest, early chemopreventive effect that decreases over time.
The present study is limited by its retrospective design and its relatively small sample size. First, there was a lack of highly detailed information regarding COX inhibitor use in the available database. Subjects were classified as COX inhibitor users or nonusers on the basis of whether there was a standing order for a COX inhibitor on their outpatient pharmacy orders. Therefore, it was impossible to measure patient compliance with therapy or the overall duration of therapy. In addition, there were relatively few (27%) COX inhibitor nonusers in the study population. A possible explanation for this is the managed patient care model of the Department of Veterans Affairs system, in which a large percentage of patients are receiving platelet-inhibiting medications owing to the high rate of cardiovascular disease within the population. Observed differences in median overall survival times between COX inhibitor users and nonusers may be due primarily to reduced deaths from coronary artery disease and stroke. Lastly, only nonselective COX inhibitors were used; therefore, the study provides no information on the potential utility of selective COX inhibitors in head and neck cancer chemoprevention.

In conclusion, to our knowledge, the present study is among the first large reviews of COX inhibitor use in patients with head and neck cancer. Although in vitro studies suggest an antitumor effect of COX inhibitors in head and neck cancer, this study found no difference in head and neck cancer recurrence or overall survival in COX inhibitor users vs nonusers. The improved median survival in COX inhibitor users suggests a limited but potential beneficial effect that may be observed in a larger study population. Therefore, a randomized, double-blind controlled trial is needed to determine the true benefit of COX inhibitor use in head and neck cancer chemoprevention.

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Author Contributions: Drs Gillespie, Moody, Poole, Lathers, Young, and Day had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gillespie, Moody, and Poole. Acquisition of data: Gillespie, Moody, and Poole. Analysis and interpretation of data: Gillespie, Moody, Lee, Hornig, Lathers, Young, and Day. Drafting of the manuscript: Gillespie. Critical revision of the manuscript for important intellectual content: Gillespie, Moody, Lee, Poole, Hornig, Lathers, Young, and Day. Statistical analysis: Gillespie and Lee. Administrative, technical, and material support: Gillespie. Study supervision: Gillespie, Hornig, Lathers, Young, and Day.

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REFERENCES