Antihypertensive Drugs and Lip Cancer in Non-Hispanic Whites

Gary D. Friedman, MD, MS; Maryam M. Asgari, MD, MPH; E. Margaret Warton, MPH; James Chan, PharmD, PhD; Laurel A. Habel, PhD

Background: In screening pharmaceuticals for possible carcinogenic effects we noted an association between lip cancer risk and the photosensitizing antihypertensive drugs hydrochlorothiazide and nifedipine. In this study, we further characterized the risk of lip cancer associated with these and other commonly used antihypertensive drugs.

Methods: In a comprehensive medical care program, we evaluated prescriptions dispensed and cancer occurrence from August 1, 1994, to February 29, 2008. We identified 712 patients with lip cancer (cases) and 22,904 comparison individuals (controls) matched for age, sex, and cohort year of entry in the susceptible group, non-Hispanic whites. We determined use, at least 2 years before diagnosis or control index date, of the commonly prescribed diuretics hydrochlorothiazide and hydrochlorothiazide combined with triamterene, the angiotensin-converting enzyme inhibitor lisinopril, the calcium channel blocker nifedipine, and the β-adrenergic blocker atenolol, the only nonphotosensitizer agent studied. We analyzed the use of each drug exclusively and regardless of use of the others, and focused on duration of use. Conditional logistic regression was used for analysis of matched case-control sets, with control for cigarette smoking.

Results: At least a 5-year supply of a drug yielded the following odds ratios (95% CIs), respectively, compared with no use: hydrochlorothiazide, 4.22 (2.82-6.31); hydrochlorothiazide-triamterene, 2.82 (1.74-4.55); lisinopril, 1.42 (0.95-2.13); nifedipine, 2.50 (1.29-4.84); and atenolol, 1.93 (1.29-2.91). When the other drugs were excluded, the odds ratio for atenolol was reduced to 0.54 (0.07-4.08).

Conclusion: These data support an increased risk of lip cancer in non-Hispanic whites receiving treatment for hypertension with long-term use of photosensitizing drugs.


In screening pharmaceuticals for possible carcinogenic effects, an increased risk of cancer of the lip was identified in persons who received 3 or more prescriptions of the diuretic hydrochlorothiazide and the calcium channel blocker nifedipine. A causal relationship is biologically plausible because sun exposure is an established risk factor for lip cancer and hydrochlorothiazide and nifedipine are photosensitizers. For the present study, we conducted more extensive analyses of the risk of lip cancer in relation to hydrochlorothiazide, nifedipine, and the following other commonly used antihypertensive drugs: the combination of hydrochlorothiazide with triamterene, a potassium-sparing diuretic; lisinopril, an angiotensin-converting enzyme inhibitor; and atenolol, a β-adrenergic blocker. In addition to hydrochlorothiazide and nifedipine, triamterene is an established photosensitizer, and lisinopril is likely to be a photosensitizer; atenolol is not recognized as such.

Associations were analyzed by the number of prescriptions received and duration of use of the drug with adjustment for cigarette smoking, a known risk factor for lip cancer.

Methods

Cohort and Drug Selection

The study cohort consisted of subscribers of the Kaiser Permanente Medical Care Program in northern California from August 1994, when all of the program’s pharmacies had begun computer storage of dispensed prescriptions, through February 2008. Kaiser Permanente Medical Care Program is a comprehensive integrated health care program. The population

See Editor’s Note at end of article
served is centered in the San Francisco Bay area and central valley of California. The membership is approximately 3.2 million and is ethnically and socioeconomically diverse, with some underrepresentation of persons at the highest and lowest ends of the economic spectrum. The target cohort for the study was subscribers with at least partial coverage of payment for prescriptions (>90%). Ascertainment of cancer, including lip cancer, was through the program’s cancer registry, which contributes to the Surveillance, Epidemiology and End Results (SEER) program (http://www.seer.cancer.gov).

Case-control analyses have been performed within this cohort, using conditional logistic regression implemented with commercial software (SAS, version 9.1.2). In the initial screening of commonly used drugs, up to 50 risk-set controls were randomly selected for each case, matched on age, sex, and year of entry into the cohort. Relative risk is represented by the odds ratio. The index date for cases is the date of cancer diagnosis and, for controls, the date that gives them equal follow-back time to cohort entry. Cohort entry is the date when at least partial drug coverage started if later than August 1, 1994. Duration of use of a drug is based on summing the number of days supplied recorded for each dispensed prescription in the pharmacy database. Our analyses allow for a lag period of 2 years so that drug exposure within 2 years before index date is ignored.

The drugs selected for study were, in this setting, by far the most commonly prescribed representatives of the 4 classes of antihypertensives listed in the program’s formulary. Diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers, and β-adrenergic blockers were represented, respectively, by hydrochlorothiazide and combined hydrochlorothiazide-triamterene, lisinopril, nifedipine, and atenolol. In the entire study cohort, the numbers of patients aged 20 years and older who received 3 or more prescriptions for these drugs were as follows: hydrochlorothiazide, 333,695; hydrochlorothiazide-triamterene, 178,290; lisinopril, 567,620; nifedipine, 141,132; and atenolol, 415,638. Because more than 1 antihypertensive drug may be prescribed to achieve adequate blood pressure control, we assessed the risk associated with each of the single-drug preparations, both without regard to use of the others before the index date and excluding patients who received any of the others before the index date. Triamterene alone was rarely prescribed and the combination of lisinopril and hydrochlorothiazide was not prescribed frequently until the last year of case ascertainment. Therefore, these preparations were not analyzed.

**CONSIDERATION OF POSSIBLE CONFOUNDERS**

Race/ethnicity, human immunodeficiency virus infection, organ transplantation, and cigarette smoking were considered confounders. Organ transplantation followed by immunosuppressive drug therapy and human immunodeficiency virus infection increase the risk of lip cancer, and cases and controls with these conditions before the diagnosis or index date were excluded. Race/ethnicity was determined from demographic data sets in which approximately 81% of the data were derived from either administrative systems or self-report. The remainder were imputed on the basis of the last name and census tract, using the Bayesian Improved Surname and Geocoding algorithm. Categories were white/non-Hispanic, white/Hispanic, Asian, African American, other or multiracial, and unknown. We found very few cases and evidence of markedly reduced risk of lip cancer among all of the minority groups and therefore restricted the present analysis to non-Hispanic whites. Cigarette smoking status was based on computer-stored information collected at outpatient clinic visits starting in 1996. An algorithm (available on request) was applied to this information to determine, as well as possible, whether a person smoked at any time during the observation period between first use of the drug studied and the index date or, if not, whether he or she smoked formerly or never, or whether smoking status was unknown. This study was approved by the Institutional Review Board, Kaiser Foundation Research Institute.

**RESULTS**

In our initial screening analysis there were 812 patients with lip cancer (cases) aged 30 years and older and 40,434 individuals serving as controls (average, 49.8 controls per case). The step-by-step exclusion of organ transplant and HIV-positive patients and persons who were not of non-Hispanic white race/ethnicity led to a final study group of 712 cases and 22,904 controls (average, 32.2 controls per case). The disproportionately greater loss of controls was mainly the result of the relatively few nonwhites and Hispanic whites among cases compared with controls. The derivation and characteristics of participants in the current study are shown in the **Figure** and reported in **Table 1**. Almost all the cancers were squamous cell. Men predominated the participants by a ratio of approximately 3:1. The disproportionately greater exclusion of controls resulting from our race/ethnicity criteria also led to a mean age 2.4 years higher in controls than cases. Current cigarette smokers were relatively more frequent among cases,
whereas former smokers and persons with unknown smoking habits were more frequent among controls. In the 4 analyses of single-drug use, exclusion of patients receiving other drugs resulted in 438 to 464 cases and 15 135 to 16 329 controls for analyses.

Three or more prescriptions were received by a higher proportion of cases vs controls for all the drugs studied except lisinopril only and atenolol, and the excess use in the cases was statistically significant, except for the smaller number of patients receiving hydrochlorothiazide only. The deficit of use of atenolol only by cases was statistically significant, except for the smaller number of patients receiving hydrochlorothiazide only.

The risk of lip cancer increased with the duration of use for hydrochlorothiazide, hydrochlorothiazide-triamterene, and nifedipine, with the relative risk asso-
ciated with reduced risk. Lisinopril’s weaker association lost statistical significance when other drugs were excluded. Atenolol was not associated with increased risk and, when studied alone, was associated with reduced risk.

### Multivariable Analysis

When the analysis of hydrochlorothiazide was controlled for smoking habits, the results were hardly affected and restricting attention to users of hydrochlorothiazide only made little difference (Table 3). The increased susceptibility of cigarette smokers was confirmed, but reduced risk was observed in former smokers.

Findings for the other antihypertensive drugs unadjusted and adjusted for cigarette smoking are reported in Table 4. The odds ratios for smoking categories in the multivariable analyses of these drugs were very similar to those reported for hydrochlorothiazide (Table 3) (available on request). These analyses confirmed the statistically significant associations of hydrochlorothiazide, hydrochlorothiazide-triamterene, and nifedipine with lip cancer. Lisinopril’s weaker association lost statistical significance when other drugs were excluded. Atenolol was not associated with increased risk and, when studied alone, was associated with reduced risk.

### Analysis by Duration of Use

The risk of lip cancer increased with the duration of use for hydrochlorothiazide, hydrochlorothiazide-triamterene, and nifedipine, with the relative risk associated with hydrochlorothiazide use for at least 5 years exceeding a 4-fold increase (Table 5). The risk for lisinopril was highest among individuals with 1 to 5 years of use. Risk was increased for patients who received a 5-year or more supply of atenolol. Since this finding was inconsistent with the observed lack of association noted with atenolol, the atenolol analysis was repeated, excluding patients who received any of the other drugs. The number of cases exposed to atenolol for at least 5 years fell from 29 to 1 and the odds ratio dropped below unity (Table 5). Of the 28 cases who had received other drugs, 24 had received hydrochlorothiazide with or without other drugs, 8 had received nifedipine with or without other drugs, and 19 had received lisinopril with or without other drugs.
Lesions occur on the lower lip. Based on SEER data, histologic type is predominantly squamous cell, and most val. We did not find published incidence data for other ethnicities. Lip cancer is usually detected and treated early and, as a result, regional metastases occur in only 5% to 20% of cases and distant metastases in only 0.5% to 2.0%. The protection afforded by darker pigmentation and this cancer’s more frequent occurrence on the lower lip correspond with the main known risk factor: prolonged engagement in outdoor occupations and use of lipstick and other lip coatings. The incidence in SEER was 7% of cases and distant metastases in only 0.5% to 2.0%.

### Table 4. Analysis of Risk of Lip Cancer Associated With Receipt of 3 or More Prescriptions for Hydrochlorothiazide-Triamterene, Lisinopril, Nifedipine, and Atenolol, Unadjusted and Adjusted for Cigarette Smoking

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prescriptions of the drug analyzed</td>
<td>Any Use [Reference]</td>
</tr>
<tr>
<td>≥3 Hydrochlorothiazide-triamterene prescriptions, unadjusted</td>
<td>1.98 (1.52-2.58)</td>
</tr>
<tr>
<td>≥3 Hydrochlorothiazide-triamterene prescriptions, adjusted</td>
<td>1.98 (1.52-2.58)</td>
</tr>
<tr>
<td>≥3 Lisinopril prescriptions, unadjusted</td>
<td>1.44 (1.16-1.79)</td>
</tr>
<tr>
<td>≥3 Lisinopril prescriptions, adjusted</td>
<td>1.42 (1.15-1.77)</td>
</tr>
<tr>
<td>≥3 Nifedipine prescriptions, unadjusted</td>
<td>2.37 (1.78-3.17)</td>
</tr>
<tr>
<td>≥3 Nifedipine prescriptions, adjusted</td>
<td>2.33 (1.74-3.11)</td>
</tr>
<tr>
<td>≥3 Atenolol prescriptions, unadjusted</td>
<td>1.07 (0.83-1.37)</td>
</tr>
<tr>
<td>≥3 Atenolol prescriptions, adjusted</td>
<td>1.06 (0.83-1.36)</td>
</tr>
</tbody>
</table>

Abbreviation: OR, odds ratio.

None of the other drugs studied was dispensed. Users of the other drugs were excluded from analysis.

### Table 5. ORs of Developing Lip Cancer According to the Amount of Drugs Dispensed, Measured in Years Supply, Regardless of Whether Other Drugs Were Given

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;1-Year Supply</th>
<th>1-Year to 5-Year Supply</th>
<th>≥5-Year Supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>0.98 (0.66-1.46)</td>
<td>2.03 (1.54-2.68)</td>
<td>4.22 (2.92-6.31)</td>
</tr>
<tr>
<td>Hydrochlorothiazide-triamterene</td>
<td>0.91 (0.60-1.39)</td>
<td>1.87 (1.37-2.57)</td>
<td>2.82 (1.74-4.55)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.04 (0.74-1.46)</td>
<td>1.60 (1.25-2.04)</td>
<td>1.42 (0.95-2.13)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>1.77 (1.20-2.59)</td>
<td>2.26 (1.58-3.23)</td>
<td>2.50 (1.29-4.84)</td>
</tr>
<tr>
<td>Atenolol</td>
<td>0.88 (0.62-1.26)</td>
<td>0.88 (0.63-1.21)</td>
<td>1.93 (1.29-2.91)</td>
</tr>
<tr>
<td>Atenolol only</td>
<td>0.68 (0.30-1.55)</td>
<td>0.42 (0.15-1.14)</td>
<td>0.54 (0.07-4.08)</td>
</tr>
</tbody>
</table>

Abbreviation: OR, odds ratio.

a No exposure OR, 1 [Reference].

b Analysis of atenolol repeated, excluding the other drugs. Adjusted for cigarette smoking.

We found that the commonly used photosensitizing antihypertensive drugs hydrochlorothiazide, hydrochlorothiazide-triamterene, and nifedipine were associated with an increased risk of lip cancer. The risk seemed to rise with increasing duration of use and was unexplained by confounding by cigarette smoking. Nonphotosensitizing atenolol, when used alone, was not associated with increased risk. Findings for lisinopril, a photosensitizer, were equivocal.

Lip cancer includes malignant neoplasms of the vermilion border, commissure, and labial mucosa, but excludes cancers originating on the skin of the lip. The histologic type is predominantly squamous cell, and most lesions occur on the lower lip. Based on SEER data, the overall age-adjusted incidence in the United States in 2003-2007 was low, 0.7/100,000 per year, and the incidence in men (1.2) was 4 times that in women (0.3). The relative protection of women has been linked to less pigmentation of the lips. However, it does not seem likely that users of the antihypertensive drugs associated with lip cancer experience a great deal more sun exposure than nonusers or than users of atenolol. To account for the 2- to 4-fold associations observed for at least 5 years’ use of hydrochlorothiazide, hydrochlorothiazide-triamterene, and nifedipine, a much greater than 2- to 4-fold difference in carcinogenic sun exposure would be required.

When we narrowed our focus to the susceptible group of non-Hispanic whites, we lost a disproportionate number of control subjects, which led to the mean age at index date of the controls being 2.4 years higher than that of the cases. Before the exclusions, the mean ages were virtually identical (cases, 66.95 years; controls, 66.84 years). This age discrepancy did not bias our results or require further adjustment, because conditional logistic regression analysis bases the odds ratio on the findings within each case plus matched controls risk set, where the ages were matched within 1 year.

We were unable to adjust for sun exposure, the most important lip cancer risk factor, along with relative lack of pigmentation of the lips. However, it does not seem likely that users of the antihypertensive drugs associated with lip cancer experience a great deal more sun exposure than nonusers or than users of atenolol. To account for the 2- to 4-fold associations observed for at least 5 years’ use of hydrochlorothiazide, hydrochlorothiazide-triamterene, and nifedipine, a much greater than 2- to 4-fold difference in carcinogenic sun exposure would be required.

Other than a few self-reports or case reports (http://www.ehealthme.com/ds/atenolol/photosensitivity+reaction), the absence of a scientifically established association of atenolol use alone with lip cancer adds specificity to these findings and suggests that hypertension, the condition being treated, is not responsible. There may also have been uncontrolled confounding based on different characteristics of patients re-
ralen and UV radiation26 and the association of hydro-
psoriasis with repeated exposures to photosensitizing pso-
cals, which damage DNA and other components of skin
cells and produce an inflammatory response.24,25 The cau-
sion of squamous cell skin cancer by the treatment of
or squamous cell skin cancer27 support the biological plau-
sibility of an increased risk of lipid cancer caused by pho-
tosensitizing antihypertensive drugs. However, another
study28 surprisingly found more evidence for an associa-
tion of short- than long-term use of photosensitizing drugs
with skin cancer.

We were unable to include basal cell and squamous cell
skin cancers in this study because these diagnoses have
not been recorded in our cancer registry. Melanoma is also
related to sun exposure, but none of the antihypertensive
drugs studied screened positive for an association with this
cancer in the screening study.1 Melanoma has been more
strongly associated with intermittent exposures, es-
pecially those producing sunburn, than with long-term ex-
posure, so the timing of use of photosensitizing drugs could
be an important consideration.26

In the study1 that brought our attention to antihy-
pertensive drugs and lip cancer, the screening criteria for
drug-cancer associations of interest were odds ratio for 3
or more prescriptions of at least 1.5 and greater than
3 or more prescriptions of at least 1.5 and greater than
odds ratio for 1 prescription, as a rough indicator of dose-
response, and \( P < .01 \). Hydrochlorothiazide and nified-
ipine met these criteria, but lisinopril did not because its
odds ratio was 1.36 (\( P = .004 \)) and the odds ratio for 1
prescription was 1.38. The findings regarding lisinopril
in the present study were also weaker in that the clear
positive association became only of borderline statisti-
cal significance when individuals who received other antihy-
pertensive drugs were excluded.

One of the main reasons for the analysis of single-
drug exposures was the unexpected finding of a posi-
tive association between 5 or more years’ use of atenolol
and lip cancer. These proved to be attributable to the
associated use of the other antihypertensive drugs.

Because lip cancer is a relatively infrequent form of
cancer, it is not surprising that associations with antihy-
pertensive drugs have not been observed in large clin-
cal trials of their efficacy. For example, 33 357 patients,
mean age 66.9 years, were monitored for a mean of 4.9
years in the ALLHAT (Antihypertensive and Lipid-
Lowering Treatment to Prevent Heart Attack Trial) study.30
Approximately half the participants were non-
Hispanic white and approximately half were women, who
have a lower incidence of lip cancer than white men. How-
ever, if all 33 357 participants were white males aged 65
to 69 years whose overall annual incidence of orophary-
genel cancer in 2003-2007 was 55.1/100 000 person-
years, of which 8% were lip cancers,15 approximately 7
lip cancers would have been expected during follow-up
in all 3 treatment groups combined.

Although the relatively high odds ratios, the evi-
dence for specificity, and the biological mechanism are
consistent with a causal relationship, causality cannot usu-
ally be established by a single observational study such as
ours. Further investigations are needed to confirm and
characterize relationships between photosensitizing anti-
hypertensive drugs and lip cancer.

A search of the clinical literature revealed consider-
able attention to the effects of photosensitivity on the
skin,23,31-32 some attention on its effects on the eye,33,34 but
little or no attention directed toward the lips, except for a
listing of a few lip sunscreens in the review by Ting et al.35

Antihypertensive drugs are commonly prescribed26 and
most are photosensitizing as are many other commonly
prescribed drugs.3,4 Lip cancer is rare and an increased
risk of its development is generally outweighed by the
benefits of drugs that are effective for other conditions.
However, physicians prescribing photosensitizing drugs
should ascertain whether patients are at high risk of lip
cancer because of their fair skin and long-term sun ex-
posure and discuss lip protection with them. Although
not confirmed by clinical trials, likely preventive mea-
sures are simple: a hat with a sufficiently wide brim to
shade the lips and lip sunscreens.

Accepted for Publication: April 11, 2012.
Published Online: April 11, 2012. doi:10.1001
/archinternmed.2012.2754

Correspondence: Gary D. Friedman, MD, MS, Division
of Research, Kaiser Permanente Medical Care Program,
2000 Broadway, Oakland, CA 94612.

Author Contributions: All the authors had full access to
to all of the data in the study and take responsibility for the
integrity of the data and the accuracy of the data analy-
sis. Study concept and design: Friedman. Acquisition of data:
Warton and Habel. Analysis and interpretation of data:
Friedman, Asgari, Warton, Chan, and Habel. Drafting of the
manuscript: Friedman. Critical revision of the manu-
script for important intellectual content: Asgari, Warton,
Chan, and Habel. Statistical analysis: Warton and Habe.
Obtained funding: Habel. Administrative, technical, and
material support: Asgari and Habel. Study supervision:
Friedman.

Financial Disclosure: Dr Friedman has consulted for The
Degge Group, Inc; Robinson Law Firm; Williams and
Connolly Law Firm; and Allergan, Inc. None of these as-
sociations is related to, or has had any effect on, the pres-
ent study. Dr Asgari and Ms Warton have a grant from
Genentech, Inc, unrelated to and not affecting the pres-
ent study. Dr Habel’s research in the Division of Re-
search, Kaiser Permanente Medical Care Program has re-
ceived support from Takeda, sanofi-aventis, Merck, and
Genentech, Inc, that is unrelated to and not affecting the
present study.

Funding/Support: The study was supported by grant R01
CA 098838 from the National Cancer Institute.

Presentative Presentation: This study was presented as a sci-
cientific poster at the Bay Area Clinical Research Sym-
podium, November 4, 2011; San Francisco, California.
The findings are important because simple interventions, such as lip protector, sunscreen, large-brim hats, rash guard swim shirts, and avoiding times of the day when the sun is most intense, are likely to decrease the harmful effects of the sun for everyone, regardless of whether they are receiving a photosensitizing agent. When initiating use of photosensitizing agents for our patients, we need to remind them of these simple measures to avoid sun exposure.

Mitchell H. Katz, MD