Published OnlineFirst July 9, 2015; DOI: 10.1158/1940-6207.CAPR-15-0091

Research Article

Cancer Prevention Research

Leukoplakia, Oral Cavity Cancer Risk, and Cancer Survival in the U.S. Elderly

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Abstract

Screening for oral leukoplakia, an oral cavity cancer (OCC) precursor, could lead to earlier detection of OCC. However, the progression rate from leukoplakia to OCC and the benefits of leukoplakia screening for improving OCC outcomes are currently unclear. We conducted a case–cohort study of U.S. adults ages ≥65 years in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linkage. We identified leukoplakia diagnoses through Medicare claims, and OCC diagnoses through SEER cancer registries. Weighted Cox regression was used to estimate leukoplakia associations with OCC incidence, and the absolute OCC risk following leukoplakia diagnosis was calculated. Among OCC cases, we compared OCC stage and OCC survival between cases with a prior leukoplakia diagnosis versus those without prior leukoplakia. Among 470,266 individuals in the SEER-Medicare subcohort, 1,526 (0.3%) had a leukoplakia diagnosis. Among people with leukoplakia, the cumulative OCC incidence was 0.7% at 3 months and 2.5% at 5 years. OCC risk was most increased <3 months after leukoplakia diagnosis (HR, 115), likely representing the diagnosis of prevalent cancers. Nonetheless, risk remained substantially increased in subsequent follow-up [HR ≥ 3 months, 24; 95% confidence interval (CI), 22–27; HR ≥ 12 months, 22, 95% CI, 20–25]. Among OCC cases ($N = 8{,}927$), those with prior leukoplakia were less likely to be diagnosed at regional/distant stage (OR, 0.36; 95% CI, 0.30–0.43), and had lower mortality (HR, 0.74; 95% CI, 0.65–0.84) when compared with OCC cases without a prior leukoplakia. Individuals with leukoplakia have substantially elevated risk of OCC. Lower stage and better survival after OCC diagnosis suggest that leukoplakia identification can lead to earlier OCC detection and reduced mortality. *Cancer Prev Res; 8(9); 857–63. ©2015 AACR.*

Introduction

The burden of oral cavity cancer (OCC) is substantial with approximately 28,000 annual incident cases in the United States, and 300,000 annual incident cases worldwide (1, 2). Survival differs dramatically based on the stage of OCC diagnosis, with less than 20% of early-stage cases dying within 5 years compared with more than 60% of late-stage cases (1, 3). Nonetheless, less than 50% of OCC cases are currently diagnosed at an early stage, underscoring the need for early detection (3). Notably, the amenability of the oral cavity for visual inspection and the availability of established clinically defined precursors (leukoplakia, erythroplakia, and oral submucous fibrosis) provide an ideal opportunity for early detection and secondary prevention of OCC. However, there are currently no guidelines for screening and early detection of OCC (4), in part, due to knowledge gaps regarding the natural history of OCC precursors and the potential benefits of screening for precursors in reducing OCC mortality.

Although it has long been recognized that oral leukoplakia, the most common precursor (5, 6), can progress to OCC, there is wide variability in malignant transformation rates reported in the literature (0.1%–36%; refs. 7–11). This variability partly arises due to differences in study populations (i.e., clinic-based vs. population-based) and durations of follow-up after leukoplakia diagnosis (10–12). In addition, most prior studies relied on clinical records for OCC diagnoses, which may lead to inconsistent cancer ascertainment (7, 9, 13). The identification of leukoplakia could aid in the recognition of individuals with pre-existing, prevalent OCC as well as individuals at increased OCC risk during subsequent follow-up, both of which are relevant for early OCC detection. If a patient with leukoplakia has clinical evaluation and follow-up for OCC, then OCC cases (whether prevalent or incident) may be detected at earlier stages, potentially leading to improvements in survival (14, 15). However, few studies have examined the relationship between leukoplakia identification and subsequent OCC diagnosis in large, population-based settings with complete outcome ascertainment.

In this study, we investigated the natural history of oral leukoplakia within Surveillance, Epidemiology, and End Results (SEER)-Medicare, a U.S. population-based database of individuals ages ≥65 years, with extended follow-up and well-validated cancer diagnoses and outcomes. Specifically, we examined the relationship between leukoplakia and OCC diagnosis, stage at the time of OCC diagnosis, and survival following OCC diagnosis.

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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Prior Presentation: This work was previously presented at the NIH Research Festival, Bethesda, MD (September 22–26, 2014).

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doi: 10.1158/1940-6207.CAPR-15-0091

Published OnlineFirst July 9, 2015; DOI: 10.1158/1940-6207.CAPR-15-0091

Materials and Methods

Study population and study design

The SEER-Medicare database links 17 SEER cancer registries, which cover approximately 28% of the U.S. population, with Medicare claims. Medicare is a U.S. federal health insurance program for people ages ≥65 years. The database includes all linked SEER cancer cases with their Medicare claims, as well as Medicare claims for a random sample of 5% of the entire Medicare population living in SEER areas, hereafter referred to as the subcohort. SEER-Medicare has previously been described in detail (16, 17). Of note, individuals in the subcohort have information on all Medicare claims dating back to January 1, 1991, whereas cancer cases outside of the subcohort have claims for shorter lengths of time depending upon the date of cancer diagnosis (17). For instance, cancers diagnosed in 2008 to 2009 only have Medicare claims dating back to January 1, 2002. Therefore, to ensure similar claims coverage for the subcohort and cancer cases, we limited our study population to the most recent time period with complete Medicare claims information January 1, 2002 to December 31, 2009.

To evaluate the relationship between leukoplakia diagnosis and OCC incidence, we conducted a case–cohort study, including the 5% subcohort and 100% of OCC cases within SEER-Medicare. Follow-up started at the latest date of: age 65; January 1, 2002; first date living in a SEER area; start of cancer registry coverage; beginning of Medicare coverage for inpatient, outpatient, and physician care; and first Medicare claim. Time when individuals were in a health maintenance organization was excluded as Medicare would not have data on their claims. Individuals with a history of head and neck cancer as captured in the SEER cancer registries before the start of follow-up were excluded. Follow-up ended at the earliest of: incident OCC, death, first migration out of SEER area, first discontinuation of the specified Medicare coverage, or December 31, 2009.

Exposure and outcome definitions

Oral leukoplakia diagnosis was defined as the first occurrence of a Medicare hospital, outpatient, or physician/provider diagnosis claim for International Classification of Diseases (ICD), version 9 code 528.6 (leukoplakia of oral mucosa including tongue) after January 1, 2002. Data on histopathologic characteristics, anatomic site, or treatments of leukoplakia were unavailable.

OCC diagnoses were identified through SEER cancer registries using ICD for Oncology third edition codes C003–C069. Only first OCC diagnoses were counted as events. We also assessed incidence of OCC at specific anatomic sites: lip (C003–C009, excluding external lip), tongue (C020–C029, excluding base of tongue), gum (C030–C039), floor of mouth (C040–C049), palate (C050–C059), and other mouth (C060–C069). Cancer registries were used to obtain information on cancer stage at diagnosis, primary course of cancer treatment, death dates, and causes of death. American Joint Committee on Cancer (AJCC) staging was not available on cancers before 2004, and so stage was categorized using the SEER historic staging system, which classifies cancers into localized, regional, and distant stages. Compared with AJCC staging, localized stage mostly includes stages I and II, whereas regional/distant stages mostly include stages III and IV (Supplementary Table S1). Cancer-specific deaths were defined as deaths with ICD, version 10 codes C00.0–C97.0.

Analyses of incident OCC

For case–cohort analyses, individuals were given sampling weights to create an analytic population representative of the entire Medicare population. Non-cancer cases in the subcohort were given a weight of 20, as our sample included 5% of cancer-free individuals in Medicare, whereas all cancer cases were given a weight of 1, as our sample included 100% of OCCs in Medicare. Incidence rates were calculated using the resulting weighted person-time. Weighted Cox regression, with follow-up time as the time scale, was used to estimate HRs comparing OCC incidence among individuals with a leukoplakia diagnosis versus those without (18). Oral leukoplakia was considered a time-varying risk factor, with individuals categorized as leukoplakia free before their first leukoplakia claim and as leukoplakia diagnosed for all time after the first claim. Adjusted HRs (aHR) were estimated using multivariable, weighted Cox regression, with adjustment for race, sex, age, and calendar year at the start of follow-up.

We recognized that some OCC diagnoses made soon after leukoplakia diagnosis represent prevalent cancers. Therefore, stratified HRs were calculated during time ≤3 and >3 months after leukoplakia diagnosis. This cutoff was chosen based on the noticeably higher OCC incidence in the first 3 months, likely driven by OCCs prevalent at leukoplakia diagnosis. In sensitivity analyses, this cutoff was extended to 12 months to further exclude possible prevalent OCCs from the later time period. HRs were calculated within subgroups of age and sex, for follow-up beginning 3 months, and 12 months, after leukoplakia diagnosis.

Among individuals with a leukoplakia diagnosis, we used sampling weights to calculate the hazard and cumulative incidence of OCC. Hazards were estimated at 3-month intervals using the life-table method. Cumulative incidence was estimated accounting for the competing risk of death (19). Jackknife resampling was used to calculate 95% confidence intervals (CI) for the cumulative incidence at 3 months, 1 year, 3 years, and 5 years after leukoplakia diagnosis (20).

Analyses of OCC stage and survival after cancer diagnosis

We conducted analyses among all OCC cases to examine the relationship of leukoplakia diagnosis before OCC with OCC stage and survival. This includes potentially prevalent OCCs first diagnosed within 3 months of leukoplakia, as these represent cancers that would be diagnosed as a part of initial identification of leukoplakia and subsequent clinical monitoring/follow-up. Cancers diagnosed at the time of death were excluded. We used polytomous logistic regression to estimate the association between prior leukoplakia and stage at cancer diagnosis. We also assessed the association between leukoplakia and primary course of OCC treatment (surgery and radiation), overall and stratified by cancer stage.

For survival analyses among OCC cases, follow-up started at OCC diagnosis and ended at death or December 31, 2009. We used Cox regression to estimate leukoplakia associations with all-cause mortality, cancer-specific mortality, and non-cancer mortality, adjusted for sex, race, age, calendar year at cancer diagnosis, and in some models, cancer stage at diagnosis. Cancer-specific mortality included deaths from any cancer, as this has been shown to accurately capture the deaths attributable to specific cancer types (21).

We also estimated associations of leukoplakia with OCC stage and survival stratified by time between leukoplakia diagnosis and OCC diagnosis (≤3 and >3 months).

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Table 1. Characteristics of individuals in SEER-Medicare during follow-up 2002 to 2009

Characteristics	5% Subcohort (*N* = 470,266)	OCC cases[a] (*N* = 8,927)
Sex, *N* (%)		
Female	272,739 (58.0)	3,872 (43.4)
Male	197,527 (42.0)	5,055 (56.6)
Race, *N* (%)		
White, non-Hispanic	386,929 (82.3)	7,869 (88.2)
Black, non-Hispanic	39,822 (8.5)	550 (6.2)
Other	43,515 (9.3)	508 (5.7)
Age at cohort entry in years, median (IQR)	70 (65–78)	72 (66–78)

NOTE: SEER registries cover individuals living in Alaska; California; Connecticut; Detroit, Michigan; Georgia; Hawaii; Iowa; Kentucky; Louisiana; New Jersey; New Mexico; Seattle, Washington; Utah; and American Indians living in Arizona or the Cherokee Tribal Service Area of Oklahoma.

Abbreviation: IQR, interquartile range.

[a]473 OCC cases were diagnosed in the 5% subcohort and 8,454 OCC cases were diagnosed outside of the subcohort.

Results

Population characteristics

Our study included 470,266 people over age 65 in the subcohort (including 473 OCC cases) and an additional 8,454 OCC cases outside the subcohort. The most frequent sites of OCC diagnosis were the tongue (2,265 cases) and the floor of the mouth (1,018 cases). OCC cases were more likely to be male, white, and older (Table 1). Within the subcohort, 1,526 individuals had a leukoplakia diagnosis during follow-up (0.3% of the subcohort). Among OCC cases, 647 had a prior leukoplakia diagnosis (7% of cases).

OCC incidence

Individuals with leukoplakia had an OCC diagnosis rate of 593 cases per 100,000 person-years. OCC diagnoses were especially common ≤3 months after a leukoplakia claim, corresponding to a very high hazard rate, whereas >3 months after leukoplakia, we observed a lower hazard rate that was stable across time (Fig. 1). In the first 3 months after leukoplakia diagnosis, the cumulative incidence of OCC was 0.67%. After 3 months, an additional 0.43% of the population was diagnosed by 1 year, and between 1 and 5 years 1.45% was diagnosed, for a total 5-year cumulative incidence of 2.54%. Cumulative incidence of OCC after leukoplakia diagnosis was higher among women (5-year cumulative incidence = 2.73%), and among individuals ≥75 years of age at leukoplakia diagnosis (5-year cumulative incidence = 3.21%; Fig. 1).

OCC risk was strongly elevated ≤3 months after leukoplakia diagnosis (HR, 115; 95% CI, 100–134), but OCC incidence remained 24 times higher beyond 3 months (HR, 24.1; 95% CI, 21.5–27.1) and 22 times higher beyond 12 months (HR, 22.3; 95% CI, 19.6–25.4; Table 2). These associations did not change after multivariable adjustment. After 3 months, leukoplakia was more strongly associated with OCC among women (aHRs, 34.8 among women vs. 14.7 among men, $P < 0.001$) and among older individuals (aHRs, 28.6 among those ≥75 vs. 16.7 among those <75 years of age, $P = 0.002$; Table 2).

Beyond 3 months after leukoplakia diagnosis, individuals with leukoplakia had significantly elevated cancer risk at all oral cavity sites. However, the strength of the association varied markedly by site, being strongest for tongue cancer (aHR, 44.6; 95% CI, 37.9–52.4) and weakest for lip cancer (aHR, 8.66; 95% CI, 4.06–18.45; Table 3). All associations were similar when

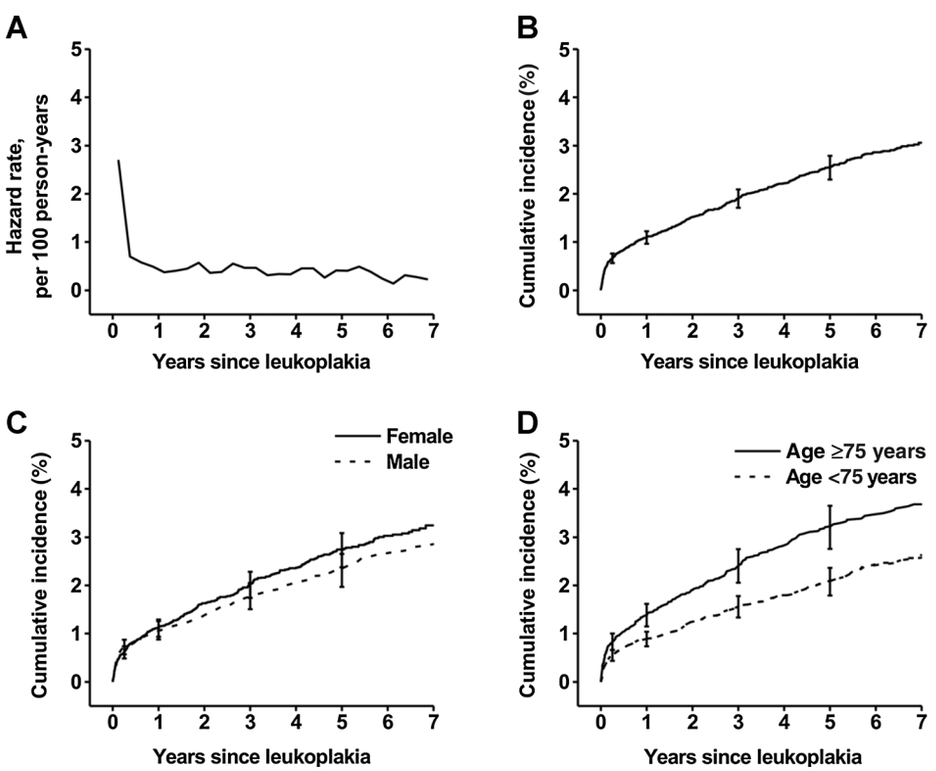

Figure 1.
Hazard rate and cumulative incidence of OCC following a leukoplakia diagnosis. Hazard rates were estimated among all U.S. elderly adults with a leukoplakia diagnosis at 3-month intervals following leukoplakia diagnosis using the life-table method (A). Cumulative incidence accounting for the competing risk of death was calculated among all elderly U.S. adults with a leukoplakia diagnosis (B), stratified by sex (C), and stratified by age at leukoplakia diagnosis (D). Errors bars, 95% CIs for cumulative incidence at 3 months, 1 year, 3 years, and 5 years.

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Table 2. Association of leukoplakia with OCC

Categories of demographic characteristics and leukoplakia status	OCC cases	Incidence rate[a]	HR (95% CI) Unadjusted	HR (95% CI) Adjusted[b]
Overall				
No prior leukoplakia	8,280	19	Reference	Reference
Prior leukoplakia	647	593	32.8 (29.7–36.3)	31.3 (28.2–34.7)
≤3 months after leukoplakia	202	2,703	115 (100–134)	110 (95.3–128)
>3 months after leukoplakia	445	438	24.1 (21.5–27.1)	23.0 (20.5–25.9)
>12 months after leukoplakia	324	399	22.3 (19.6–25.4)	21.3 (18.6–24.3)
Women				
No prior leukoplakia	3,504	13	Reference	Reference
Prior leukoplakia				
>3 months after leukoplakia	268	458	36.7 (31.5–42.8)	37.3 (32.0–43.5)
>12 months after leukoplakia	192	434	33.0 (27.8–39.3)	33.5 (28.1–39.9)
Men				
No prior leukoplakia	4,776	27	Reference	Reference
Prior leukoplakia				
>3 months after leukoplakia	177	371	14.9 (12.5–17.8)	14.7 (12.3–17.5)
>12 months after leukoplakia	132	356	14.3 (11.7–17.4)	14.0 (11.5–17.1)
Age <75 years				
No prior leukoplakia	4,024	18	Reference	Reference
Prior leukoplakia				
>3 months after leukoplakia	147	278	17.5 (14.6–21.0)	16.7 (13.9–20.1)
>12 months after leukoplakia	94	254	15.4 (12.4–19.1)	14.7 (11.8–18.3)
Age ≥75 years				
No prior leukoplakia	4,256	20	Reference	Reference
Prior leukoplakia				
>3 months after leukoplakia	298	538	30.6 (26.4–35.4)	28.6 (24.6–33.1)
>12 months after leukoplakia	230	520	28.4 (24.2–33.4)	26.6 (22.6–31.3)

Abbreviations: OCC, oral cavity cancer; HR, hazard ratio; CI, confidence interval.
[a]Per 100,000 person-years.
[b]Adjusted for sex, race, age, and calendar year at start of follow-up.

Table 3. Associations of leukoplakia with OCC by OCC site

Leukoplakia status and oral cavity site	Cases	Adjusted HR (95% CI)[a]
Lip (excluding external lip)		
No prior leukoplakia	369	Reference
Prior leukoplakia		
>3 months after leukoplakia	7	8.66 (4.06–18.45)
>12 months after leukoplakia	4	6.25 (2.31–16.87)
Tongue (excluding base of tongue)		
No prior leukoplakia	1,970	Reference
Prior leukoplakia		
>3 months after leukoplakia	198	44.6 (37.9–52.4)
>12 months after leukoplakia	144	41.1 (34.2–49.5)
Gum		
No prior leukoplakia	808	Reference
Prior leukoplakia		
>3 months after leukoplakia	53	27.5 (20.5–37.0)
>12 months after leukoplakia	39	26.0 (18.6–36.3)
Floor of Mouth		
No prior leukoplakia	943	Reference
Prior leukoplakia		
>3 months after leukoplakia	45	22.6 (16.6–30.9)
>12 months after leukoplakia	34	22.0 (15.4–31.4)
Palate		
No prior leukoplakia	871	Reference
Prior leukoplakia		
>3 months after leukoplakia	33	17.9 (12.5–25.6)
>12 months after leukoplakia	24	16.5 (10.9–24.9)
Other		
No prior leukoplakia	3,319	Reference
Prior leukoplakia		
>3 months after leukoplakia	109	14.1 (11.5–17.3)
>12 months after leukoplakia	57	12.8 (10.1–16.3)

Abbreviations: OCC, oral cavity cancer; HR, hazard ratio; CI, confidence interval.
[a]Adjusted for sex, race, age, and calendar year at start of follow-up.

limiting to time beyond 12 months after leukoplakia (Table 2 and Table 3).

OCC stage and survival after cancer diagnosis

OCCs among people with leukoplakia were less likely to be diagnosed at a regional or distant stage compared with OCCs among people without a preceding leukoplakia (adjusted OR, 0.36; 95% CI, 0.30–0.43; Table 4). This effect on cancer stage was stronger for cancer diagnoses made ≤3 months after a leukoplakia claim (adjusted OR for distant/regional vs. localized, 0.32; 95% CI, 0.23–0.44; Table 4). A change in the stage distribution was observed for all OCC sites (not shown), though it was most strongly evident for tongue cancer (adjusted OR for distant/regional vs. localized, 0.17; 95% CI, 0.13–0.23).

Among OCC cases with prior leukoplakia, 84% of cases had surgery as part of their primary course of treatment, compared with 62% of cases with no prior leukoplakia ($P < 0.001$; Supplementary Table S2). By comparison, 29% of OCC cases with prior leukoplakia claim had radiation included in their primary treatment, compared with 50% of cases with no prior leukoplakia ($P < 0.001$). Cancer treatment was related to stage at diagnosis, but in analyses stratified by stage, cases with a prior leukoplakia diagnosis were still more likely to receive surgery and less likely to receive radiation at every stage (Supplementary Table S2).

Of the 8,686 OCCs not identified on the date of death, 4,463 died during follow-up (including 3,149 cancer-related deaths and 1,252 non–cancer-related deaths). Compared with OCCs without a prior leukoplakia diagnosis, those with leukoplakia had better overall survival at 1 year (78% vs. 71%) and 5 years (42% vs. 38%) after cancer diagnosis. Prior leukoplakia was associated with 26%

Published OnlineFirst July 9, 2015; DOI: 10.1158/1940-6207.CAPR-15-0091

Table 4. Associations between leukoplakia claim before OCC diagnosis and stage of cancer at diagnosis

Cancer stage	Localized	Regional	Distant	Regional or distant
Total, *N* (%)	3,336 (43%)	3,581 (46%)	825 (11%)	4,406 (57%)
No prior leukoplakia, *N* (%)	2,942 (41%)	3,411 (48%)	803 (11%)	4,214 (59%)
Prior leukoplakia, *N* (%)	394 (67%)	170 (29%)	22 (4%)	192 (33%)
OR (95% CI)	Reference	0.37 (0.31–0.45)	0.21 (0.13–0.32)	0.34 (0.29–0.41)
Adjusted OR (95% CI)[a]	Reference	0.39 (0.32–0.47)	0.22 (0.14–0.34)	0.36 (0.30–0.43)
No prior leukoplakia, *N* (%)	2,942 (41%)	3,411 (48%)	803 (11%)	4,214 (59%)
Leukoplakia ≤3 mo. before cancer diagnosis, *N* (%)	120 (70%)	[b]	[b]	52 (30%)
OR (95% CI)	Reference	0.32 (0.23–0.46)	0.21 (0.10–0.46)	0.30 (0.22–0.42)
Adjusted OR (95% CI)[a]	Reference	0.33 (0.24–0.47)	0.23 (0.11–0.50)	0.32 (0.23–0.44)
No prior leukoplakia, *N* (%)	2,942 (41%)	3,411 (48%)	803 (11%)	4,214 (59%)
Leukoplakia >3 months before cancer diagnosis, *N* (%)	274 (66%)	[b]	[b]	140 (34%)
OR (95% CI)	Reference	0.39 (0.32–0.49)	0.20 (0.12–0.34)	0.36 (0.29–0.44)
Adjusted OR (95% CI)[a]	Reference	0.42 (0.33–0.52)	0.22 (0.13–0.37)	0.38 (0.31–0.47)

NOTE: The table excludes 258 cases that were diagnosed at the time of death and 944 cases that were unstaged at diagnosis. Of the unstaged cases, 43 had a prior leukoplakia claim and 901 had no prior leukoplakia claim.

Abbreviations: OCC, oral cavity cancer; OR, odds ratio; CI, confidence interval.

[a]Adjusted for sex, race, age at cancer diagnosis, and calendar year at cancer diagnosis.

[b]To preserve subject's anonymity, numbers and percentages are suppressed when a count of <11 can be derived, in accordance with the SEER-Medicare data use agreement.

lower overall mortality (aHR, 0.74; 95% CI, 0.65–0.84) and 31% lower cancer-specific mortality (aHR, 0.69; 95% CI, 0.60–0.81; Table 5). Non-cancer mortality also appeared 17% lower, though this association was not statistically significant (aHR, 0.83; 95% CI, 0.67–1.04). For cancer cases diagnosed ≤3 months after leukoplakia, the association with lower cancer-specific mortality was stronger, whereas an association with non-cancer mortality was not observed. Importantly, the associations with overall and cancer-specific mortality were not observed after adjusting for cancer stage (aHR for overall mortality, 0.88; 95% CI, 0.78–1.00; aHR for cancer-specific mortality, 0.88, 95% CI, 0.75–1.03; Table 5), indicating that mortality reductions arose from detection of OCCs at earlier stages.

Discussion

In this large, population-based study of the U.S. elderly, we found that people with oral leukoplakia had a substantially elevated risk of OCC. Notably, OCCs that occurred among individuals with prior leukoplakia were diagnosed at lower stages, were more frequently treated with surgery, and had better survival than OCCs diagnosed without a prior leukoplakia. Our observations provide preliminary evidence for the potential benefit of leukoplakia screening in reducing mortality from OCC through early detection.

In the present study, individuals with leukoplakia had a high absolute risk of being diagnosed subsequently with a cancer. Approximately 0.7% were diagnosed with OCC within 3 months of leukoplakia diagnosis. This high early risk partly reflects prevalent OCCs identified during the diagnostic work-up following a leukoplakia diagnosis. Thereafter, however, approximately 0.4% of individuals with leukoplakia continued to develop OCC per year, and the incidence was constant over time (Fig. 1). This malignant transformation rate is substantial, although it is lower than rates reported in the literature (8, 9, 13, 22). We believe the population-based design of our study

Table 5. Association between leukoplakia diagnosis before OCC diagnosis and mortality after cancer diagnosis

	Deaths	Mortality rate, per 100 person-years	Unadjusted HR (95% CI)	Adjusted 1[a] HR (95% CI)	Adjusted 2[b] HR (95% CI)
			All-cause mortality		
No leukoplakia	4,207	22.6	Reference	Reference	Reference
Leukoplakia	256	17.4	0.76 (0.67–0.87)	0.74 (0.65–0.84)	0.88 (0.78–1.00)
≤3 months before cancer	83	16.4	0.75 (0.60–0.92)	0.73 (0.59–0.90)	0.86 (0.69–1.06)
>3 months before cancer	173	18.0	0.77 (0.66–0.90)	0.75 (0.64–0.87)	0.90 (0.77–1.05)
			Cancer-specific mortality[c]		
No Leukoplakia	2,980	16.0	Reference	Reference	Reference
Leukoplakia	169	11.5	0.71 (0.60–0.82)	0.69 (0.60–0.81)	0.88 (0.75–1.03)
≤3 months before cancer	48	9.49	0.62 (0.47–0.81)	0.61 (0.46–0.81)	0.76 (0.58–1.00)
>3 months before cancer	121	12.6	0.75 (0.63–0.90)	0.74 (0.61–0.89)	0.94 (0.78–1.13)
			Non-cancer mortality[d]		
No leukoplakia	1,170	6.29	Reference	Reference	Reference
Leukoplakia	82	5.60	0.89 (0.71–1.11)	0.83 (0.67–1.04)	0.88 (0.70–1.10)
≤3 months before cancer	33	6.52	1.02 (0.73–1.43)	0.94 (0.67–1.33)	0.98 (0.70–1.38)
>3 months before cancer	49	5.11	0.82 (0.62–1.09)	0.77 (0.58–1.03)	0.82 (0.61–1.09)

Abbreviations: OCC, oral cavity cancer; HR, hazard ratio; CI, confidence interval.

[a]Adjusted for sex, race, age at cancer diagnosis, and calendar year at cancer diagnosis.

[b]Adjusted for sex, race, age at cancer diagnosis, calendar year at cancer diagnosis, and cancer stage.

[c]Cancer-specific mortality was defined as codes C00.0–C97.0 for causes of death coded with ICD-10.

[d]Non-cancer mortality was defined as deaths that were not coded as C00.0–C97.0 with ICD-10 and were not categorized as unknown causes of death. Sixty-two deaths were attributable to unknown causes (57 among oral cancer cases with no prior leukoplakia, and 5 among oral cancer cases with prior leukoplakia).

Published OnlineFirst July 9, 2015; DOI: 10.1158/1940-6207.CAPR-15-0091

likely explains this lower transformation rate. Indeed, reported transformation rates have generally been lower in population-based studies relative to clinic-based studies, which often include higher risk individuals (11).

Even discounting the OCC cases diagnosed in the first 3 months after a leukoplakia diagnosis (or even the first year), our study shows that people with leukoplakia had approximately 20 times higher OCC risk compared with those without leukoplakia. This elevated risk was observed for all oral cavity sites, among men and women, and across all ages. Nonetheless, we found that associations were strongest for cancers of the tongue and floor of the mouth, among women, and among individuals $\geq$75 years of age, consistent with prior literature (8, 11, 14). Notably, despite the strong association of leukoplakia with OCC risk, only 7% of OCCs were preceded by a leukoplakia diagnosis. Because leukoplakia presumably occurs as a precursor for a large fraction of OCCs, this observation highlights significant underdiagnosis in the elderly population.

Beyond providing an estimate of OCC risk after leukoplakia, our results indicate that screening for leukoplakia could potentially lead to early OCC detection, and as a consequence, reduced mortality from OCC. In support of this possibility, we found that OCCs that occurred after leukoplakia were diagnosed at a lower stage when compared with OCCs that occurred among individuals without a leukoplakia. Furthermore, OCCs diagnosed after leukoplakia were more often treated with surgery, even after accounting for differences in stage, indicating that these tumors were probably smaller in size. Indeed, the attenuation of the associations with mortality that we observed in our stage-adjusted regression models indicates that almost all of the survival benefit can be attributable to lower stage at cancer diagnosis.

Admittedly, our results are based on nonrandomized comparisons, and improved survival could reflect lead-time bias, in which time to cancer-related death appears longer because the diagnosis is made earlier in the course of cancer progression (23). It is also possible that cancers preceded by an easily diagnosable oral leukoplakia may be less aggressive in nature than cancers not preceded by a leukoplakia. In addition, our observation of nonsignificantly lower non-cancer mortality among OCC cases with a preceding leukoplakia diagnosis suggests that people with a leukoplakia diagnosis were healthier or had better access to clinical care. These alternative explanations notwithstanding, a prior community-randomized trial of leukoplakia screening in India found that OCCs were diagnosed at significantly lower stages, and that OCC mortality was reduced, similar to the findings in our study (24).

Limitations of our study should be acknowledged. First, as we only had information on Medicare claims after age 65, we were unable to determine the duration of time individuals had leukoplakia. Second, our leukoplakia diagnoses were identified through Medicare claims, without standardized leukoplakia diagnostic criteria or supporting information on histopathology or anatomic site. Thus, our observation of elevated risks for all OCC sites could reflect leukoplakias at the same anatomic sites and the effect of field carcinogenesis, a well-recognized phenomenon for OCCs (25, 26). In addition, leukoplakia Medicare claims may disproportionately capture larger and more severe leukoplakias, which could lead to overestimation of OCC risk. Finally, we did not have data on tobacco smoking or chewing, which could affect progression to OCC. We also did not have data on leukoplakia treatment, but prior studies have reported inconsistent results for the efficacy of treatment in preventing malignant transformation (22, 27, 28).

Our study also has important strengths. One was the use of a large population-based sample representative of the U.S. elderly population. Consequently, our study has high generalizability when compared with studies restricted to high-risk populations in tertiary care. As our study had extended follow-up and used an efficient case–cohort design, we identified a large number of OCC cases resulting in precise estimates of relative risk and cumulative incidence. The use of SEER cancer data strengthens the reliability of our outcome measurement as the SEER registries have strict data quality standards for case ascertainment and follow-up (http://seer.cancer.gov/). In addition, the availability of detailed SEER cancer data allowed us to examine associations with cancer stage, primary course of treatment, and survival after a cancer diagnosis.

Our results have important clinical implications. Our observations of a substantially elevated OCC risk among individuals with leukoplakia, the diagnosis of OCCs at earlier stages, and reduced mortality among individuals with leukoplakia, all point to the potential for oral leukoplakia screening in reducing OCC mortality. Although observational in nature, our study provides support for randomized trials to evaluate the benefits and harms of oral leukoplakia screening among high-risk individuals in the United States. Additional studies are needed to identify high-risk populations, validate methods for oral leukoplakia screening, including the standardization of diagnostic criteria, and ultimately evaluate the cost effectiveness of screening in the United States. Indeed, in their most recent evaluation of screening for oral cancer, the U.S. Preventive Services Task Force underscored all of these aspects as key research needs (4).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The interpretation and reporting of the data presented in this article are the sole responsibility of the authors.

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Acknowledgments

The authors acknowledge the efforts of the Applied Research Program, National Cancer Institute; the Office of Research, Development and Information, Centers for Medicare and Medicaid Services; Information Management Services, Inc.; and the SEER Program tumor registries in the creation of the SEER-Medicare database.

Grant Support

E.L. Yanik, H.A. Katki, E.A. Engels, and A.K. Chaturvedi were supported by the Intramural Research Program of the National Cancer Institute at the NIH.

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Received March 5, 2015; revised June 18, 2015; accepted July 5, 2015; published OnlineFirst July 9, 2015.

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Published OnlineFirst July 9, 2015; DOI: 10.1158/1940-6207.CAPR-15-0091

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Cancer Prev Res 2015;8:857-863. Published OnlineFirst July 9, 2015.