Original Article

Time-Varying Survival Effects for Squamous Cell Carcinomas at Oropharyngeal and Nonoropharyngeal Head and Neck Sites in the United States, 1973-2015

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BACKGROUND: Anatomical site is strongly associated with head and neck cancer etiology, and etiology and patient sociodemographic characteristics are prognostic factors for survival. It is not known whether the effects of these predictors persist over the postdiagnosis period or are strongest proximal to the time of diagnosis. **METHODS:** Using survival times and causes of death for 180,434 patients with head and neck cancer in the Surveillance, Epidemiology, and End Results cancer registry (1973-2015), the empirical cumulative incidences of cancer-specific death and other-cause death were calculated with a competing risks framework, and the time-dependent effects (hazard ratios) of anatomical tumor site (oropharynx, oral cavity, or hypopharynx/larynx), age, sex, race, and year of diagnosis on cancer-specific death and other-cause death, stratified by tumor stage, were estimated. **RESULTS:** All effects were significantly time-varying ($P < .001$). Patients with nonoropharyngeal cancer had a higher hazard of cancer-specific death but a similar cumulative fraction of deaths because of a higher rate of death from other causes. Cancer-specific survival has not changed for patients with nonoropharyngeal cancer over the past decades but has improved since 2000 for patients with oropharyngeal cancer. The effects of age and sex on cancer survival were strongest proximal to the diagnosis, whereas the effect of race persisted over time. **CONCLUSIONS:** Recent improvements in survival for patients with oropharyngeal cancer may be due more to an increasing fraction of cancers attributable to human papillomavirus than to increasing treatment effectiveness. The prognostic strength of anatomical site and other predictors changes over the postdiagnosis period. ***Cancer* 2020;126:5137-5146**. © *2020 American Cancer Society*.

LAY SUMMARY:

- It is generally assumed that the effects of tumor and personal characteristics on the survival of patients with head and neck cancer are fixed over time, but this study shows that many factors are most important only in the first few years after diagnosis.
- Also, recent improvements in the survival of patients with head and neck cancer appear to benefit only patients with cancers of the oropharynx. The improvements may be due more to an increasing fraction of cancers caused by human papillomavirus (which generally have better outcomes) than to advances in head and neck cancer treatment overall.

KEYWORDS: hazard model, head and neck cancer, human papillomavirus, oropharynx cancer, survival analysis.

INTRODUCTION

Cancers of the head and neck are primarily squamous cell carcinomas originating in the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, or sinonasal tract.[1] There are 2 primary etiologies for these cancers: 1) tobacco and alcohol use and 2) human papillomavirus (HPV).[2,3] Each has its own distinct presentation, outcomes, and molecular markers.[4] Most cancers caused by HPV are in the oropharynx because of HPV's preference (tropism) for that site.[5] In the United States, it is estimated that the fraction of oropharynx cancers attributable to HPV is 70% or more and increasing,[6-8] whereas HPV-attributable cancer in the oral cavity, hypopharynx, and larynx is relatively rare.[9] Globally, it is estimated that approximately 45% of oropharynx cancers are attributable to HPV, whereas the fraction is only 20% to 25% for other head and neck sites.[10]

HPV status and related biomarkers are strongly associated with improved cancer-specific and overall survival times.[1,11-13] HPV-negative tumors are less responsive to treatment, especially if the patient continues smoking,[14,15] and many patients with HPV-negative tumors have smoking-related comorbidities. Because it is strongly predictive of disease

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outcomes, HPV status has become a major factor in clinical care.[16,17] In addition to HPV status, the tumor stage at the time of diagnosis is strongly associated with future disease outcomes. Demographic factors such as age and sex are also likely associated with survival. As with most cancers, socioeconomic disparities in head and neck cancer survival persist.[18]

Although most analyses treat such factors as having a constant effect on survival, it is not well understood whether this is an appropriate assumption or whether some of these effects might be attenuated or otherwise change over the postdiagnosis period. For head and neck cancer, disease progression after diagnosis has a well-understood time frame. Locoregional disease recurrence happens in 15% to 50% of patients with head and neck cancer, with the rate depending on the subsite, stage, treatment, and other factors, and if the disease is going to recur, it does so in less than 2 years in approximately 80% of patients.[19] Survival after recurrence is usually poor with a median survival time of approximately 2 years,[19,20] although outcomes have improved in the past decades.[21] Thus, it is likely that the magnitude of the importance of tumor characteristics such as the tumor site and stage will change over the postdiagnosis period. Similarly, it is likely that the influence of demographic and socioeconomic disparities as well as other covariates such as age will change over the postdiagnosis period, and this necessitates estimation of time-dependent effects (nonproportional hazards). Any temporal effects of these factors on survival could have implications for risk prediction, treatment, and care.

Our focus in this analysis is death due to head and neck cancer rather than overall survival. It is clear that some factors such as tumor stage are likely to be more strongly associated with death from cancer than death from other causes. Other factors such as age are likely to be more strongly associated with death from other causes than death from head and neck cancer. Death due to head and neck cancer is directly affected by the quality of the treatment both for the initial primary occurrence and at the time of any recurrence as well as the quality and effectiveness of the postdiagnosis monitoring for recurrence. Thus, we might expect the date of diagnosis, a proxy for temporal changes in treatment and surveillance, to also be associated with cancer-specific death rates, especially over the period considered by this study (1973-2015).

In this analysis, we consider cause-specific cancer death data for head and neck squamous cell carcinomas (HNSCCs) from the US Surveillance, Epidemiology, and End Results (SEER) cancer registry grouped into 3 sites: oropharyngeal, oral cavity, and hypopharynx/larynx. We use a competing risks framework to observe the empirical evolution of cancer-specific and other-cause mortality and a Cox model framework with time-dependent coefficients to estimate how the effects of baseline covariates change over a patient's time since diagnosis. Although previous studies have used Cox proportional hazards models to explore head and neck cancer survival in SEER (eg, Janz et al[22]), no studies, to our knowledge, have looked at time-dependent effects.

MATERIALS AND METHODS

Data

We used cancer-specific survival data from the SEER 18 cancer registry (1973-2015 [varying by subregistry])[23] for malignant HNSCCs. This analysis included only patients whose first cancer was HNSCC because cancer-specific survival in SEER is defined only for first cancers.[24] Similarly to previous analyses,[25,26] we grouped anatomical sites of carcinomas by their *International Classification of Diseases, Tenth Revision* codes. The following sites were considered to be oropharyngeal with a possibly HPV etiology: base of tongue (C01), lingual tonsil (C2.4), palate excluding hard palate (C5.1-C5.9), tonsil (C9.0-C9.9), oropharynx (C10.0-C10.9), pharynx not otherwise specified (C14.0), and Waldeyer ring (C14.2). The following sites were considered to be oral cavity and to likely not have an HPV etiology: oral tongue (C2.0-2.3 and C2.8-C2.9), gum (C3.0-C3.9), floor of mouth (C4.0-C4.9), hard palate (C5.0), and other and unspecified parts of the mouth (C6.0-C6.9). The following sites were considered to be hypopharyngeal/laryngeal and to likely not have an HPV etiology: pyriform sinus (C12), hypopharynx (C13), and larynx and glottis (C32). Other head and neck sites, including the lips (C00), salivary gland (C07-C08), and nasopharynx (C11), were not included in this analysis. We included only cancers with squamous cell histology (histology type codes 8050-8076, 8078, 8083, 8084, and 8094 from the *International Classification of Diseases for Oncology, Third Edition*). This analysis was not regulated as human subjects research because it involved deidentified data.

Because cause-specific death is vulnerable to misclassification of death on death certificates, the SEER registry takes into account the tumor sequence, the site of the original tumor, and comorbidities when determining which deaths are attributable to the cancer diagnosis.[24] Specifically, if a patient has died with only 1 cancer diagnosis, then his or her death is attributed to cancer if

TABLE 1. Number of Individuals Diagnosed With Oropharyngeal, Oral Cavity, or Hypopharyngeal/Laryngeal Squamous Cell Carcinomas in the SEER Cancer Registry (1973-2015) by Covariate and Number of People at Risk (ie, Not Dead or Censored) 5, 10, and 15 Years After Diagnosis

	At Diagnosis		5 y		10 y		15 y	
Covariate	No.	%	No.	%	No.	%	No.	%
All	180,434		69,469		33,066		13,722	
Age								
<50 y	24,386	13.5	12,309	17.7	7317	22.1	3661	26.7
50-59 y	52,689	29.2	22,372	32.2	11,406	34.5	5027	36.6
60-69 y	55,881	31.0	21,348	30.7	9746	29.5	3873	28.2
≥70 y	47,478	26.3	13,440	19.3	4597	13.9	1161	8.5
Sex								
Male	135,416	75.1	51,986	74.8	24,503	74.1	9964	72.6
Female	45,018	24.9	17,483	25.2	8563	25.9	3758	27.4
Race								
White	150,160	83.2	59,845	86.1	28,565	86.4	11,870	86.5
Black	21,563	12.0	6263	9.0	2818	8.5	1107	8.1
Other/unknown	8711	4.8	3361	4.8	1683	5.1	745	5.4
Anatomical site								
Oropharynx	60,859	33.7	21,579	31.1	9110	27.6	2943	21.4
Oral cavity	48,834	27.1	18,444	26.5	8952	27.1	3881	28.3
Hypopharynx and larynx	70,741	39.2	29,446	42.4	15,004	45.4	6898	50.3
Tumor stage								
Localized	47,790	26.5	27,098	39.0	15,829	47.9	7854	57.2
Regional	80,653	44.7	28,422	40.9	13,237	40.0	4853	35.3
Distant	19,212	10.6	3356	4.8	1230	3.7	425	3.1
Unstaged	32,779	18.2	10,593	15.2	2770	8.4	599	4.4
Year of diagnosis								
1973-1984	24,863	13.8	10,998	15.8	7093	21.5	4482	32.7
1985-1999	39,461	21.9	18,504	26.6	12,042	36.4	7840	57.1
2000-2015[a]	116,110	64.4	39,967	57.5	13,931	42.1	1400	10.2

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.
[a]More recent diagnoses have not yet made it to 5, 10, or 15 years after diagnosis.

the cause of death is given as cancer at that site, cancer within the same organ system, any malignant cancer, or AIDS with cancer. If a patient has more than 1 cancer diagnosis, then cancer-specific survival is calculated only for the first cancer diagnosed, and the cancer death variable is similarly derived, with the exception that the cause of death from other malignant cancers is not included as death from the primary cancer. Three event types were derived from the SEER cause-specific death variables: censored (alive), dead from cancer, and dead from other causes. Only events with event times of at least 1 month were considered (ie, we removed diagnoses occurring at the time of death). This data set includes 180,434 individuals with events spanning from 1 month to 41 years. We provide the number of individuals at risk (ie, not dead or censored) by covariate at 0, 5, 10, and 15 years after diagnosis in Table 1. The median length of follow-up (ie, time to censoring) was 5.4 years (range, 0.1-42.9 years); there was no substantial difference in the length of follow-up for the different anatomical subsites (oropharynx, 4.9 years; oral cavity, 5.6 years; hypopharynx and larynx, 5.9 years).

Statistical Analysis

We considered 6 covariates available in the SEER registry: tumor stage at diagnosis, age at diagnosis, sex, race, anatomical site (oropharynx, oral cavity, or hypopharynx/larynx), and year of diagnosis. We used SEER historic stages (localized, regional, and distant) to be consistent across the 1973-2015 time period. Because we were considering long-term survival, we used a competing risks framework[27-29] to acknowledge that the underlying at-risk population was changing on account of mortality from causes other than the disease. This framework can be simply expressed with a multistate model (Fig. 1A). In the presence of competing risks, the Kaplan-Meier estimator for standard survival analyses is not appropriate because censoring is no longer uninformative.[27,28] Instead, we estimated the cumulative incidence in each state with an Aalen-Johansen estimator[30] (Fig. 1B).

Although these multistate cumulative incidence estimates were empirical, we also implemented cause-specific Cox regression to estimate the impact of covariates on the hazard. Because hazard models estimate instantaneous rates, we do not need to account for competing

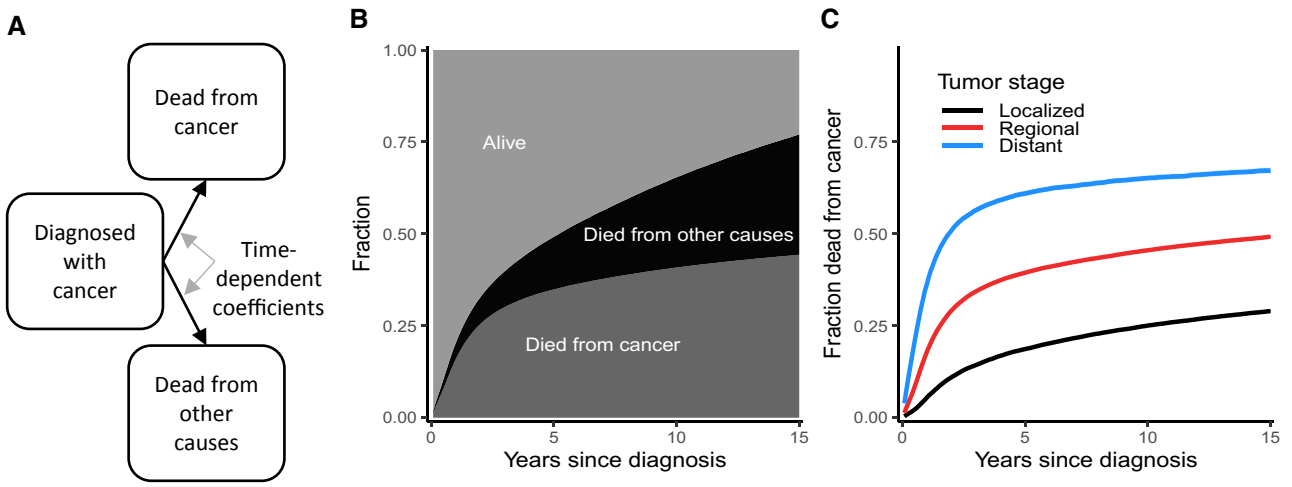

FIGURE 1. (A) Multistate model for a competing risks framework acknowledging 2 mutually exclusive (ie, competing) endpoints. We used cubic B-splines to estimate the time-dependent effects of baseline covariates on the hazard of cause-specific and other mortality. (B) Empirical fraction (cumulative incidence) of patients with head and neck cancer who are alive, have died of their cancer, or have died of other causes as a function of the time since diagnosis. (C) Empirical fraction of patients (cumulative incidence) diagnosed with head and neck cancer who have died of that cancer (stratified by tumor stage). Those who have not died of their cancer may have died of other causes or are alive.

risks unless we want to use the hazard model to estimate overall survival (both the cancer and other-cause hazard models would need to be simultaneously integrated to model cumulative incidence).[31] Time-dependent effects have been used to relax the proportional hazards assumption of Cox regression,[32] and this has allowed us to detect if certain covariates are important immediately after detection or across the entire postdiagnosis period. The hazard $\lambda(t)$ is given as a function of the baseline hazard $\lambda_0(t)$, the time-varying coefficient $\beta(t)$, and the fixed covariate x:

$$\lambda(t) = \lambda_0(t)\, e^{\beta(t)x}$$

Stratification by another covariate allows separate baseline hazards to be computed for each stratum j while the estimated values of β are constant across strata:

$$\lambda_j(t) = \lambda_{0,j}(t)\, e^{\beta(t)x}$$

Here we stratified by tumor stage because there were substantial differences in the baseline hazards by tumor stage (Fig. 1C). As in the traditional Cox model, a nonparametric Breslow estimator was used to calculate the Cox partial likelihood.

Previous work with time-dependent coefficients has been largely limited to basic functions and has incorporated linear effects or step functions. Here we implemented a spline estimator. Splines are piecewise polynomials that are smoothly joined: 2 n-degree polynomials are smoothly joined at a point known as a knot if the functions and their n–1 derivatives are continuous at that point. Here we used cubic B-splines with an intercept.[33,34] Knots were chosen by quintiles of the times of cancer death, namely 6, 12, 22, and 50 months, with boundary knots at 1 and 477 months, but we constrained the presentation of results to a 15-year period of interest. All Cox regression models were stratified by tumor stage (localized/regional/distant/unstaged). The other 5 cancer survival factors were model variables: anatomical site, age at diagnosis, sex, race, and year of diagnosis. We also ran the models separately for patients with oropharyngeal cancer and patients with nonoropharyngeal cancer, with anatomical site dropped as a variable. We implemented the multivariable, cause-specific Cox regression by using a stochastic gradient ascent method[35,36] in R (v3.6.1). Confidence intervals for the spline effects were calculated as reported by Durrleman and Simon.[37]

RESULTS

In plots in Figures 2 to 4, we show the fraction of patients diagnosed with head and neck cancer who have died of the disease as a function of the time since diagnosis (ie, cumulative incidence); these are empirical results from the Aalen-Johanson estimator. Below these plots, we also show the corresponding estimated time-dependent hazard ratio, that is, how much more likely someone is to

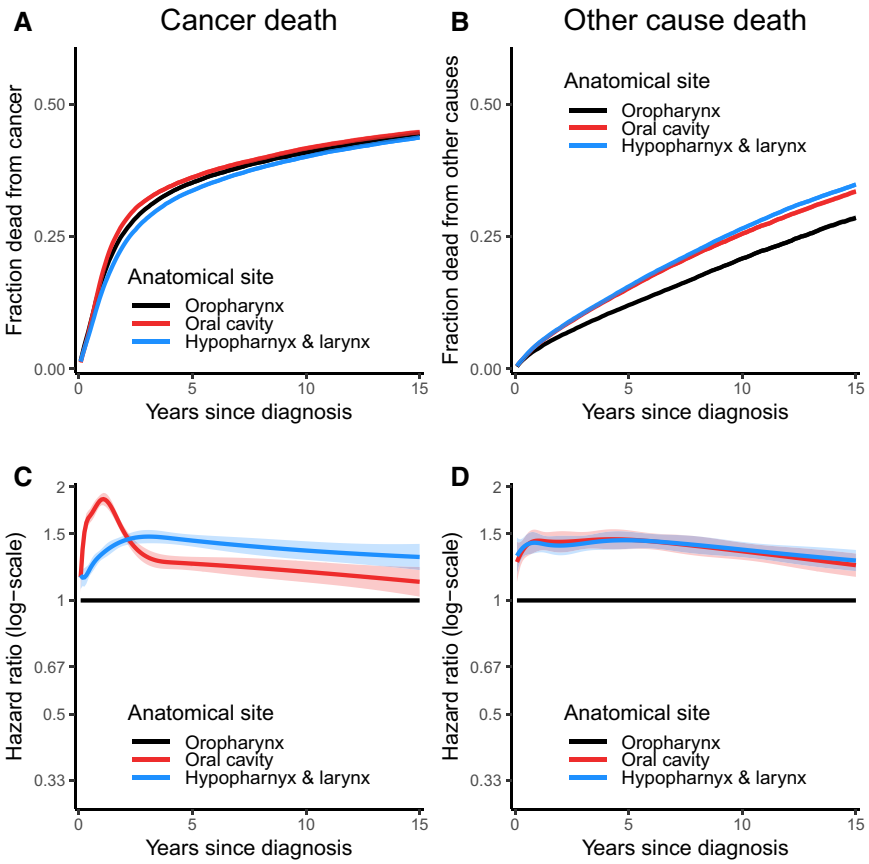

FIGURE 2. Fraction of patients (ie, cumulative incidence) diagnosed with head and neck cancer who have died of (A) that cancer or (B) other causes as a function of the time since diagnosis for each anatomical site. Time-dependent hazard ratios ($e^{\beta(t)x}$) for (C) cancer death and (D) other-cause death for each anatomical site in multivariable models stratified by tumor stage. The ribbons in all plots represent 95% confidence intervals for the estimate; confidence intervals for the cumulative incidence plots may be obscured by line thickness. $\beta(t)$ indicates time-varying coefficient; x, fixed covariate.

die of cancer at that time than someone in the reference group; these are results from the Cox models with time-varying effects. All effects on cancer death are significantly time-varying ($P < .001$).

We see that the empirical fraction of patients who die of their cancers does not differ dramatically by anatomical sites (Fig. 2A). In part, this result reflects the improved survival of patients with oropharyngeal cancer despite their tumors being more advanced overall (for patients with oropharyngeal cancer whose cancer was staged, 13% of cancers were localized, 69% were regional, and 18% were distant, whereas 45% were localized, 45% were regional, and 10% were distant for patients with nonoropharyngeal cancer). However, we also see that because of the competing risk of other death, important underlying differences are masked when cancer-specific survival is considered on its own. Patients with cancer of the oral cavity or the hypopharynx/larynx are more likely to die of other causes than patients with oropharyngeal cancer (Fig. 2B). When we examine the time-dependent hazard ratios (which take tumor stage into account through baseline hazard stratification) for cancer death (Fig. 2C) and other-cause death (Fig. 2D), we see that patients with oral cavity and hypopharyngeal/laryngeal cancers have a higher hazard of both cancer death and death from other causes. The relative hazard of death due to oral cavity cancer in particular appears to peak in the 1 to 2 years after diagnosis, possibly because of recurrence. The relative hazard of death due to other causes is similarly high for patients with oral cavity and hypopharyngeal/laryngeal cancer; a larger fraction of these cancers may be caused by tobacco exposure, which can cause myriad other morbidities and result in higher overall mortality. The higher hazards of both death due to cancer and death due to other causes together result in the empirical fraction seen in Figure 2A; that is, although the hazard of cancer death is higher in the nonoropharyngeal

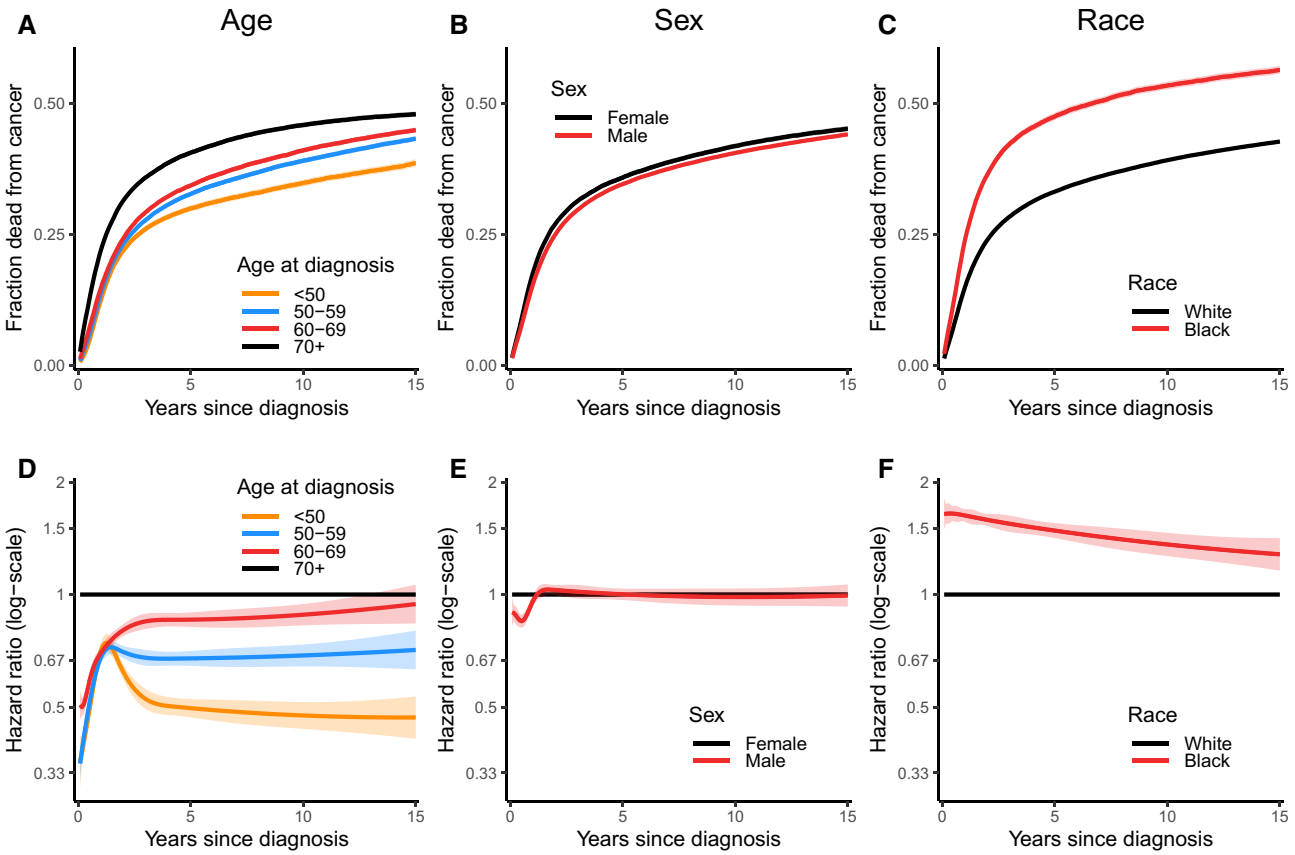

FIGURE 3. Fraction of patients (ie, cumulative incidence) diagnosed with head and neck cancer who have died of that cancer as a function of the time since diagnosis for (A) age at diagnosis, (B) sex, and (C) race. Time-dependent hazard ratios ($e^{\beta(t)x}$) for cancer death for (D) age at diagnosis, (E) sex, and (F) race in multivariable models (adjusted for sex, race, year of diagnosis, and anatomical site) stratified by tumor stage. The ribbons in all plots represent 95% confidence intervals for the estimate; confidence intervals for the cumulative incidence plots may be obscured by line thickness. $\beta(t)$ indicates time-varying coefficient; x, fixed covariate.

head and neck cancer groups, there are also fewer patients alive who can die of cancer.

We similarly consider the time-varying effect of age of diagnosis, sex, race, and year of diagnosis on cancer survival (Fig. 3). As expected, survival decreases with the age at diagnosis (Fig. 3A,D). Although the effect of age is substantial at the time of diagnosis, it appears to be attenuated dramatically over the first 1 to 2 years before stabilizing or slowly increasing in magnitude again. This means that younger patients have an initially lower likelihood of death from cancer but that the rate of cancer death accelerates after the first year. When considering sex, the hazard of cancer death is lower for men than women in the first 1 to 2 years but is the same afterward (Fig. 3B,E). A more substantial difference can be seen by race, with higher hazard rates in Black patients than White patients (Fig. 3C,F). This disparity is initially high and is attenuated slightly over subsequent decades. Corresponding results for other-cause mortality are shown in the supporting information.

Finally, we see a moderate impact of the year of diagnosis (Fig. 4A), with head and neck tumors diagnosed after 2000 associated with lower rates of death due to cancer, particularly after the first year after diagnosis. Although the impact of age at diagnosis, sex, and race is largely qualitatively similar for oropharyngeal and nonoropharyngeal cancers (with covariates generally having a stronger effect on the hazard of cancer death for oropharyngeal cancer; see the supporting information), there is a dramatic difference between the 2 groups in survival by year of diagnosis (oropharyngeal in Fig. 4B and nonoropharyngeal in Fig. 4C). For the oropharyngeal cancers, survival has improved dramatically over time, with the hazard of cancer death for those diagnosed in 2000-2015 up to less than half of that for those diagnosed in 1973-1984 (Fig. 4E). For

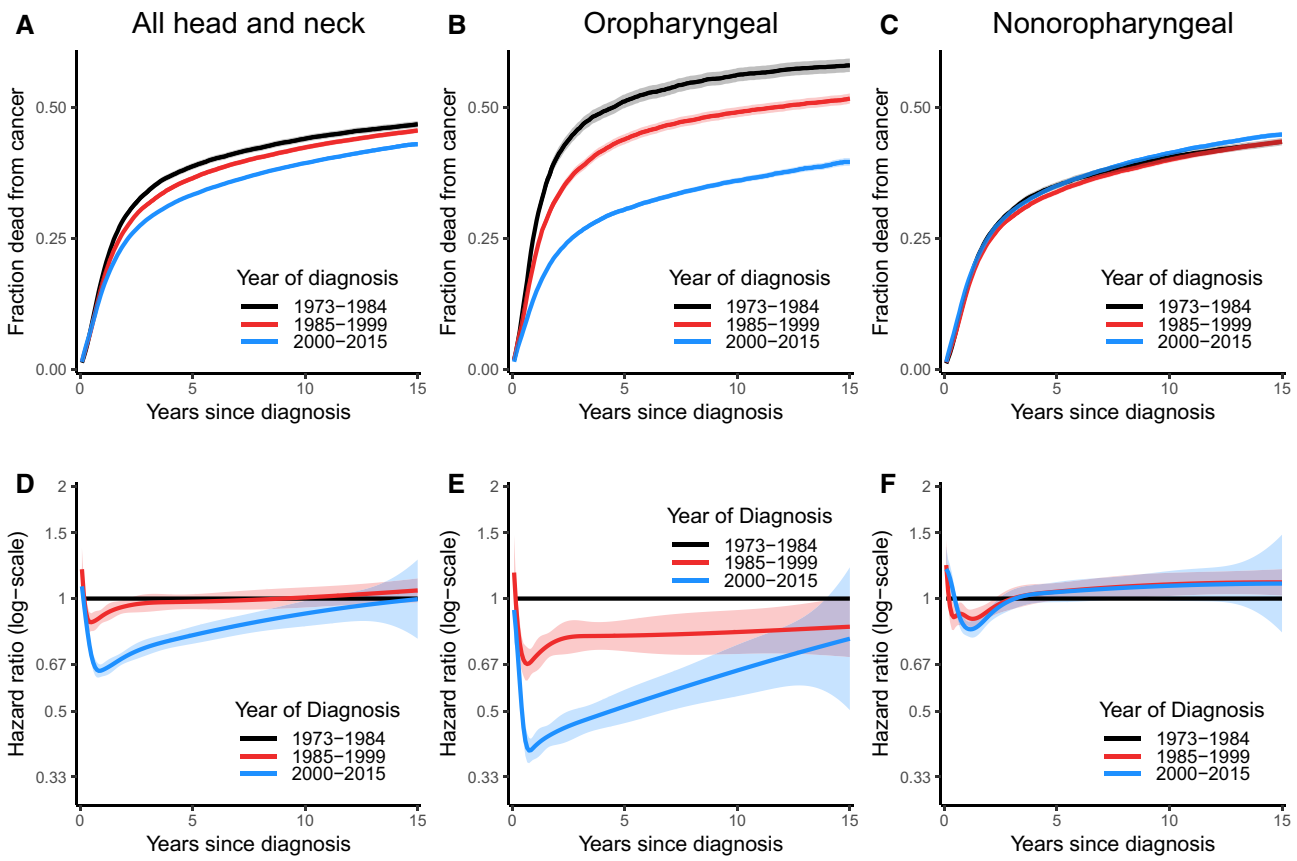

FIGURE 4. Fraction of patients (ie, cumulative incidence) diagnosed with head and neck cancer who have died of that cancer as a function of the time since diagnosis for (A) all head and neck cancers, (B) oropharyngeal cancers, and (C) oral cavity and hypopharyngeal/laryngeal cancers. Time-dependent hazard ratios ($e^{\beta(t)x}$) for cancer death for the year of diagnosis for (D) all head and neck cancers, (E) oropharyngeal cancers, and (F) oral cavity and hypopharyngeal/laryngeal cancers in multivariable models (adjusted for sex, race, year of diagnosis, and anatomical site) stratified by tumor stage. The ribbons in all plots represent 95% confidence intervals for the estimate; confidence intervals for the cumulative incidence plots may be obscured by line thickness. $\beta(t)$ indicates time-varying coefficient; x, fixed covariate.

the nonoropharyngeal head and neck cancers, on the other hand, survival has been relatively constant over time (Fig. 4F).

DISCUSSION

Here we have assessed how the cause-specific hazard of death from head and neck cancer changes over the 15 years after diagnosis. Our results demonstrate that many factors in head and neck cancer survival do not have a constant effect across a patient's postdiagnosis trajectory. Indeed, we have found that the effects of baseline age and sex are attenuated in the first few years after diagnosis, whereas the effects of race and year of diagnosis are attenuated more slowly over a 15-year time frame. These results indicate that the proportional hazards assumptions made in Cox models with constant effects are violated in many cases and may result in misleading estimates. However, the need to investigate time-varying effects in cancer survival has only recently begun to be appreciated (eg, Andreassen et al[38] and Mozumder et al[39]). Because clinical decisions are often informed by the survival prognosis, it is essential to accurately characterize both how and when prognostic factors are associated with survival. As individualized risk calculators continue to be developed and refined (eg, Wang et al[40] and Emerick et al[41]), time-dependent effects should be considered during model development. For example, risk-prediction models could integrate the time-dependent cancer-specific and other-cause mortality hazard rates specific to a patient's sociodemographic and tumor characteristics to create predictions of the likelihood of survival, cancer death, and other-cause death over time.

We know that HPV status is predictive of cancer survival and that HPV is the etiological agent of a larger fraction of oropharyngeal cancers than oral cavity or hypopharyngeal/laryngeal cancers.[11,13] Our analysis is consistent with the prior literature: we have found that patients with oropharyngeal cancers have a lower cancer-specific death rate (Fig. 2C). There has been a modest improvement from 1973 to 2015 in the number who will die of any head and neck cancer within 15 years (Fig. 4). However, as we have shown, this improvement is predominantly due to the lower hazard for oropharyngeal cancers diagnosed in 2000-2015 in comparison with those diagnosed in 1973-1984. The improvement in survival then may be more a reflection of changing etiologies at the population level[6]—that is, an increase in the proportion of cancers caused by HPV versus tobacco, alcohol, or other risk factors—than improvements in care in general.

Despite the differences in cancer-specific death rates across anatomical sites, the overall probability of dying of cancer is similar across the anatomical sites (Fig. 2A) because the other-cause mortality is also higher for the nonoropharyngeal head and neck cancers (Fig. 2B). Our results emphasize the importance of the competing risks perspective in cancer survival, particularly for cancers with a comparatively low initial hazard rate. Cancer specialists may need to consider patients' health more broadly (eg, by encouraging smoking cessation[42,43]), particularly when patients are not seeing a primary care provider for general preventive care.

We have found a notable difference in the hazard rate of death from head and neck cancer in the first year after diagnosis for older patients in comparison with younger patients, and this may be a result of the fact that older patients are less likely to be prescribed or able to complete the aggressive treatments (surgery or high-dose cisplatin chemotherapy) that are standard in head and neck cancer. This analysis expands on previous work that considered the prognostic significance of age in oropharyngeal cancer.[44]

Furthermore, we have found that men are overall less likely to die of their head and neck cancer and that this difference is largely due to lower hazard in the first 2 years after diagnosis (and is not due to a difference in other-cause mortality). When considering the sites separately (see the supporting information), we see that this effect is seen only for oropharyngeal cancers. Previous work has also suggested that there appears to be no sex differences in survival for nonoropharyngeal sites.[45] However, the same previous analysis found that female patients with oropharyngeal cancer had better, rather than worse, survival.[45] A second study that did not distinguish between oropharyngeal and nonoropharyngeal sites found a nonsignificant advantage to being female.[18] More work is needed to determine the effect of sex on head and neck cancer survival. It possible that conflicting results may be due to different prevalences of HPV status by sex in the studied populations.

Racial disparities are well documented in head and neck cancer survival.[18,45-47] In our analysis, the hazard ratio plots indicate an initial hazard ratio of more than 1.5 for Blacks versus Whites, and it diminishes only slightly over time. Because this hazard ratio considers tumor stage and adjusts for age and other covariates, our interpretation is that this may be a genuine disparity due to access to and quality of care. The differences in the hazard in the first few years after diagnosis may suggest that on average White patients tend to receive better treatment and care than Black patients. The fact that the differences persist for longer times after treatment may also reflect that on average White patients tend to have better access to follow-up care and better follow-up care than Black patients. Other work has suggested that racial disparities are attributable almost entirely to differential HPV status (with Black patients less likely to have HPV-positive tumors).[45,46] Although our work cannot directly address this point, we find that racial disparities are larger among patients with oropharyngeal cancer but are still present for patients with oral cavity and hypopharyngeal/laryngeal cancer (see the supporting information). These results are consistent with differences in HPV status for oropharyngeal cancer but suggest that HPV status is not sufficient to completely account for survival disparities.

According to these data, fewer than 50% of patients diagnosed with head and neck cancer die of that cancer. Of those who do die of their cancer, 50% will die within the first 2 years. Head and neck cancer is generally considered to be curable in the sense that if the tumor does not recur within the first 5 years after treatment, it is unlikely to recur later.[19] This fact is reflected in the cumulative incidence plots, which stop increasing sharply after approximately 4 years. It is also notable and perhaps surprising that in this data set there are many deaths due to head and neck cancer after 10 years, so the cumulative incidence curves never completely level off, even after 15 years. These later deaths may be caused by second primary malignancies but be attributed to the first primary.[24] Second primaries are relatively common in the head and neck, possibly because of field cancerization[48] or continued

smoking. The cumulative incidence of second head and neck primaries may be as high as 25% in 10 years.[49]

There are 2 main limitations to this study. First, the available SEER data do not currently include important risk factor data, including HPV status (except for a subset of patients in the SEER Head and Neck With HPV Status Database[13]) and smoking and alcohol histories. Although anatomical site is a first-level proxy for head and neck cancer etiology, both HPV-positive tumors and HPV-negative tumors can be found at each head and neck site but with different prevalences. Hence, although this analysis is revealing and suggestive, any true effects of etiology are likely to be attenuated. Future analysis could investigate survival patterns for subgroups of the anatomical sites to possibly derive different, functional groupings of subsites. Next, although smoking is a strong risk factor for developing head and neck cancer, its impact on disease progression after diagnosis is less well defined. It is well known that smoking history and continued smoking are associated with worse cancer outcomes (both for all cancers and for head and neck cancers specifically).[50-52] Because of smoking's association with lung cancer and other lung diseases, it will have a strong association with the hazard of death from other causes, but the strength of this association is less clear. Similarly, comorbidities would be expected to be strongly associated with the hazard of death from other causes. Comorbidities also affect the hazard of death from head and neck cancer because they can preclude candidacy for surgery or chemotherapy, including high-dose cisplatin. However, because SEER does not provide these data, these interesting questions cannot be addressed here.

The second limitation is that long-term survival is subject to improper cause-of-death ascertainment and coding. Although SEER has developed methodologies to classify causes of death into cancer-related and other causes,[24] the classifications rely on physician cause-of-death coding, which is subject to human error, may have institutional or regional idiosyncrasies, and may be less likely to be linked to the cancer as the time since diagnosis increases. In the case of multiple tumors at the same or different sites in the same organ system, a cancer cause of death is attributed to the primary tumor; this methodology may account for the continued cancer-specific deaths more than 10 to 15 years after diagnosis.

In summary, we find that although patients with oropharyngeal cancer and patients with nonoropharyngeal cancer have similar probabilities of dying of their cancer over time, this result belies the lower overall survival of patients with nonoropharyngeal cancer. Moreover, cancer-specific survival has improved for patients with oropharyngeal cancer but not for patients with nonoropharyngeal cancer since 2000, likely because of an increasing fraction of HPV-attributable cancers among the patients with oropharyngeal cancer. We find that the effects of predictors of head and neck cancer–specific survival, including age, sex, and race, are not constant over the postdiagnosis period, and this suggests that future cancer survival analyses and risk calculators should take time-dependent effects into account.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Andrew F. Brouwer: Conceptualization, methodology, formal analysis, writing–original draft, writing–review and editing, and visualization. **Kevin He:** Methodology, software, and writing–review and editing. **Steven B. Chinn:** Methodology and writing–review and editing. **Alison M. Mondul:** Writing–review and editing. **Christina H. Chapman:** Writing–review and editing. **Marc D. Ryser:** Writing–review and editing. **Mousumi Banerjee:** Methodology and writing–review and editing. **Marisa C. Eisenberg:** Conceptualization, writing–review and editing, and funding acquisition. **Rafael Meza:** Conceptualization, writing–review and editing, and funding acquisition. **Jeremy M. G. Taylor:** Conceptualization, methodology, and funding acquisition.

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