Cause-specific mortality in patients with head and neck cancer: long-term follow-up of a population-based cohort from 1986 to 2012 accounting for competing risks

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ABSTRACT

Objectives: Recent recommendations for treating head and neck cancer (HNC) patients favor an individualized approach. Expected long-term survival – together with short-term survival – after diagnosis is the primary focus in assessing the treatment modality and follow-up scheme. "Disease-specific" survival up to five years is often used for measuring the prognosis and for assessing treatment methods. However, especially long-term survival is strongly affected by competing causes of death among HNC patients.

Materials and Methods: The long-term prognosis of patients with HNC in terms of mortality from both cancer and competing causes was analyzed according to recent methodological guidelines by examining cumulative incidence functions and models for cause-specific hazards and sub-distribution hazards in a population based cohort of 220 patients treated in a tertiary care center in Northern Finland.

Results: In addition to well-known tumor-related factors, mortality from HNC was associated with older age. The mortality from other causes of death was strongly dependent on age and Charlson's Comorbidity Index, but less on gender. When demonstrating the importance of individualized approach in simulated patients, the mortality was highly variable across patients with similar cancer status, but with different comorbidities or age.

Conclusion: The overall survival pattern of HNC patients depends not only on their cancer characteristics, but also varies greatly according to their age and comorbidities. Our findings support the need for individualized treatment and follow-up protocols, and active management of comorbid diseases. Appropriate methods for analyzing competing risks should be used when presenting survival estimates of cancer patients.

Key words: head and neck cancer; competing mortality; survival; follow-up; individualized prognosis

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is a common malignancy with approximately 630,000 annual cases diagnosed worldwide.[1] Despite the declining prevalence of smoking, the incidence of HNSCC is increasing[2], although the 5-year relative survival rate has improved somewhat through a changing etiology coupled with a rise in human papillomavirus (HPV)-associated disease and advances in treatment.[3,4]

From a clinical point of view, the first 5 years after treatment of HNSCC are usually considered to be the most important, as the majority of recurrences and deaths from HNSCC occur within that time frame. Typically, the prognosis is based solely on TNM classification, which gives a robust, but quite rough estimate of prognosis. A more individualized approach is nowadays recommended, and other factors that influence survival should be considered when counseling the patient about treatment. Realistic expectations of the long-term prognosis also help patients deal with the disease and participate in treatment planning. Moreover, in order to decide on follow-up schedules and inform patients properly, more accurate knowledge about the mortality of HNSCC patients with analysis of cause-specific mortality with a longer follow-up time is required.

The mortality of HNSCC patients has been widely explored in the literature, but fewer reports of long-term follow-ups of HNSCC patients in terms of causes of death have been presented. Most of these data are based on selected patient materials: cases with either advanced diseases or heavily treated patients from randomized controlled trials, so their results are not generalizable to all stages of HNSCC.[5-8] There are some reports that have analyzed causes of death in non-selected HNSCC patients, but these studies either have relatively short follow-up times or they address mortality in patients who have already survived the critical first few years after treatment.[9-12]

Traditionally, 5-year “cause-specific survival” or “disease-specific survival” and 5-year overall survival estimates of HNSCC patients have been used to quantify the prognosis of patients with different HNSCC sites and stages. However, “cause-specific survival” is computed using the Kaplan-Meier method, so that an individual experiencing a competing event (i.e. death from other cause) during the follow-up is

treated as “censored”, i.e. as if he or she continued to be eligible to die from the cause of interest. It is well known[13,14] that such a simplified application of the Kaplan-Meier method leads to overestimation of the cumulative incidence of an endpoint of interest (e.g. cumulative mortality from the disease under consideration) and accordingly, underestimation of competing causes of interest, such as death for other reasons. Proper analytic methods are especially important in long-term follow-up studies of cancer patients when mortality from causes other than the cancer itself are of interest, too.

Recently, several analyses of competing risks in head and neck carcinoma have been reported.[5-12, 14] We present a population-based study, analyzed with recently recommended methods, of long-term cause-specific mortality of patients with HNSCC in three different sites with a maximum of 26 years of follow-up. Also, to demonstrate the importance of individualized treatment approach and follow-up schemes, we show with simulated patients the differences in mortality due to different age, comorbidity, gender, or cancer status, the simulations being based on regression modelling of cause-specific mortalities.

MATERIALS AND METHODS

Study design

We used a population-based cohort design.

Catchment population

The cancer patients were identified from the area served by Oulu University Hospital, with a total population of about 740,000. The area covers 87 municipalities, each of which maintains one primary health center. The area is served by four central hospitals in addition to one university hospital (Oulu University Hospital). The health care system in Finland is based on a general health insurance scheme and provides equal access to medical services for all citizens. Municipalities are responsible for health care, which is covered by tax revenues. All patients must first present in primary care service before referral to secondary or tertiary care,

excluding emergency visits. Finnish law obligates all licensed physicians to keep medical records of each medical visit.

Patients with head and neck cancer

All patients diagnosed with cancer of the larynx, pharynx, or anterior mobile tongue (*International Classification of Diseases*, ninth and tenth revision, codes 161, 146-148, 141, C32, C09-C11, C13, C02) between January 1986 and December 1996 were identified from the registers of Oulu University Hospital, where all such patients in the catchment population are treated. In the following, cancer of the tongue refers to the anterior two-thirds, i.e. the mobile oral tongue. Only cases of histologically verified squamous cell carcinoma were included. We have shown earlier that our patient series was population-based by cross-checking our records with those of the nationwide Finnish Cancer Registry, the files of which are practically complete.[15,16] Our cohort included 220 head and neck carcinoma patients whose primary care and hospital medical charts were available. All the patients were Caucasian.

We collected all the details of the primary site of the tumor (larynx, pharynx, or tongue) and the patients' histopathologic diagnosis, TNM stage[17], age, gender, and comorbidities from the medical charts of the university hospital, the central hospitals, or primary care. The follow-up time was calculated from the date of the HNSCC diagnosis to the end of the follow-up (latest Dec. 31, 2012) or death, whichever came first. Thus, even the latest cancer patients were followed up for at least 16 years, if they had not died earlier. We used the Charlson's Comorbidity Index (CCI) to classify comorbidities.[18] Dates and causes of death were obtained from the Causes of Death Registry maintained by Statistics Finland and the causes were dichotomized into HNSCC and other causes, respectively. The Finnish Ministry of Social Affairs and Health granted permission to collect these data.

The treatment of all head and neck cancer patients at the university hospital was planned in a weekly joint clinical meeting with oncologists and head and neck and plastic surgeons. Treatment was based

primarily on the clinical stage and location of the tumor and followed the contemporary suggested guidelines.[19]

Statistical methods

Descriptive analyses of mortality from HNSCC and from other causes accounting for competing risks were performed using the non-parametric Aalen-Johansen estimator (AJ) of the pertinent cause-specific cumulative incidence function[13,20]. Following recent recommendations,[21] described in more detail elsewhere[14], we applied two different regression approaches in parallel to analyze cause-specific mortality: 1: conventional Cox regression for cause-specific hazards, and 2: the Fine-Gray model for sub-distribution hazards. In these models the following prognostic factors were included categorically: age band, sex, primary site, tumor size T, nodal involvement N, and Charlson's Comorbidity Index. Based on the fitted Cox models we then constructed predictions of CIFs, i.e. cumulative probabilities of death, both from HNSCC and from other causes, respectively, by time since diagnosis for a few selected types of model patients representing different prognostic profiles. All the computations were performed using the R environment for statistical computing and graphics[22], especially tools found in the survival, Epi, mstate, and riskRegression packages.

RESULTS

Baseline data

Of the 220 patients, 71% were men, although over half of the tongue cancer patients were women (Table 1). The majority of the patients were initially treated with curative intent. A little over half of the tumors were stage T1–T2, and two-thirds were N0. More than half of the patients were at stage III or IV, the stage distribution being least favorable in pharynx cancer. About half of the patients had comorbidities, of which peripheral vascular disease (22 % of all patients), congestive heart failure (12 %), chronic pulmonary disease (11 %), history of myocardial infarction (10 %), and diabetes (6%) were the most common. Half of the 21 patients treated with palliative intent had CCI over 1.

Cause-specific cumulative mortality by prognostic factors

During the follow-up until the end of 2012, 181 patients (82%) died (Table 1). The cause of death was HNSCC in half of the cases, this proportion being largest in pharynx cancer and smallest in larynx cancer.

Site

The 15-year cumulative mortality from HNSCC was 20%, 34%, and 72%, in larynx, tongue, and pharynx carcinoma, respectively (Figure 1). In patients with larynx cancer or pharynx cancer, nearly all deaths from the disease occurred before 5 years had passed since diagnosis, whereas in patients with tongue cancer some increase was still observed in the cancer-specific cumulative mortality curve beyond 5 years. Overall mortality up to 15 years since diagnosis was about 73% in larynx cancer, 66% in tongue cancer, and 91% in pharynx cancer.

Stage

During the risk period of 15 years, less than 10% of all the patients with stage I, about 33% with stage II or III, and 74% with stage IV cancer died because of HNSCC (Figure 2). In stages I and IV, nearly all the HNSCC deaths occurred in the first 5 years since diagnosis, while in stages II and III some cancer deaths occurred after that. Total 15-year mortality was about 63%, 73%, and 95% in stages I, II&III, and IV, respectively.

Age

When stratified by age at the time of diagnosis with three broad age bands (Figure 3), 15-year cumulative mortality from HNSCC was about 33% for patients younger than 55 years. In patients aged 55 to 74 years 15-year HNSCC mortality was 36%, and among patients 75 years or more it was 62%. Cumulative mortality from other causes of death over the 15-year period since diagnosis was about 22%, 44%, and 35% among

those under 55 years, 55–74 years, and at least 75 years old, respectively. Total mortality in these three age bands reached the levels of 55%, 80%, and 97%, respectively, in the 15-year period.

Comorbidity

During 15 years after diagnosis, cumulative mortality from HNSCC was about 36%, 50%, and 40% among patients with no (CCI = 0), low (CCI = 1), and high (CCI = 2 or more) comorbidity, respectively (Figure 4). Nearly all cancer deaths in the high comorbidity group occurred in the first 5 years, but some increase in the cumulative HNSCC death curves was still seen in patients with CCI less than 2. Total mortality over the 15-year period was about 66%, 78%, and 95%, respectively, in the three comorbidity categories.

Regression modeling of mortality by cause

The results from modeling the dependence of mortality by cause on the available prognostic factors are reported in Table 2. Mortality from HNSCC was positively associated with age at diagnosis, tumor size, and lymph node involvement, and it was clearly higher for patients with pharynx cancer compared with the two other primary sites. No clear evidence was found for gender or Charlson's index having any effect. Very similar findings were obtained from both the Cox regression on cause-specific hazards and the Fine-Gray model for sub-distribution hazards. Cause-specific mortality from other causes was strongly dependent on age and Charlson's index. In addition, patients with larynx cancer had a higher mortality rate compared with the other two primary sites. There was no sufficient evidence of women having lower mortality than men, nor of T or N class having any effect. The results from fitting the Fine-Gray model to the sub-distribution hazards were somewhat different in that age, primary site, and Charlson's index appeared to have a lesser impact than in the Cox model for cause-specific hazards.

Simulated patients

Based on the fitted Cox models for the two cause-specific hazards, we computed predicted probabilities of relevant outcomes by time since diagnosis for four types of example patients representing different prognostic profiles (Figure 5). Patient A is a 45-year-old male with T1N0 larynx carcinoma with no co-morbidities, while patient B is an older male with T4N0 larynx cancer and high co-morbidity. Due to the different tumor, age, and comorbidity profile, model patient B, as opposed to patient A, has not only a 6-fold chance of dying from larynx carcinoma, but also a 5-fold probability of dying from causes other than HNSCC in the next 5 years. Patient C is a rather young female with T2N0 tongue carcinoma and no comorbidities, while patient D is an older male with the same kind of cancer characteristics, but with high comorbidity. They have almost similar probabilities of dying from tongue cancer, but because of his age and comorbidities, patient D has an over 8-fold chance of dying from other causes in the first 5 years after treatment.

DISCUSSION

We presented a population-based study of 220 patients with three different HNSCC sites and prognostic patterns over a long follow-up time and followed recent recommendation on statistical methodology in analyzing cause-specific mortality.[13,14,21] This study shows the usability of these methods on HNSCC patients with three different tumor sites which are generalizable to the whole head and neck area. The results emphasize the importance of the physician assessing the overall situation of HNSCC patients in individual treatment planning and also during the follow-up. HNSCC patients not only face the risk of dying from the cancer itself, they also have varying risks of dying from other causes. Many factors affect the outcome of patients with HNSCC. These may be related to the tumor (e.g. the anatomical site and extent of the disease), but when planning treatment, at least age and comorbidity should also be considered as additional predictive factors, and active interventions should be made on comorbid diseases whenever possible.

In the regression analyses, age, site, and T and N stage were strong predictors of mortality from HNSCC, and the results from both modeling approaches were coherent in that regard. The cause-specific hazard from other causes of death was strongly dependent on age and comorbidity, as could be expected. Elevated mortality in patients with larynx cancer is understandable in the light of what is known about the higher attributable fraction of smoking in the etiology of that cancer when compared with the two other primary sites, coupled with the fact that smokers tend to have an elevated risk of dying from various important causes of death. For age and Charlson's index, at least the estimated sub-distribution hazard ratios from the Fine-Gray modeling were somewhat attenuated in comparison with the corresponding estimates of the cause-specific hazard ratios, but they were still consistent with the marginal cumulative incidence functions in Figures 3 and 4. This apparent discrepancy is explained by the fact that the sub-distribution hazard ratio only partly reflects the effect of the factor of interest on the pertinent cause-specific hazard, but is also essentially influenced by the effect of this factor on the other component of mortality. Other scenarios concerning cause-specific hazard ratios and sub-distribution hazard ratios and their mutual dependency in various circumstances are illustrated by Dignam et al.[23] Nevertheless, the fact that old age and high comorbidity were strong predictors of mortality from non-HNSCC causes in this cohort emphasizes the importance of individual treatment planning.

To elucidate the importance of an individualized approach when assessing a patient's prognosis over a long term, we also presented predicted probabilities of outcomes for four types of simulated patients representing different prognostic profiles based on the fitted Cox models for the two cause-specific hazards of cancer death and other deaths, respectively. These simulated example patients show clearly that overall mortality, which obviously is of greatest interest to the patient, may depend even more on age and comorbidity profile than on the cancer's characteristics. All physicians who treat HNSCC patients should be aware of this.

An abundant number of studies exist which evaluate tumor-specific factors predicting the prognosis for the patient and facilitate tailoring of individual planning of treatment beyond traditional TNM

classification, but only very few of these markers are used yet in clinical practice. Nowadays, an individualized approach for each patient that takes into account at least comorbidities and age when counseling with him/her will help the patient deal with expectations also over a long time period. Also, in treatment planning, the clinician should consider the side effects of treatments (e.g. microvascular flap surgery; chemoradiotherapy) against the expected survival scenario. In the future, it may well be possible to apply the kind of personal prognosis pattern described here to each patient, and this might act as a tool for individualizing treatment and follow-up protocols.

Recently, a similar approach of analyzing cause-specific death from oral squamous cell carcinoma was presented,[14] but to our knowledge, this is the first time such a death risk modeling tool is applied in statistical analysis of cause-specific mortality of patients with three different sites of HNSCC.

We found that 40% of all the patients died from HNSCC during the 26-year follow-up, and the proportion of HNSCC deaths out of all mortality was about half. In this patient material, overall mortality was highest in pharynx carcinoma, followed by larynx and tongue. Of all the mortalities, most of the deaths were caused by HNSCC in pharynx carcinoma, about half in tongue cancer, and one-third in larynx cancer. This is in line with the findings of Rose et al[9], who reported that a little under half of deaths were HNSCC-related in their study of over 34,000 HNSCC patients. Ryu et al reported a 60% death rate for HNSCC reasons, and Shen et al reported 65% HNSCC-related mortality out of all deaths, but their shorter follow-up times explain the differences compared with our findings.[10,11]

The majority of HNSCC-related deaths occurred in the first 5 years after cancer diagnosis. However, about 30% of cancer deaths in tongue cancer occurred after 5 years, some as late as 16 years into the follow-up. Patients with high comorbidity were more likely to die because of non-HNSCC causes. Baxi et al did an analysis of causes of death in almost 36,000 HNSCC patients with a very long follow-up time, but they included only patients who had survived for the first 3 years.[12] Therefore, their cumulative mortality up to 18 years from HNSCC was lower than reported here, only 29%, and they also reported that 37% of the mortality attributable to HNSCC occurred after the first 5 years, in contrast to our findings. Shen et al[11] showed that

increasing age, tumor size, and advanced T and N classifications were associated with increasing HNSCC-specific mortality, which is in line with our results. They also found that single people, African-Americans, and those with high grade tumor experienced a higher risk of HNSCC death.

It has been shown previously that high comorbidity in head and neck cancer patients has a negative prognostic impact on the overall survival, but it has less effect on the mortality from cancer itself. It has been suggested that the impaired survival may be caused by either comorbidities themselves, less aggressive treatment, or accelerated ageing caused by cancer treatments.[24,25,26] In our material, elevated CCI was strongly associated with the cause-specific mortality from other causes, but no evidence was found for an association with the HNSCC mortality, which is consistent with previous literature. However, half of the 21 patients treated with palliative intent had CCI over 1, which may indicate that patients with severe comorbidity were treated less aggressively, but we were not able to address the association between given treatment and comorbidity more closely.

The strengths of this work are that it is population-based, involving an unselected patient series, and we had a very long follow-up time with a maximum of 26 years, and cause-specific survival is analyzed with recently recommended methods. However, some limitations in this work should be noted. Our patient cohort was relatively small, and we lacked relevant data about the patients' health behavior and other important risk factors. Also, the patients in this cohort were treated before the increasing incidence of HPV-associated oropharyngeal cancer, and before wider use of chemoradiotherapy.[27]

We conclude that in a long-term follow-up, the overall survival pattern of HNSCC patients depends not only on their cancer characteristics, but also varies greatly according to their age and comorbidities, and this must be considered when counseling the patient about prognosis and treatment. Age and high comorbidity predicted more probable death due to non-HNSCC causes. T4 tumors of any site, old age, pharynx carcinoma, and advanced nodal status were independent predictors of HNSCC death. Old age may predispose to treatment-related death. Our findings support the need for individualized treatment and follow-up protocols, and active management of comorbid diseases. Furthermore, we state that the recently

recommended methods of statistical analysis should be used when presenting survival estimates of cancer patients.

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TABLE 1. Characteristics of 220 patients with head and neck cancer in Finland. Numbers are numbers of patients (percentages), unless otherwise stated

Characteristics	**Site** Larynx (n=93)	Pharynx (n=65)	Tongue* (n=62)	All sites (n=220)
Age (years)				
Mean (range)	64 (37-86)	64 (34-89)	61 (26-86)	63 (26-89)
Gender				
Male	80 (86)	47 (71)	29 (47)	156 (71)
Female	13 (14)	18 (29)	33(53)	64 (29)
T Stage				
1	38 (41)	5 (8)	8 (13)	51 (23)
2	19 (20)	21 (32)	30 (48)	70 (32)
3	30 (32)	18 (27)	18 (29)	66 (30)
4	6 (7)	21 (33)	6 (10)	33 (15)
N Stage				
0	79 (86)	19 (29)	43 (70)	142 (64)
1	4 (4)	12 (19)	12 (19)	28 (13)
2	7 (8)	18 (27)	5 (8)	30 (13)
3	2 (2)	15 (24)	2 (3)	19 (9)
Unknown	0 (0)	1 (1)	0 (0)	1 (1)
M Stage				
0	92 (99)	62 (95)	60 (97)	214 (97)
1	1 (1)	3 (5)	2 (3)	6 (3)
TNM Stage				
I	37 (40)	1 (2)	8 (13)	46 (21)
II	15 (16)	10 (16)	22 (36)	47 (22)
III	29 (32)	11 (16)	25 (40)	65 (29)
IV	12 (12)	41 (66)	7 (11)	62 (28)
Comorbidity†				
0	46 (50)	35 (54)	33 (53)	114 (53)
1	16 (17)	12 (19)	12 (19)	40 (18)
2	19 (21)	9 (14)	12 (19)	40 (18)
3 or more	12 (12)	9 (13)	5 (8)	26 (11)
Outcome by the end of follow-up				
HNSCC death	19 (20)	47 (72)	22 (35)	88 (40)
Other death	56 (60)	13 (20)	24 (39)	93 (42)
Alive	18 (20)	5 (8)	16 (26)	39 (18)

*anterior two-thirds †Charlson index

Table 2. Mortality from head and neck squamous cell carcinoma (HNSCC) and other causes of death: cause-specific hazard ratios (CSHR) and sub-distribution hazard ratios (SDHR) associated with selected prognostic factors from fitting a Cox model and a Fine-Gray model, respectively, together with the pertinent 95% confidence intervals (CI).

	HNSCC				*Other Causes*			
	CSHR	95% CI	SDHR	95% CI	CSHR	95% CI	SDHR	95% CI
Female gender	1.06	(0.64 -1.76)	1.08	(0.65-1.77)	0.85	(0.51-1.43)	0.88	(0.51-1.53)
Age at diagnosis (vs. 25-54 y)								
55-65	0.86	(0.44-1.68)	0.82	(0.43-1.56)	2.11	(1.11-4.03)	2.04	(1.10-3.77)
65-75	1.67	(0.88-3.15)	1.62	(0.86-3.05)	2.22	(1.12-4.42)	1.67	(0.87-3.21)
75-90	2.26	(1.10-4.68)	2.16	(1.03-4.54)	4.70	(1.90-11.61)	1.62	(0.68-3.85)
Site (vs. tongue)								
Pharynx	2.24	(1.26-3.99)	2.06	(1.14-3.74)	1.36	(0.65-2.86)	0.59	(0.27-1.33)
Larynx	0.62	(0.32-1.22)	0.56	(0.28-1.11)	1.93	(1.10-3.37)	1.57	(0.90-2.74)
Tumour size (vs. T1)								
T2	1.46	(0.61-3.46)	1.17	(0.46-2.97)	1.19	(0.67-2.12)	0.99	(0.60-1.63)
T3	2.32	(1.02-5.27)	2.13	(0.94-4.82)	1.22	(0.69-2.16)	0.83	(0.49-1.42)
T4	4.29	(1.79-10.29)	4.01	(1.66-9.64)	1.56	(0.60-4.03)	0.53	(0.20-1.43)
N2-3 (vs N0-1)	2.21	(1.35-3.62)	2.13	(1.26-3.60)	1.12	(0.52-2.41)	0.48	(0.21-1.10)
Charlson index (vs. 0)								
1	1.89	(1.08-3.31)	1.82	(1.05-3.15)	0.79	(0.39-1.58)	0.65	(0.31-1.32)
2	1.46	(0.71-3.00)	1.28	(0.57-2.88)	1.86	(1.00-3.46)	1.40	(0.77-2.52)
≥3	1.15	(0.56-2.36)	1.03	(0.48-2.24)	5.60	(2.84-11.05)	2.66	(1.44-4.94)

FIGURE LEGENDS:

Figure 1. Cumulative incidence of death from head and neck carcinoma (HNSCC; lower curve & darker gray area), from other causes (light gray area between the two curves), and from all causes (total, the upper curve) by years since diagnosis, estimated by the Aalen-Johansen method. Stratification according to primary tumor site (larynx; tongue; and pharynx).

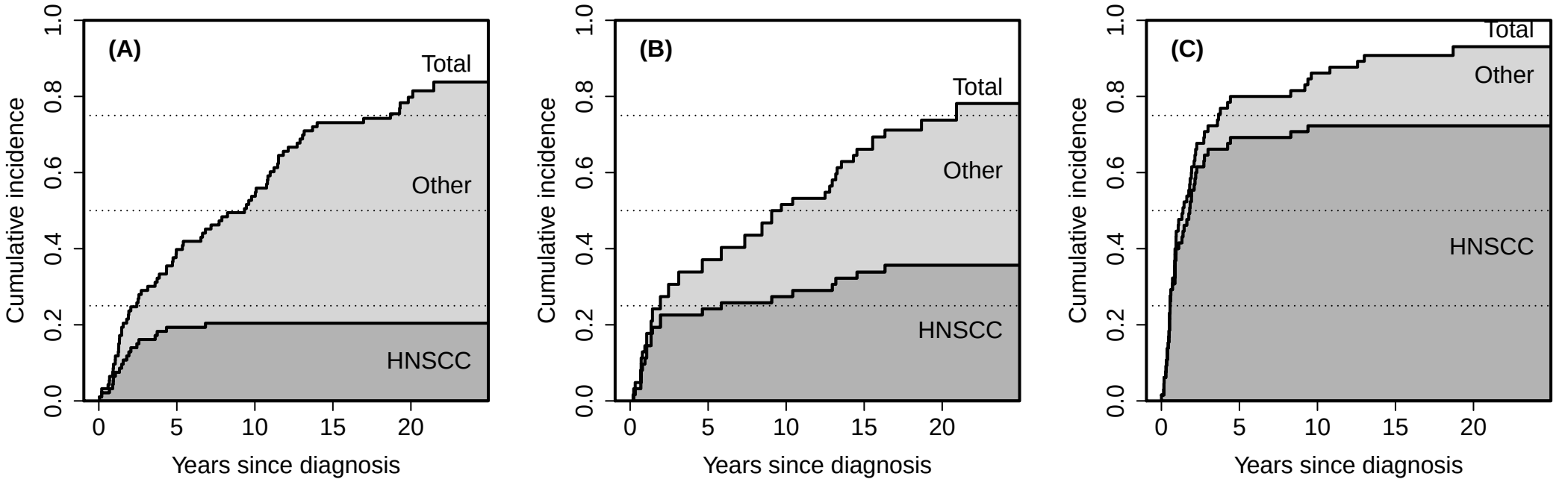
Figure 2. Cumulative incidence of death from head and neck carcinoma (HNSCC; lower curve & darker gray area), from other causes (light gray area between the two curves), and from all causes (total, the upper curve) by years since diagnosis, estimated by the Aalen-Johansen method. Stratification according to stage (Stage I; II&III combined; and IV).

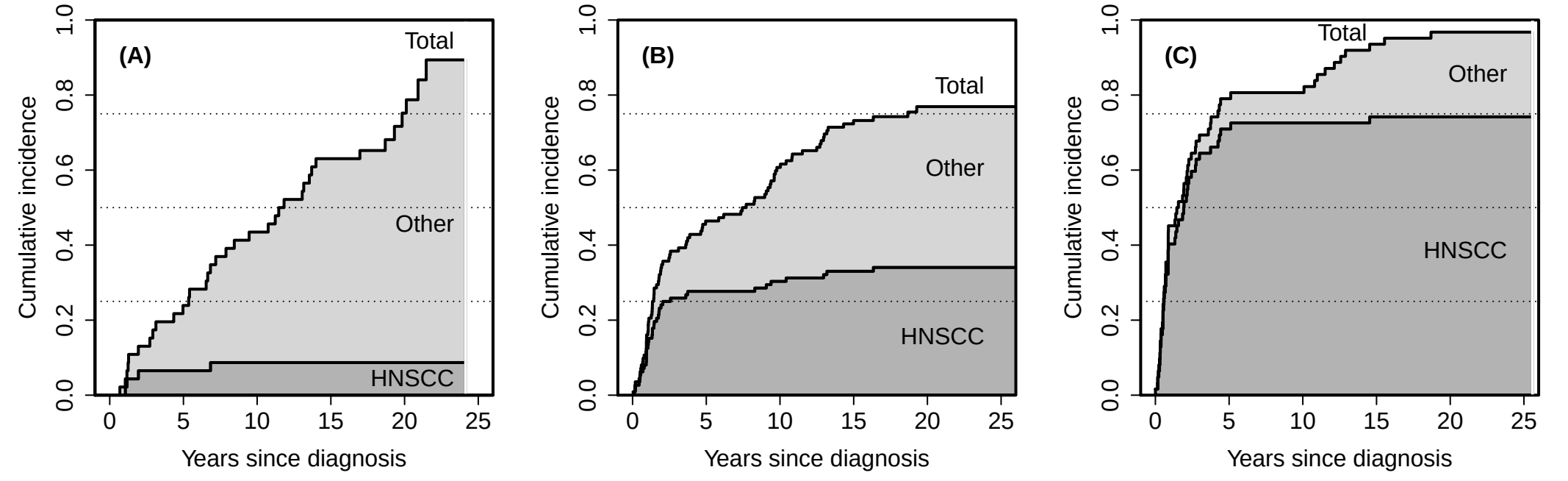
Figure 3. Cumulative incidence of death from head and neck carcinoma (HNSCC; lower curve & darker gray area), from other causes (light gray area between the two curves), and from all causes (total, the upper curve) by years since diagnosis, estimated by the Aalen-Johansen method. Stratification according to age with three age groups (25–54; 55–74; and 75–89 years at diagnosis).

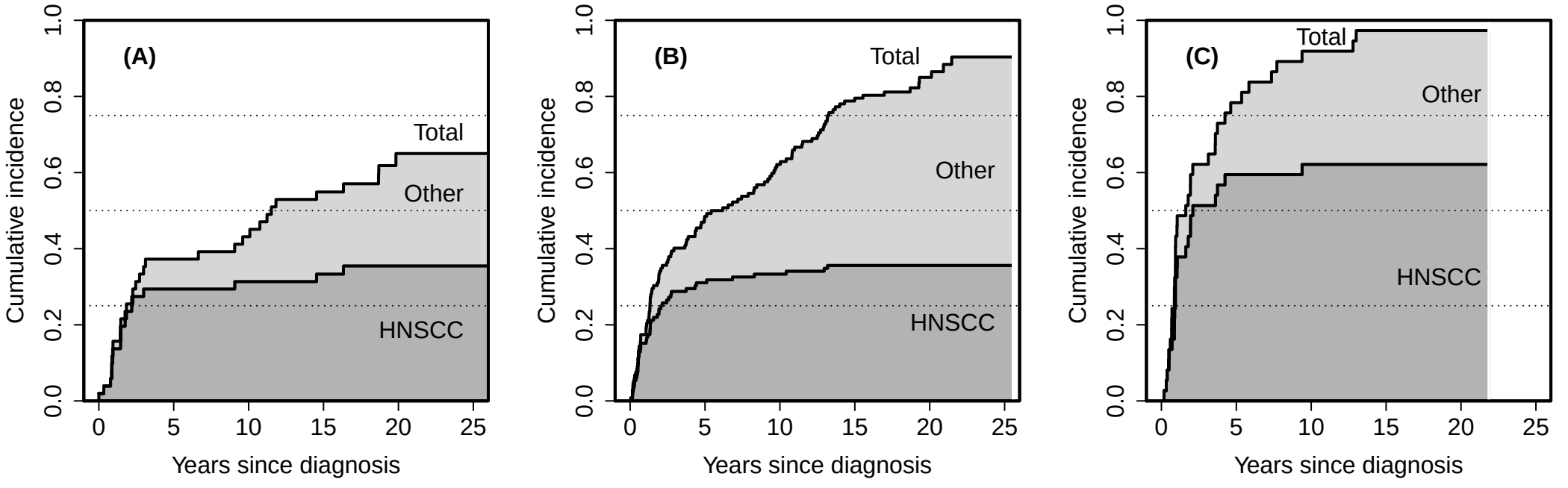
Figure 4. Cumulative incidence of death from head and neck carcinoma (HNSCC; lower curve & darker gray area), from other causes (light gray area between the two curves), and from all causes (total, the upper curve) by years since diagnosis, estimated by the Aalen-Johansen method. Stratification according to the Charlson Comorbidity Index (CCI = 0; CCI = 1; and CCI $\geq$ 2).

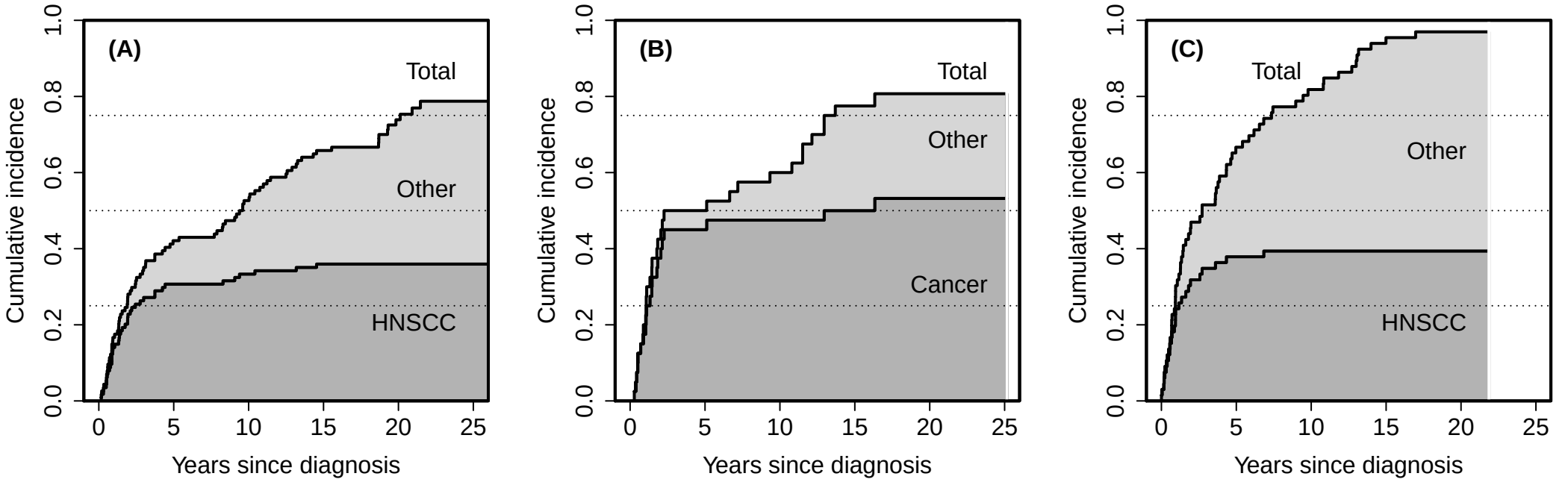
Figure 5. Predicted probabilities of dying from head and neck carcinoma (HNSCC; lower curve & darker gray area), from other causes (light gray area between the two curves), and from all causes (total, the upper curve) by years since diagnosis for four kinds of model patients: A; B; C; and D (T1, T2, and T4 refer to the tumor

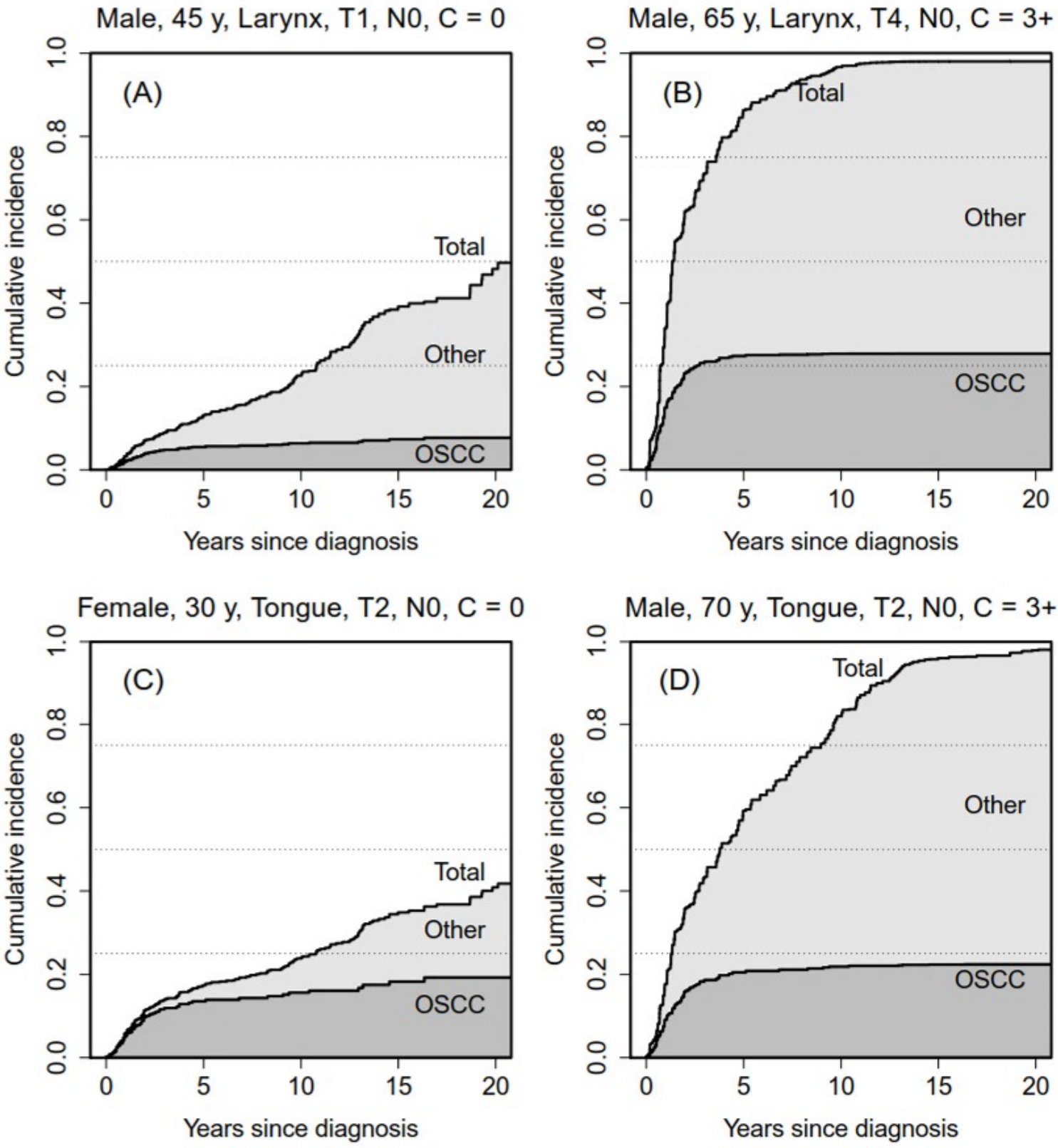
classification; N0 to the nodal classification; and C to the value of Charlson's Comorbidity Index, respectively, in these patients).


(A)
Total
Other
HNSCC
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
Years since diagnosis
(B)
Total
Other
HNSCC
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
Years since diagnosis
(C)
Total
Other
HNSCC
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
Years since diagnosis


(A)
Total
Other
HNSCC
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
Years since diagnosis
(B)
Total
Other
HNSCC
Cumulative incidence
Years since diagnosis
(C)
Total
Other
HNSCC
Cumulative incidence
Years since diagnosis


(A)
Total
Other
HNSCC
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
Years since diagnosis
(B)
Total
Other
HNSCC
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
Years since diagnosis
(C)
Total
Other
HNSCC
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
Years since diagnosis


(A)
Total
Other
HNSCC
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
Years since diagnosis
(B)
Total
Other
Cancer
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
Years since diagnosis
(C)
Total
Other
HNSCC
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
Years since diagnosis


Male, 45 y, Larynx, T1, N0, C = 0
(A)
Total
Other
OSCC
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
Years since diagnosis
Male, 65 y, Larynx, T4, N0, C = 3+
(B)
Total
Other
OSCC
Cumulative incidence
Years since diagnosis
Female, 30 y, Tongue, T2, N0, C = 0
(C)
Total
Other
OSCC
Cumulative incidence
Years since diagnosis
Male, 70 y, Tongue, T2, N0, C = 3+
(D)
Total
Other
OSCC
Cumulative incidence
Years since diagnosis