VOLUME 31 · NUMBER 4 · FEBRUARY 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Population-Based Study Evaluating and Predicting the Probability of Death Resulting From Thyroid Cancer and Other Causes Among Patients With Thyroid Cancer

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Published online ahead of print at www.jco.org on December 26, 2012.

Supported by Grant No. 24-20 from the National Center for Child Health and Development.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/13/3104-468/$20.00

DOI: 10.1200/JCO.2012.42.4457

ABSTRACT

Purpose
The purpose of this study was to evaluate the probability of death for patients with thyroid cancer and construct a comprehensive nomogram based on a competing risks model to predict cumulative incidence of death resulting from thyroid cancer, other cancers, and non–cancer-related causes.

Patients and Methods
Patients diagnosed with thyroid cancer between 1988 and 2003 were selected for the study from the Surveillance, Epidemiology, and End Results program. We estimated probabilities of death resulting from thyroid cancer, other cancers, and noncancer causes and analyzed associations of patient and tumor characteristics with probability of death. A nomogram for predicting probability of death was built using a proportional subdistribution hazard competing risks model.

Results
The entire cohort comprised 29,225 patients with malignant thyroid cancer. Median duration of follow-up until censoring or death was 85 months (range, 0 to 239 months). Five-year probabilities of death resulting from thyroid cancer, other cancer, and noncancer causes were 1.9%, 0.8%, and 1.7%, respectively. Increasing age and tumor size, male sex, poorly differentiated carcinoma, lymph node involvement, and regional and metastatic disease were associated with increased cumulative incidence of death resulting from thyroid cancer.

Conclusion
A nomogram based on a competing risks model was developed for predicting the probability of death for patients with thyroid cancer. Performance of the model was excellent. This nomogram may be useful for patients and clinicians when predictions are needed.

J Clin Oncol 31:468-474. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy. In the United States, in 2011, it was estimated that 11,470 men and 36,550 women were diagnosed with thyroid cancer and 1,740 men and women died from the disease.[1] Thyroid cancer has been considered a disease with excellent prognosis. The overall survival rate has remained at 90% to 95% in recent decades according to a Surveillance, Epidemiology, and End Results (SEER) report.[1] Almost 90% of all thyroid cancers are papillary thyroid carcinoma, a low-risk histologic type. Moreover, as diagnostic techniques for thyroid cancer have become more sensitive, especially with the advent of ultrasonography and fine-needle aspiration, a higher proportion of a large subclinical reservoir of thyroid cancer can be detected. Furthermore, thyroid cancer can remain in situ and asymptomatic for long periods without affecting overall survival. Pathologists report that thyroid cancer is a common autopsy finding, and one autopsy study identified that almost 9% of cadavers had thyroid cancer, even if the cause of death was not thyroid cancer.[2] Given the potential for long-term survival in patients with thyroid cancer, a considerable number of patients may die of other causes. As a result, consideration about the presentation of other causes of death is necessary when evaluating the prognosis for thyroid cancer.

To better estimate the prognosis of patients with thyroid cancer and give clinicians a practical predictive tool for calculating probability of death at the level of the individual, we evaluated the cumulative incidence of death resulting from thyroid cancer, nonthyroid cancers, and other noncancer causes among patients with thyroid cancer using a population-based cohort and established a comprehensive nomogram based on a proportional subdistribution hazards model.

PATIENTS AND METHODS

The study population was obtained from the records of the SEER program of the National Cancer Institute. The SEER database covers approximately 26% of the US population, and the characteristics of the SEER population are comparable to the general US population. Patients diagnosed with thyroid cancer as a first primary malignancy between 1988 and 2003 were selected for the study from the SEER database for public use.[3] Only histologically confirmed malignant tumors of the thyroid were included. Cancers diagnosed at autopsy or by death certificate only were excluded. Other exclusion criteria for this study included tumor size larger than 20 cm; tumor extent code of 00 (in situ) or 99 (unknown extent); lymph node involvement (unknown or lymph node involvement, not otherwise specified); race code of 7 (other unspecified) or 9 (unknown); and radiotherapy code of 7 (patient or guardian refused radiotherapy), 8 (radiation recommended, unknown if administered), or 9 (unknown if radiation administered). We excluded SEER surgical codes indicating that either no cancer-directed surgery was performed or it was unknown whether cancer-directed surgery was performed. Finally, patients with a SEER cause of death (COD) record stating that a death certificate was unavailable or was available but with no COD recorded or for whom COD was unknown, missing, or invalid were excluded from the cohort. After exclusion criteria were fulfilled, the study cohort comprised 29,225 postoperative patients with thyroid cancer. The flow chart for data selection is shown in Figure 1.

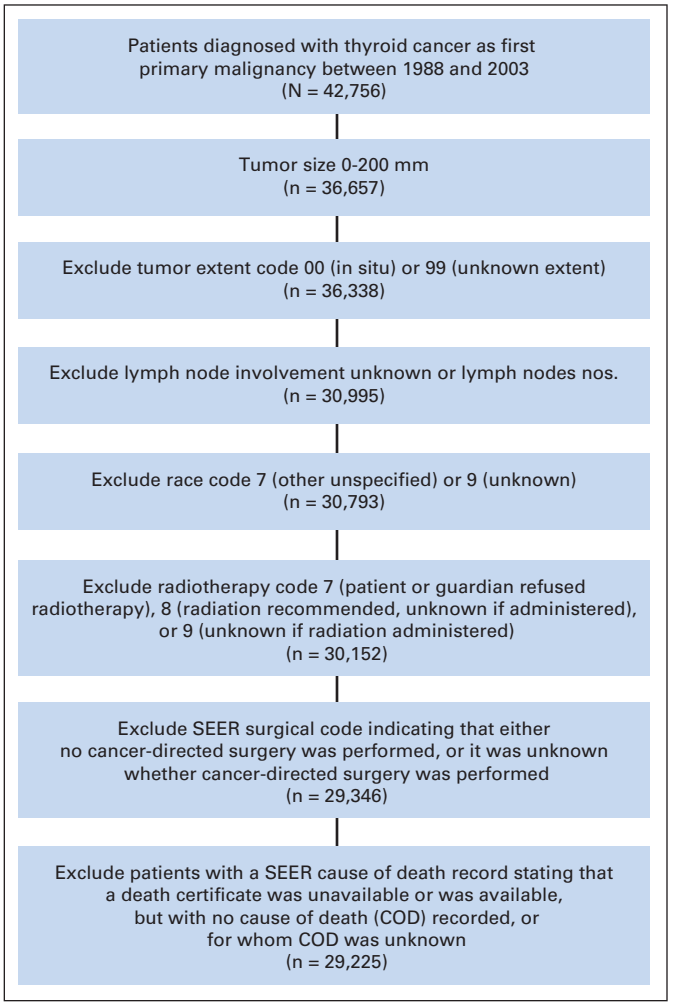

Fig 1. Flow chart for creation of the SEER data set.

Variables in the analysis included age at diagnosis, sex, race, histologic subtype, tumor extent, tumor size, lymph node involvement, and radiotherapy. The variables of age at diagnosis and tumor size were treated as categorical variables for calculating cumulative incidence of death. Tumor size was grouped as follows: less than 1, 1 to 1.9, 2 to 2.9, 3 to 3.9, and ≥ 4 cm. Tumor extent was defined as local (confined to the gland), regional (extension into adjacent tissue or lymph node involvement), or distant (metastatic). Lymph node involvement was recorded as no lymph node involvement, regional lymph node involvement, or distant lymph node involvement.

Patients with missing values were excluded, rather than imputing missing values. Patients in the cohort were observed for vital status until the earliest of the following dates: death; last contact if before December 31, 2007; or December 31, 2007, if date of last contact was after 2007. We grouped COD into the following three categories: death resulting from thyroid cancer (SEER COD record No. 32010), death resulting from other cancers, or death resulting from noncancer causes.

We used the cumulative incidence function (CIF) to describe the probability of death. Gray's test was conducted to test the CIF difference between category groups.[4] In establishing a competing risks nomogram, the population we selected was randomly divided into development (n = 14,612) and external validation (n = 14,613) cohorts. Fine and Gray proportional subdistribution hazards regression modeling was performed to construct the competing risks model.[5] The restricted cubic splines with three knots at the 10%, 50%, and 90% empirical quantiles were fitted to model the continuous variables. Interactions were not evaluated. To avoid overfitting, we used a model selection technique based on the Bayesian information criteria when establishing competing risks models.

For model validation, an external validation procedure was adopted. We assessed both discrimination and calibration with the validation cohort. Discrimination is the ability of a model to separate subject outcomes. Discrimination is quantifiable, with an index of probability of concordance (c-index) between predicted probability and response.[6-9] The c-index is defined as the proportion of all evaluable ordered patient pairs for which predictions and outcomes are concordant. In the context of the competing risks, an ordered pair is regarded as evaluable if the first patient experiences the event of interest at a time point when the second patient is still at risk. Patients who experience failure from the competing event remain in the risk set and are at risk at any time.[8] In model validation, 200 bootstraps were used to generate the CI for the c-index. Calibration is the ability of the model to make unbiased estimates of outcome. We used the external cohort to compare the final reduced model-predicted probability of death with the observed cumulative incidence of death at 5 and 10 years. We averaged the model-predicted probabilities within quintiles defined by the magnitude of the predictions. Within each quintile of individuals, the marginal cumulative incidence of death was calculated using the method provided by Gray.[4] Finally, the marginal estimate versus model average predictive probability was plotted to form a calibration plot. In a well-calibrated model, the predictions should fall on a 45-degree diagonal line.

All statistical analysis was performed using R version 2.10.1 software (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org).[10] The R packages cmprsk[10] and rms[11] and a c-index function for competing risks model[8] were used for modeling and developing the nomogram. All *P* values resulted from the use of two-sided statistical testing.

RESULTS

Patient Characteristics

The entire cohort comprised 29,225 patients with histologically confirmed malignant thyroid cancer. Table 1 lists clinical characteristics for these patients. The majority of tumors were the well-differentiated histologic subtype (papillary, 88.9%; follicular, 9.4%), were diagnosed at a local stage (72.2%), and occurred in non-Hispanic

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Characteristic	All Patients (N = 29,225)		Modeling Cohort (n = 14,612)		Validation Cohort (n = 14,613)	
	No.	%	No.	%	No.	%
Age at diagnosis, years						
Mean	45.3		45.4		45.2	
Median	44		44		44	
Range	4-100		5-100		4-99	
Sex						
Male	6,602	22.6	3,332	22.8	3,270	22.4
Female	22,623	77.4	11,280	77.2	11,343	77.6
Race						
Black	1,506	5.2	752	5.1	754	5.2
White	24,222	82.9	12,062	82.5	12,160	83.2
Other	3,497	12.0	1,798	12.3	1,699	11.6
Tumor size, cm						
Mean	2.1		2.1		2.1	
Median	1.8		1.8		1.8	
Range	1-20		1-18		1-20	
Extent of tumor						
Localized	21,110	72.2	10,494	71.8	10,616	72.6
Regional	7,717	26.4	3,899	26.7	3,818	26.1
Distant	398	1.4	219	1.5	179	1.2
Histologic subtype						
Papillary	25,995	88.9	13,024	89.1	12,971	88.8
Follicular	2,759	9.4	1,337	9.2	1,422	9.7
Medullary	213	0.7	112	0.8	101	0.7
Anaplastic	126	0.4	70	0.5	56	0.4
Other	132	0.5	69	0.5	63	0.4
Lymph node involvement						
No involvement	21,865	74.8	10,891	74.5	10,974	75.1
Regional lymph nodes	7,252	24.8	3,666	25.1	3,586	24.5
Distant lymph nodes	108	0.4	55	0.4	53	0.4
Radiotherapy						
None	13,892	47.5	6,932	47.4	6,960	47.6
Yes	15,333	52.5	7,680	52.6	7,653	52.4
Death resulting from thyroid cancer	789	2.7	432	3.0	357	2.4
Death resulting from nonthyroid cancer	523	1.8	269	1.8	254	1.7
Death resulting from noncancer cause	1,028	3.5	492	3.4	536	3.7
Follow-up, months						
Mean	99.8		100.2		99.5	
Median	85		85		85	
Range	0-239		0-239		0-239	

whites (82.9%) and in females (77.4%). Median age at diagnosis was 44 years (range, 4 to 100 years). Median length of follow-up until censoring or death was 85 months (range, 0 to 239 months). At last contact, 26,885 patients (92.0%) had been censored, and 2,340 patients (8.0%) had died, including 789 deaths (2.7%) from thyroid cancer, 523 (1.8%) from other cancers, and 1,028 (3.5%) from other noncancer causes. The most frequent causes of noncancer mortality were heart diseases (33.9%), cerebrovascular diseases (10.4%), and chronic obstructive pulmonary disease and associated conditions (5.7%). The most frequent causes of second cancer death were cancers of the lung and bronchus (22.6%), colon excluding rectum (6.3%), pancreas (5.9%), and breast (5.2%).

Probability of Death

Estimates of probabilities of death resulting from thyroid cancer, other cancer, and other noncancer causes according to patient and tumor characteristics are listed in Table 2. Five-year probabilities of death resulting from thyroid cancer, other cancer, and other noncancer causes were 1.9%, 0.8%, and 1.7%, respectively; 10-year probabilities of death were 3.0%, 2.0%, and 3.9%, respectively. Five- and 10-year probability of death increased with age ($P < .001$ for all outcomes). Male patients showed higher cumulative incidence of death compared with their female counterparts ($P < .001$ for all outcomes). Tumor size, histologic subtype, and extent showed significant associations with probability of death. A significant association between lymph node involvement and cumulative incidence of death was observed only within the thyroid cancer death cohort ($P < .001$). Radiotherapy was associated with a significantly higher cumulative incidence of death among patients who died of thyroid cancer but was associated with a significantly lower cumulative incidence of death among patients who died of other noncancer causes ($P < .001$). CIF curves are shown in the Data Supplement.

Table 2. Five- and 10-Year Cumulative Incidences of Death Among Patients With Thyroid Cancer

Characteristic	Cumulative Incidence of Death Resulting From Thyroid Cancer			Cumulative Incidence of Death Resulting From Other Cancer			Cumulative Incidence of Death Resulting From Noncancer Causes		
	5 Years (%)	10 Years (%)	*P**	5 Years (%)	10 Years (%)	*P**	5 Years (%)	10 Years (%)	*P**
All patients	1.9	3.0		0.8	2.0		1.7	3.9	
Age at diagnosis, years			< .001			< .001			< .001
< 45	0.3	0.5		0.1	0.4		0.5	0.9	
45-64	1.9	3.5		0.8	2.4		1.4	3.3	
65-74	6.8	10.3		2.9	6.1		4.4	12.6	
≥ 75	12.2	16.0		4.0	10.4		12.9	29.9	
Sex			< .001			< .001			< .001
Male	3.8	6.1		1.3	3.2		2.8	6.4	
Female	1.4	2.1		0.6	1.6		1.3	3.1	
Race			.53			.29			< .001
Black	2.2	3.7		1.0	2.5		3.5	6.5	
White	2.0	3.0		0.8	2.0		1.6	3.8	
Other	1.7	3.1		0.7	2.0		1.4	3.6	
Tumor size, cm			< .001			< .001			< .001
< 1	0.4	0.6		0.9	2.0		2.1	4.4	
1 to 1.9	0.5	1.0		0.5	1.6		1.1	2.7	
2 to 3.9	1.7	2.8		0.6	1.8		1.3	3.2	
≥ 4	8.1	11.8		1.2	3.2		3.0	6.9	
Extent of tumor			< .001			< .001			< .001
Localized	0.5	0.9		0.6	1.6		1.5	3.4	
Regional	4.0	6.4		1.0	2.8		2.1	5.0	
Distant	37.5	47.8		4.3	7.7		3.3	5.3	
Histologic subtype			< .001			.03			< .001
Papillary	1.3	2.2		0.7	1.9		1.5	3.5	
Follicular	2.6	4.8		1.0	2.4		2.7	6.4	
Medullary	9.3	9.3		0.0	1.5		3.8	13.5	
Anaplastic	77.8	78.9		3.2	3.2		4.8	5.9	
Other	27.4	29.3		3.8	3.8		1.5	4.9	
Lymph node involvement			< .001			.82			.34
No involvement	0.9	1.6		0.8	2.0		1.7	3.9	
Regional lymph nodes	4.8	6.9		0.8	2.1		1.7	3.7	
Distant lymph nodes	15.0	21.7		0.9	3.7		2.8	2.8	
Radiotherapy			< .001			.5			< .001
None	1.2	2.0		0.8	1.9		2.3	4.9	
Yes	2.6	4.0		0.7	2.1		1.1	2.9	

*Gray's test.

Nomogram

The nomogram shown in Figure 2 was constructed based on the reduced multivariate models with training data set (Appendix Table A1, online only). The probability of 5- or 10-year death can be calculated using this nomogram. In the external validation cohort, the discrimination (c-index) was 0.92 (95% CI, 0.91 to 0.94), 0.82 (95% CI, 0.80 to 0.84), and 0.82 (95% CI, 0.80 to 0.84) for thyroid cancer death, other cancer death, and other noncancer death, respectively. This implies that the models are reasonably accurate. The calibration plot of the CIF is shown in Figure 3. The points close to the 45-degree line indicate good agreement between predicted and observed outcomes.

DISCUSSION

We found that patients registered in the SEER database with thyroid cancer had an excellence prognosis after surgery. Ten-year probabilities of death were 3.0%, 2.0%, and 3.9% for death resulting from thyroid cancer, other cancers, and noncancer causes, respectively. Patients showed a nearly two-fold higher risk of dying from causes other than thyroid cancer.

Deaths from other cancers and noncancer causes were treated as competing risk events in this study. A competing risk can be defined as an event the occurrence of which either precludes the occurrence of another event under examination or changes the probability of occurrence for the other event. According to this definition, death as a result of causes other than thyroid cancer can be regarded as a competing event, because death resulting from the non–thyroid cancer cause precludes the possibility of death resulting from thyroid cancer. Moreover, censoring those competing events would cause bias, because those censored as a result of competing risks must have a different risk of the outcome of interest than the noncensored population. For example, a patient who died from other causes would show poorer survival from thyroid cancer than patients who did not die from other causes. Patients who died from secondary cancer might be patients with thyroid cancer with distant spread who had received aggressive treatment. Censoring such patients would thus lead to informative censoring.

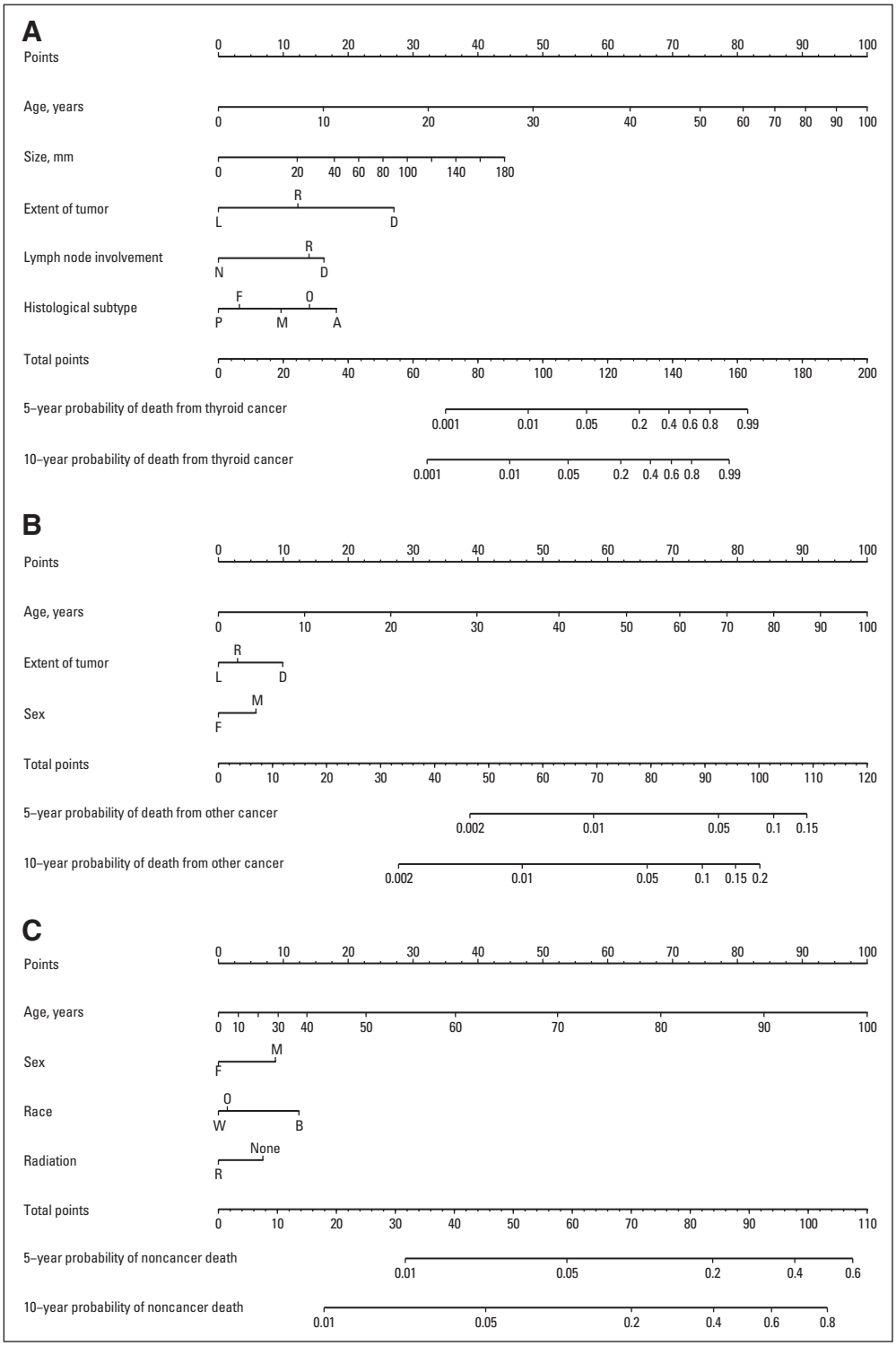

Fig 2. Nomogram for predicting 5- and 10-year probabilities of (A) thyroid cancer death, (B) other cancer death, and (C) noncancer death in patients with thyroid cancer. Race: B, black; O, other; W, white; extent of tumor: D, distant; L, localized; R, regional; lymph node involvement: D, distant lymph nodes; N, no lymph node involvement; R, regional lymph nodes; sex: F, female; M, male; radiation: R, radiotherapy; histologic subtype: A, anaplastic; F, follicular; M, medullary; O, other; P, papillary. Instructions: Locate the patient's characteristic on the variable row, and draw a vertical line straight upward to the points row to assign a value of points for the variable. Move to the next variable row, and repeat this process. Add up the total points, and drop a vertical line from the total points row to obtain the probability of death.

When competing risks are present, the 1–Kaplan-Meier (KM) estimation procedure may not be directly applicable. The KM approach is based on the premise that the censoring is noninformative. However, in a competing risks setting, if the assumption that competing risks are independent is violated, censoring a competing risk results in informative censoring. The value of 1-$KM_j(t)$ overestimates the probability of failure from cause *j*, whereas CIF provides an unbiased estimate for the probability of failure.

We used the Fine and Gray modeling approach to construct models and the nomogram. The main advantage of the subdistribution methodology is that through simply model fitting we can see the direct effect of each covariate on cumulative incidence. In a competing

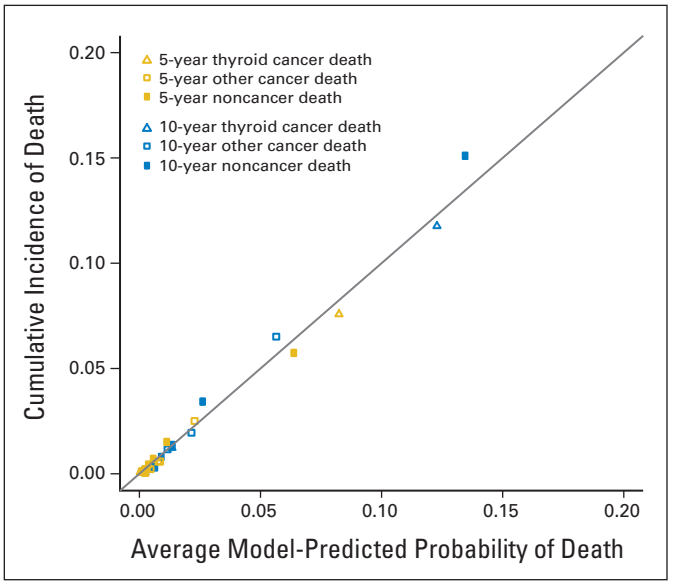

Fig 3. Calibration plot. The *x*-axis designates the mean predicted probability of the conditional cumulative incidence model. The *y*-axis indicates marginal cumulative incidence probabilities for the respective cohorts. The solid line represents equality between the predicted and observed marginal cumulative incidences.

scenario, we admit that cause-specific hazard models also yield correct absolute risk estimates. However, that requires modeling of both the event of interest and the competing events to obtain valid risk prediction, and this complex combination of cumulative hazards is difficult to incorporate into a nomogram. Given the primary focus of the present research (ie, estimating the probability of death, rather than evaluating treatment effects), we consider that application of the proportional subdistribution hazard model was suitable in this analysis.

Quantitative estimation of the clinical prognosis for an individual patient is useful in treatment counseling. Individualized prediction can also be used to identify and stratify patients for participation in clinical trials.[12] On the basis of age and other prognostic factors, several scoring systems have been established for the management of patients with thyroid cancer, such as the AGES (age, grade, extent of disease, and size),[13] MACIS (metastasis, age at presentation, completeness of surgical resection, invasion, and size),[14] and AEMS (age, metastasis, extent of disease, and size)[15] scoring systems. Unlike a scoring method, a nomogram provides more accurate prediction for individual patients, based on statistical modeling. A simple predictive graph of a statistical model is created, generating a numerical probability of a clinical event.[12] This article-based predictive tool provides clinicians with a practical tool for clinical prognostic prediction and is useful for identifying and stratifying patients at risk.

Given the excellent prognosis and relatively indolent course of some tumors, competing causes of mortality represent a critical consideration when evaluating probability of death. Competing risks models for predicting breast cancer,[16] prostate cancer,[17,18] and localized renal cell carcinoma[19,20] have been published in recent years. However, no comprehensive nomogram for thyroid cancer based on a competing risks model has been described. To the best of our knowledge, this represents the first comprehensive competing risks analysis to quantify the probability of death resulting from thyroid cancer and other causes after the diagnosis of thyroid cancer. Furthermore, the present nomogram offers a practical, predictive tool for determining prognosis, because the variables used in the model are readily available to any clinician.

Most published studies regarding the prognosis of thyroid cancer originate from the experiences of single institutions, and results are thus heterogeneous. The risk of death resulting from thyroid cancer is low, even for patients with adverse clinical features. Studies conducted in a single institution often do not have sufficient power to identify true prognostic factors for thyroid cancer because of rare death events and short follow-up periods. Unlike single-institution studies, the population-based SEER cancer registries have allowed the estimation of a number of prognostic factors based on a large sample that is not subject to selection and referral biases.[21] Outcomes from a population-based cohort are more reliable and are likely to be more generally applicable. Although disease progression, such as cancer recurrence or metastasis, is not recorded in the SEER registries, probability of death resulting from thyroid cancer and other causes can be calculated based on the recorded cause of death.

The primary strengths of the present study include the population-based design, long-term follow-up, and sufficient sample size. Despite these strengths, some limitations must also be considered for the present study. Potential misclassification of the COD might be one limitation for analyzing probability of cause-specific death. Information regarding CODs in this study was obtained from the COD variable in SEER, which is based on data from the death certificate. It is possible that some of deaths that were recorded as caused by thyroid cancer were not primarily caused by thyroid cancer. The death certification report might be inaccurate in classifying the COD but is considered to be relatively robust in patients with malignancy. Kircher et al[22] compared 272 randomly selected autopsy reports with the corresponding death certificates and found that deaths as a result of neoplasms were the most accurately diagnosed, with a sensitivity of 87% and a positive predictive value of 85%. Although comorbidity is another variable that cannot be obtained from the publicly used SEER database, the lack of comorbidity information is better considered in the competing risks model used in this study than the standard Cox model because other causes of death are accounted for in the competing risks model.

Some other words of caution should be kept in mind when using our models and nomogram. First, *P* values close to .05 should be interpreted with caution because of the huge sample size used for the hypothesis test. Second, the effect of the coefficient of covariate presented in the multivariate models should be interpreted in terms of a time-averaged effect, because proportional subdistribution hazards analysis was carried out for all CIFs.[23] In addition, separately modeling CIF for each event type with a Fine-Gray model might result in inconsistency, such as the probability of each type of event summing up to greater than 1 for the highest risk group. Third, we excluded patients who did not undergo surgery. Although the SEER data set does not provide comorbidity information, Sanabria et al[24] used the SEER data set to estimate the prognosis of patients with thyroid cancer who did not undergo surgical treatment; the results of that study implied the possibility of poor risk for surgery in this population. These investigators found that 5-year overall survival rates were 96.7% for surgical patients and 56.8% for nonsurgical patients.[24] Advanced age and stage, with more distant metastases,

were found in the nonsurgical group.[24] Therefore, predictions from that model were considered biased toward individuals who represent acceptable surgical candidates.

In summary, we determined the probability of death resulting from thyroid cancer and other causes based on a large, population-based cohort and constructed a nomogram based on a competing risks model. Patients with thyroid cancer have excellent survival, but those with high-risk factors are identified as having the worst prognosis. Our nomogram may help clinicians identify individuals at higher risk of thyroid cancer death and provide more individualized treatment planning. Performance of the model is excellent. Thus, the nomogram should be considered as an accurate tool for clinical prognosis prediction.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Financial support: Naoko Sakamoto
Collection and assembly of data: Limin Yang, Weidong Shen
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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