Using a Competing-Risks Model to Predict the Prognosis of Meningioma Patients: Fine-Gray and Cause-Specific Hazard Analyses

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Research article

Keywords: competing-risks model, meningioma, Fine-Gray, cause-specific hazard, SEER database

Posted Date: December 1st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-113915/v1

Abstract

Background: We aimed to identify the risk factors for meningioma using a competing-risks model.

Method: Patients entered into the Surveillance, Epidemiology, and End Results (SEER) database between 1973 and 2015 were selected. Univariate analysis was performed using the cumulative incidence function (CIF) to show the probability of each event and Gray's test to estimate the difference in the CIF between groups. Multivariate analysis using the Fine-Gray model and the cause-specific (CS) hazard model to explore factors affecting the cumulative incidence rate of meningioma patients.

Result: Of the 1502 eligible patients, 419 died of meningioma and 398 died of competing events. The Fine-Gray model showed that age at diagnosis (35–64 vs 18–34 years: hazard ratio [HR]=2.490, p=0.031; >64 vs 18–34 years: HR=4.486, p<0.001), sex (male vs female: HR=1.388, p=0.002), tumor grade (II/III vs unknown: HR=1.630, p<0.001), and SEER stage (distant vs localized: HR=1.711, p<0.001) were risk factors for patients. The CS model showed that age at diagnosis (35–64 vs 18–34 years: HR=2.677, p=0.031; >64 vs 18–34 years: HR=5.982, p<0.001), marital status (divorced/separated/widowed vs married: HR=1.277, p=0.047), sex (male vs female: HR=1.486, p<0.001), tumor grade (II/III vs unknown: HR=1.775, p<0.001), and SEER stage (distant vs localized: HR=1.660, p<0.001) were risk factors for patients.

Conclusion: This study is the first to establish a competing-risks analysis model for the risk assessment of meningioma patients. These results may help clinicians to better understand meningioma patients and provide them with appropriate support.

Background

Meningioma accounts for about one-third of all intracranial brain tumors and is the most-common primary intracranial tumor in the United States, with an average annual incidence of 7.44/100,000.[1–6] Only about 5% of meningiomas are atypical or malignant meningiomas (WHO II and III); most meningiomas are WHO I.[7] Although the prognosis of benign meningioma (WHO I) is generally good, atypical meningioma (WHO II) and malignant meningioma (WHO III) are invasive tumors associated with a poor prognosis and high mortality.[8, 9] One study found that WHO I meningiomas mainly affect females, while males are main affected by atypical and malignant meningiomas.[7]

Most previous reports on risk factors for meningioma survival have been based on the Cox proportional-hazards regression model. A survival analysis based on the Cox model usually considers only one endpoint: the one that is of interest to the researcher. However, in clinical trials of tumors, it is not always only the endpoints that are of interest to researchers, and there are some endings that are not of interest. These endpoints represent competing events. Traditional survival analysis will treat such competing events (or "risks") by censoring, which will lead to miscalculations of the survival function.[10] This situation means that previous studies have often been adversely affected by competing-risks bias.[11, 12]

The Surveillance, Epidemiology, and End Results (SEER) program is a coordinated system of population-based state cancer registries collecting demographic, clinical, and outcome information on all cancers diagnosed in representative geographic regions and subpopulations.[13, 14] The database is run by the National Cancer Institute, and it collects and publishes incidence and survival data from population-based cancer registries covering approximately 30% of the United States population.[15] Since 2004, the SEER database has officially begun to record information on nonmalignant brain tumors due to the “Beneficial Brain Tumor Registration Amendment”.[16, 17]

Few studies have used SEER data to examine the survival of meningioma patients. The present study attempted to identify the risk factors for meningioma by utilizing a competing-risks model, with the aim of helping to reduce the risk of bias due to competing events and thereby increase the accuracy of the analysis.

Methods

Patients

We used SEER*Stat software (version 8.3.5, https://seer.cancer.gov/) to search for relevant meningioma patients using histological type code 9530 of ICD-O-3 (the third edition of the International Classification of Diseases for Oncology). Patients were selected from 1973 to 2015. We excluded patients younger than 18 years, cases that were not confirmed by microscopy, and cases for which not all of the following analyzed variables were available: age at diagnosis, race, marital status, sex, tumor grade, SEER stage, surgery, radiation, chemotherapy, receiving the first indication of a malignant primary tumor, education level (proportion of residents with at least a bachelor’s degree), employment status (proportion of residents who are unemployed), median household income, and smoking (proportion of residents who are current smokers).

Statistical analysis

We regarded other causes of death as competing events in our competing-risks analysis. Categorical data are presented as frequency and proportion values. When there is a competing risk, the outcome is not only survival, death. The cumulative incidence function (CIF) should be used to estimate the crude incidence rate because it can estimate the total incident rate of A, B, and AB, whereas the Kaplan-Meier curve cannot. The difference test for the CIF corresponds to Gray’s test. Therefore, univariate analysis was performed using the CIF to show the probability of each event, while Gray’s test was used to estimate the difference in the CIF between groups.

The Fine-Gray model, also known as the subdistribution hazard function or CIF regression model, is designed to fit the cumulative incidence of events of interest.[18] The Fine-Gray model is suitable for research into predicting risk on an individualized basis, estimating the risk and prognosis of disease, and establishing clinical prediction models and risk scores.[11, 19]

Another model called the cause-specific (CS) hazard model should be applied when competing risks are present. This model is more suitable for etiology studies.[11, 19] The present study used multivariate analysis with the Fine-Gray and CS models to explore factors affecting the cumulative incidence rate of meningioma patients. The effects of competing risks tend to be stronger in the CS model than in the Fine-Gray model. We also obtained results using a Cox model for comparison with the results obtained using the other two models.

All statistical analyses were performed using SAS (version 9.2), and R software (version 3.5.0; https://www.r-project.org/). The R package 'cmprsk' was used to construct the model. All statistical tests were two-sided, with $P < 0.05$ considered to be indicative of statistical significance. Given that cancer is a reportable disease in every state of the USA, informed patient consent is not required. When a data use agreement was signed, data on cancer research become available to the public free of charge.

Results

Patient characteristics

Of the 1502 eligible patients, 419 died of meningioma (39.83% of the total) while 398 died of competing events such as suicide, accidents, and cardiovascular diseases (37.83% of the total). Most of the patients were aged 35–64 years, white, married, female, with an unknown tumor grade, localized SEER stage, had received surgery, had not received radiation, had not received chemotherapy, had received their first indication of a malignant primary tumor, lived where 20–50% of residents have at least a bachelor's degree, < 10% are unemployed, and < 20% are current smokers, and a median household income of USD 50,001–100,000. The baseline demographics are presented in Table 1.

Table 1
Patients Characteristics and Demographics

Variables	Alive N (%)	Death to meningioma cancer N (%)	Death to other reasons N (%)	*p*
Total	685	419	398	
Age at diagnosis				< 0.05
18–34	49 (7.2)	5 (1.2)	8 (2.0)	
35–64	429 (62.6)	163 (38.9)	96 (24.1)	
> 64	207 (30.2)	251 (59.9)	294 (73.9)	
Race				0.658
White	514 (75.0)	307 (73.3)	305 (76.6)	
Black	113 (16.5)	67 (16.0)	59 (14.8)	
Other	58 (8.5)	45 (10.7)	34 (8.5)	
Marital status				< 0.05
Married	363 (53.0)	229 (54.7)	179 (45.0)	
Unmarried	149 (21.8)	54 (12.9)	63 (15.8)	
DSW	125 (18.2)	119 (28.4)	130 (32.7)	
Unknown	48 (7.0)	17 (4.1)	26 (6.5)	
Sex				< 0.05
Female	452 (66.0)	224 (53.5)	220 (55.3)	
Male	233 (34.0)	195 (46.5)	178 (44.7)	
Grade				< 0.05

Variables	Alive N (%)	Death to meningioma cancer N (%)	Death to other reasons N (%)	*p*
I	73 (10.7)	7 (1.7)	15 (3.8)	
II/III	117 (17.0)	120 (28.6)	84 (21.1)	
Unknown	495 (72.3)	292 (69.7)	299 (75.1)	
SEER stage				0.042
Localized	358 (52.3)	210 (50.1)	212 (53.3)	
Regional	169 (24.7)	84 (20.0)	82 (20.6)	
Distant	48 (7.0)	53 (12.6)	41 (10.3)	
Unknown	110 (16.1)	72 (17.2)	63 (15.8)	
Surgery				< 0.05
Yes	530 (77.4)	314 (74.9)	248 (62.3)	
No/Unknown	155 (22.6)	105 (25.1)	150 (37.3)	
Radiation				0.023
Yes	203 (29.6)	152 (28.1)	112 (28.1)	
No/Unknown	482 (70.4)	267 (63.7)	286 (71.9)	
Chemotherapy				0.001
Yes	12 (1.8)	25 (6.0)	16 (4.0)	
No/Unknown	673 (98.2)	394 (94.0)	382 (96.0)	
First malignant primary indicator				< 0.05
Yes	620 (90.5)	419 (100.0)	238 (59.8)	
No	65 (9.5)	0 (0.0)	160 (40.2)	

Variables	Alive N (%)	Death to meningioma cancer N (%)	Death to other reasons N (%)	*p*
% At least bachelor degree				0.345
< 20%	111 (16.2)	78 (18.6)	77 (19.3)	
20%-50%	557 (81.3)	325 (77.6)	306 (76.9)	
> 50%	17 (2.5)	16 (3.8)	15 (3.8)	
% Unemployed				0.590
< 10%	525 (76.6)	332 (79.2)	311 (78.1)	
≥ 10%	160 (23.4)	87 (20.8)	87 (21.9)	
Median household income				0.100
10000–50000	159 (23.2)	97 (23.2)	105 (26.4)	
50001–100000	491 (71.7)	313 (74.7)	278 (69.8)	
> 100000	35 (5.1)	9 (2.1)	15 (3.8)	
% Current Smoker				0.688
< 20%	474 (69.2)	292 (69.7)	267 (67.1)	
≥ 20%	211 (30.8)	127 (30.3)	131 (32.9)	

Univariate analysis of the prognosis of meningioma patients

When competing risks were present, the results of Gray's test showed that age at diagnosis, marital status, sex, tumor grade, SEER stage, radiation, chemotherapy, and being the first indication of a malignant primary tumor exerted statistically significant effects in meningioma patients ($p < 0.05$). The CIF for almost all variables increased over 1, 5, and 10 years. Compared with other classifications in each group, the CIF was highest for an age at diagnosis > 64 years, race other than white or black, divorced/separated/widowed (DSW), being male, unknown tumor grade, distant SEER stage, received surgery, radiation, and chemotherapy, being the first indication of a malignant primary tumor, living where > 50% of residents have at least a bachelor's degree, < 10% are unemployed, and < 20% are current

smokers, and a median household income of United States Dollar (USD) 50,001–100,000. The data are presented in detail in Fig. 1 and Table 2.

Table 2
Univariable analysis in patients by using Cumulative incidence function

Variables	Gray's test	*p*-value	Cumulative incidence function		
			12 months	60 months	120 months
Age at diagnosis	35.588	**< 0.001**			
18–34			0.017	0.078	0.102
35–64			0.076	0.196	0.257
> 64			0.180	0.319	0.357
Race	2.802	0.246			
White			0.123	0.248	0.294
Black			0.128	0.241	0.286
Other			0.143	0.308	0.376
Marital status	12.864	**0.004**			
Married			0.129	0.263	0.325
Unmarried			0.088	0.180	0.219
DSW			0.154	0.292	0.328
Unknown			0.081	0.205	0.205
Sex	10.938	**< 0.001**			
Female			0.108	0.222	0.265
Male			0.153	0.299	0.354
Grade	48.27	**< 0.001**			
I			0.122	0.238	0.282
II /III			0.051	0.094	0.121
Unknown			0.178	0.406	0.483
SEER stage	7.837	**0.049**			
Localized			0.120	0.250	0.291
Regional			0.111	0.228	0.307
Distant			0.201	0.363	0.396
Unknown			0.119	0.227	0.271
Surgery	1.390	0.238			

Variables	Gray's test	*p*-value	Cumulative incidence function		
			12 months	60 months	120 months
Yes			0.110	0.262	0.317
No/Unknown			0.167	0.230	0.260
Radiation	8.106	**0.004**			
Yes			0.102	0.302	0.381
No/Unknown			0.137	0.232	0.268
Chemotherapy	12.354	**< 0.001**			
Yes			0.230	0.497	0.497
No/Unknown			0.122	0.243	0.293
First malignant primary indicator	101.744	**< 0.001**			
Yes			0.148	0.297	0.353
No			0.000	0.000	0.000
% At least bachelor degree	1.101	0.577			
< 20%			0.129	0.282	0.326
20%-50%			0.123	0.244	0.294
> 50%			0.168	0.317	0.340
% Unemployed	0.320	0.572			
< 10%			0.128	0.255	0.303
≥ 10%			0.119	0.243	0.290
Median household income	5.852	0.054			
10000–50000			0.104	0.244	0.294
50001–100000			0.133	0.262	0.310
> 100000			0.121	0.139	0.163
% Current Smoker	0.948	0.330			
< 20%			0.133	0.264	0.306
≥ 20%			0.110	0.229	0.288

Multivariate analysis of the prognosis of meningioma patients

The results for the Fine-Gray model showed that age at diagnosis (35–64 vs 18–34 years: hazard ratio [HR] = 2.490, 95% confidence interval [CI] = 1.089–5.691, $p = 0.031$; >64 vs 18–34 years: HR = 4.486, 95% CI = 1.961–10.262, $p < 0.001$), sex (male vs female: HR = 1.388, 95% CI = 1.130–1.705, $p = 0.002$), tumor grade (II/III vs unknown: HR = 1.630, 95% CI = 1.264–2.102, $p < 0.001$), and SEER stage (distant vs localized: HR = 1.711, 95% CI = 1.241–2.358, $p < 0.001$) were risk factors for patients. The results for the CS model showed that age at diagnosis (35–64 vs 18–34 years: HR = 2.677, 95% CI = 1.093–6.556, $p = 0.031$; >64 vs 18–34 years: HR = 5.982, 95% CI = 2.441–14.658, $p < 0.001$), marital status (DSW vs married: HR = 1.277, 95% CI = 1.003–1.625, $p = 0.047$), sex (male vs female: HR = 1.486, 95% CI = 1.208–1.829, $p < 0.001$), tumor grade (II/III vs unknown: HR = 1.775, 95% CI = 1.377–2.289, $p < 0.001$), and SEER stage (distant vs localized: HR = 1.660, 95% CI = 1.220–2.258, $p < 0.001$) were risk factors for patients. We also include the results obtained using the multivariate Cox regression for comparison in Table 3.

Table 3
Multivariable analysis in patients by using Cox, Fine-Gray and CS models

Variables	COX			Fine-Gray			CS		
	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
Age at diagnosis									
18–34	Reference								
35–64	2.020	1.149–3.553	**0.015**	2.490	1.089–5.691	**0.031**	2.677	1.093–6.556	**0.031**
> 64	5.483	3.123–9.626	**< 0.001**	4.486	1.961–10.262	**< 0.001**	5.982	2.441–14.658	**< 0.001**
Race									
White	Reference								
Black	1.199	0.983–1.462	0.070	1.184	0.093–1.553	0.222	1.248	0.950–1.640	0.111
Other	1.283	1.009–1.632	**0.042**	1.214	0.891–1.654	0.220	1.233	0.893–1.701	0.203
Marital status									
Married	Reference								
Unmarried	1.046	0.843–1.297	0.684	0.799	0.588–1.086	0.153	0.820	0.603–1.116	0.207
DSW	1.398	1.178–1.658	**< 0.001**	1.215	0.954–1.547	0.114	1.277	1.003–1.625	**0.047**
Unknown	0.924	0.670–1.274	0.629	0.769	0.463–1.278	0.311	0.746	0.452–1.232	0.253
Sex									
Female	Reference								
Male	1.480	1.274–1.720	**< 0.001**	1.388	1.130–1.705	**0.002**	1.486	1.208–1.829	**< 0.001**
Grade									
I	0.600	0.437–0.824	**0.002**	0.479	0.297–0.775	**0.003**	0.454	0.276–0.746	**0.002**
II /III	1.646	1.360–1.992	**< 0.001**	1.630	1.264–2.102	**< 0.001**	1.775	1.377–2.289	**< 0.001**
Unknown	Reference								

CS: cause specific hazard function model

Variables	COX			Fine-Gray			CS		
	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
SEER stage									
Localized	Reference								
Regional	1.001	0.833–1.202	0.995	0.962	0.741–1.249	0.771	0.951	0.735–1.230	0.702
Distant	1.345	1.071–1.689	**0.011**	1.711	1.241–2.358	**0.001**	1.660	1.220–2.258	**0.001**
Unknown	0.825	0.673–1.011	0.063	1.035	0.789–1.358	0.804	0.932	0.703–1.235	0.622
Surgery									
Yes	Reference								
No/Unknown	1.298	1.098–1.535	**0.002**	0.892	0.687–1.158	0.391	1.008	0.784–1.295	0.952
Radiation									
Yes	Reference								
No/Unknown	1.067	0.909–1.252	0.426	0.926	0.745–1.152	0.490	1.028	0.826–1.280	0.803
Chemotherapy									
Yes	Reference								
No/Unknown	0.545	0.389–0.763	**< 0.001**	0.732	0.460–1.166	0.190	0.640	0.415–0.987	**0.044**
First malignant primary indicator									
Yes	Reference								
No	1.460	1.222–1.745	**< 0.001**	0.000	0.000–0.000	< 0.001	0.000	0.000-8.42E2	0.953
% At least bachelors degree									
< 20%	Reference								
20%-50%	0.746	0.601–0.925	**0.008**	0.778	0.572–1.061	0.114	0.748	0.551–1.014	0.062
> 50%	1.041	0.656–1.653	0.865	1.201	0.632–2.282	0.577	1.200	0.640–2.252	0.570

CS: cause specific hazard function model

Variables	COX			Fine-Gray			CS		
	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
% Unemployed									
< 10%	Reference								
≥ 10%	0.949	0.781–1.153	0.599	0.935	0.709–1.232	0.633	0.958	0.730–1.258	0.758
Median household income									
10000–50000	Reference								
50001–100000	1.029	0.805–1.316	0.817	1.123	0.802–1.572	0.501	1.073	0.765–1.505	0.685
> 100000	0.565	0.334–0.954	**0.033**	0.483	0.217–1.074	0.074	0.421	0.189–0.935	**0.034**
% Current Smoker									
< 20%	Reference								
≥ 20%	0.944	0.775–1.150	0.569	0.928	0.709–1.214	0.585	0.900	0.688–1.178	0.444
CS: cause specific hazard function model									

Discussion

In medical research it is common to observe multiple endpoints that compete with each other. For example, the risk of competition for death from heart disease and cerebrovascular disease in patients with non-small-cell lung cancer increases with age.[20] Traditional survival analysis will treat the competing risks by censoring, and the incidence of the true outcome will be overestimated, leading to competing-risks bias. A study of competing-risks bias found that up to 46% of studies reported on in the literature were affected by competing-risks bias, including in advanced medical journals.[12] Meningioma accounts for 34% of all primary intracranial tumors, and approximately 7,000 new cases are diagnosed each year in the United States.[7] Meningioma arises from arachnoid cells of the leptomeninges and may occur throughout the coverings of the central nervous system.[21] Since most meningiomas follow a benign course, the State Central Cancer Registry did not collect nonmalignant cases with a diagnosis before 2004. However, studies have shown that up to 10% of meningiomas can show more-aggressive behavior and a higher tendency to relapse.[22] The Benign Tumor Registration Amendment provides for the collection of data related to benign and borderline malignant brain tumors from 2004, which represents useful information about this common but underresearched tumor.

To the best of our knowledge, the present study is the first to use the SEER database to conduct a competing-risks analysis (including Fine-Gray model and CS model) of meningioma patients with the goal of identifying more-accurate prognostic factors. Approximately one-third (n = 398) of the meningioma patients analyzed in this study died of competing events. Using a competing-risks model, we found that age at diagnosis, sex, tumor grade, and SEER stage were risk factors for meningioma patients.

Meningioma can occur at any age, but the incidence of meningioma in people younger than 18 years is only 0.06/100,000.[23] The incidence of meningioma increases with age, and is most common among elderly people older than 65 years.[24] A previous study of atypical and anaplastic meningiomas found that for every additional year of age, the risk increased by 1.03, which is consistent with our results.[2] In our study the Cox regression, Fine-Gray, and CS models all showed that being aged 35–64 and > 64 years were risk factors compared with an age of 18–34 years (p < 0.05). The prognosis is poor and the risk is high especially in the elderly (> 64 vs 18–34 years: Cox, HR = 5.483; Fine-Gray, HR = 4.486; CS, HR = 5.982). This might be because morbidity and mortality rates are higher, there are more surgical complications, and the functional prognosis is worse in elderly patients with craniotomy or subtotal resection than in younger patients.

Cox regression revealed that race other than white or black was a risk factor compared with being white (HR = 1.283, p = 0.042). However, we did not observe this result in the two competing-risks models, which indicates that the results of Cox regression are not accurate because it does not consider competing risks. Garzon-Muvdi et al. also demonstrated that race other than white or black and unknown race are not risk factors for atypical and anaplastic meningiomas compared with whites in an analysis using the Fine-Gray model (HR = 0.37, p = 0.320).[2] All three models in the present study showed that being male is a risk factor for meningioma, which is consistent with previous findings.[25–27]

Compared with married patients, DSW was a risk factor in both the Cox model (HR = 1.398, p < 0.001) and the CS model (HR = 1.277, p < 0.05), but not in the Fine-Gray model (HR = 1.215, p > 0.05). We also found this difference for chemotherapy and the median household income. Although both the Fine-Gray and CS models are competing-risks models, they produced different results, which is due to the effects being stronger in the CS model than in the Fine-Gray model. Although the directions of the correlations were essentially the same in the two models, and their HRs were similar, they can still produce different results. This has also happened in previous studies,[27] and it explains why two competing-risks models need to be employed. The CS model is more suitable for answering etiology studies, while the Fine-Gray model is increasingly being used for clinical predictive models and risk determination.[11, 19]

All three models showed that grade I is a protective factor compared to unknown grade, and that grade II/III is a risk factor. The WHO staging system classifies meningiomas into grades I, II, and III. A meningioma of grade I has a low recurrence and low invasive growth, while meningiomas of grades II and III exhibit high recurrence, high invasive growth, poor prognosis, and high mortality.[28] We also found that all three models showed distant SEER stage to be a risk factor compared to an unknown SEER

stage. However, the Cox regression model appeared to underestimate this risk (Cox, HR = 1.345; Fine-Gray, HR = 1.711; CS, HR = 1.660).

Regarding the treatment, the Fine-Gray model indicated that none of treatments—surgery, radiotherapy, or chemotherapy—exerted statistically significant effects ($p > 0.05$). Moreover, the CS model indicated that not receiving chemotherapy was a protective factor (HR = 0.640, $p < 0.05$). Surgery currently remains the cornerstone in the clinical diagnosis and treatment of malignant meningioma. However, there is still a lack of clear guidelines for chemotherapy.[29] Traditional chemotherapeutic agents are not very effective against meningioma, but hormone therapy is being investigated for patients with inoperable tumors, and radiation therapy is increasingly recommended as a standard adjuvant therapy for patients with malignant meningioma.[30]

The Cox regression performed in the present study revealed that receiving the first indication of a malignant primary tumor, having at least a bachelor's degree, and the median household income affected the survival of meningioma patients, whereas these results were not found in the competing-risks model. This may also be due to the presence of competing-risks bias.

Limitations

The large sample is one of the main strengths of this study. However, our research was also subject to limitations. First, it had inherent limitations due to its retrospective design. Second, important information is missing from the SEER database, such as the Simpson rating. Third, the records in the SEER database are not complete, and patients may be misclassified. Finally, because this study is the first to use two competing-risks models for the risk assessment of meningioma patients, further research is needed to verify the present results.

Conclusions

This study has established a competing-risks analysis model based on the SEER database for the risk assessment of meningioma patients for the first time. The age at diagnosis, sex, tumor grade, and SEER stage were found to be significant risk factors. These results may help clinicians to better understand meningioma patients and provide them with appropriate support.

Abbreviations

SEER: Surveillance, Epidemiology, and End Results; CS: cause-specific; HR: hazard ratio; WHO: world health organization; ICD-O-3: the third edition of the International Classification of Diseases for Oncology; DSW: divorced/separated/widowed; United States Dollar: USD; CI: confidence interval.

Declarations

Acknowledgments

The authors would like to thank SEER for open access to the database.

Authors' contributions

JL designed the study. JY, YJH and QH collected and analyzed the data. JY and YJH organized the manuscript. XJF and FFZ reviewed the papers and revised the manuscript. All the authors have read and approved the final manuscript.

Funding

This study was supported by the National Social Science Foundation of China (No.16BGL183).

Availability of data and materials

The data were abstracted from the Surveillance, Epidemiology, and End Results (SEER) database.

Ethics approval and consent to participate

All analyses were based on a free database, thus for this type of study informed consent is not required.

Consent to publish

Not applicable.

Competing interests

The authors declare no potential conflicts of interest.

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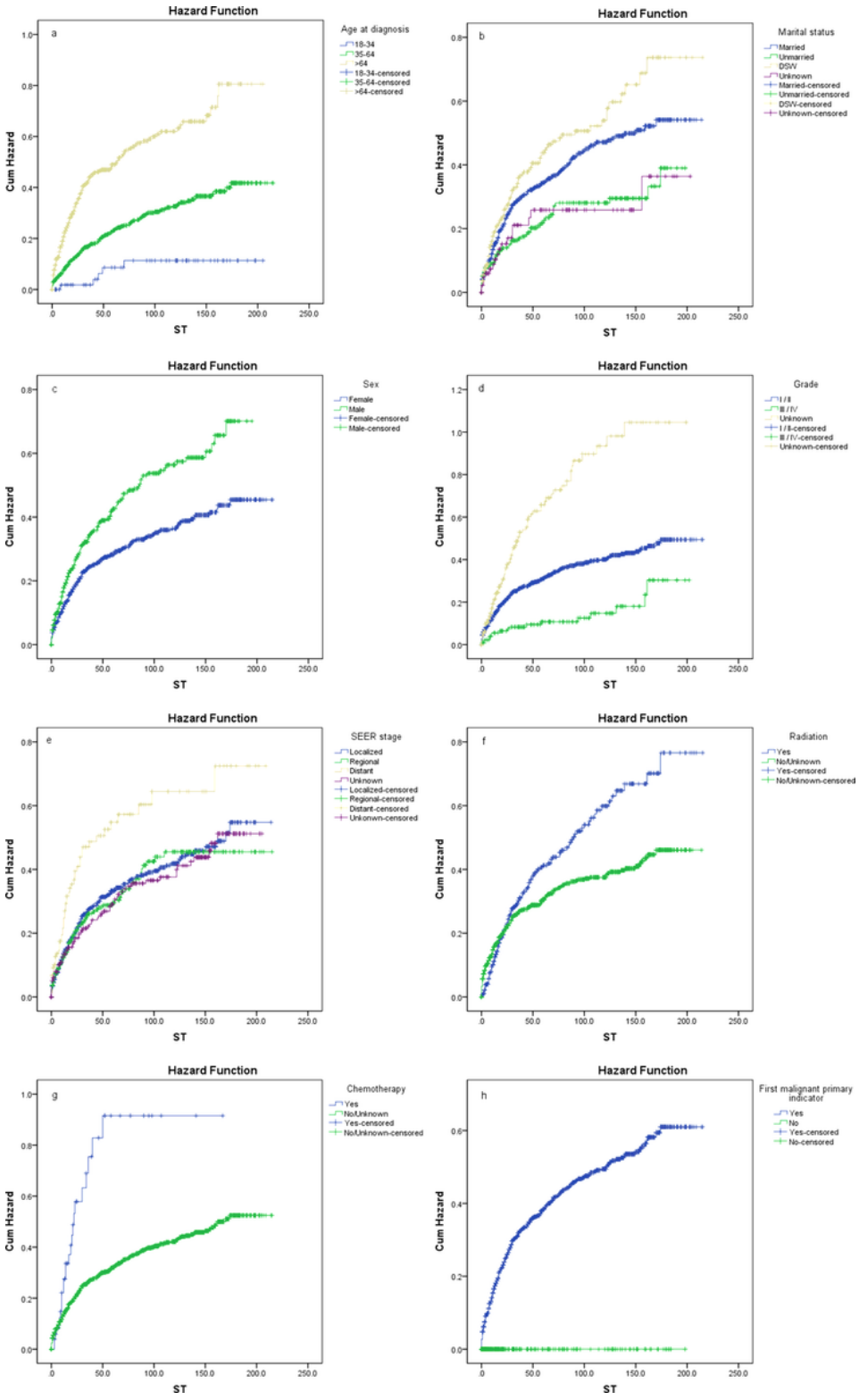
Figures

Figure 1

Cumulative hazard curves a: age at diagnosis; b: marital status c: sex; d: grade; e: SEER stage; f: radiation; g: chemotherapy; h: first malignant primary indicator



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