Marital Status is an Independent Prognostic Factor in 7 Sites of Squamous Cell Carcinoma: A Propensity-Adjusted SEER Database Analysis

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Research article

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Abstract

Background: Marital status has been proved as an independent prognostic factor in many cancer types. However, no detailed investigation of marital status on squamous cell carcinoma (SCC) has been evaluated. The aim of this essay is to explore the relationship between marital status and SCC in 7 tumor sites.

Methods: All patients diagnosed with SCC were collected from the SEER database (1975-2016). We analyzed the survival of all included SCC patients in four marital status. We utilized propensity-score matching analysis to balance baseline characteristics between married and unmarried SCC patients in 7 tumor sites. The influence of marital status on overall survival (OS) in each site was performed by Cox regression analysis.

Results: A total of 180009 SCC patients were involved in this study. After propensity-score matching, patients in the married group were 1:1 matched with patients in the unmarried group for each sites. Married group exhibited higher 5- year OS rate than unmarried group (27.3% vs 19.8%). More precisely, being divorced and widowed were observed to be related to have worse survival than single patients in most sites. Furthermore, patients with clinical stage IV were more common in the unmarried group which having a lower proportion of receiving treatment.

Conclusions: This study indicated that marital status was a significant factor for OS of SCC in 7 tumor sites. Married patients always behaved more favorable than unmarried including single, divorced, and widowed patients.

Introduction

Squamous cell carcinoma is a form of cancer that originates from squamous cells of the skin and mucous membranes. SCC occurs in tissues that provide a barrier between an organism and environment, such as the skin, oral cavity, esophagus and lung[I1]. Statistically, SCC accounted for more than 90% of the head and neck cancers and esophageal cancers[2–3]. SCC tended to have different mechanisms of tumorigenesis and progression and are frequently associated with smoking and alcohol consumption[4–6]. Besides, oral SCC have also been demonstrated to be related to human papilloma virus (HPV) infection and a lack of vitamins[7]. High-risk HPVs (HPV16, HPV18, and HPV31) were observed to be relevant to at least 99.7% of cervical SCC[8].

The correlation between the prognosis of cancer and clinical features including age, gender, TNM stage, tumor size was frequently discussed. However, other confounding factors, such as dietary habits, socioeconomic status, educational attainment, and marital status were rarely evaluated. Several previous studies had reported the relationship between marital status and SCC of the head and neck and penis[9–11]. They all indicated that marital status was an independent prognostic factor among these cancers and married patients showed a significantly better prognosis. However, other sites of SCC were less investigated.

The surveillance, epidemiology, and end result (SEER) database consisted of 18 cancer registries and covers 30% of US population[12]. In our study, we analyzed the data from the SEER database to find out the influence of marital status on SCC in 7 common sites.

Patients And Methods

Patient selection

All patients were identified in the SEER database (version 8.3.8). Patients with a pathological diagnosis of SCC (ICD-O-3 histology code: 8050-8089) in the site of the cervix, esophagus, larynx, lung, nasopharynx, oropharynx, or tongue

were enrolled in our study. The TNM staging was based on the American Joint Committee on Cancer (AJCC) 6th edition. Exclusion criteria were listed as the following: (a) Patients with the metastatic tumor or more than one primary tumor; (b) Patients with incomplete clinicopathological characteristics.

Propensity-score matching

Marital status was divided into the married group and unmarried group. To evaluate the importance of marital status of SCC, propensity-score matching was performed to regulate the difference of clinical features between two patient groups in 7 sites. After matching, clinicopathological variables and the influence of marital status were re-analyzed within the matched pairs.

Statistical analysis

The relationship between marital status and a series of clinical information, including age, gender, race, tumor site, stage, surgery, radiation, and chemotherapy was analyzed by Pearson's chi-square test. The primary endpoint of this study was overall survival (OS). The survival curves were depicted by GraphPad Prism (version: 8.4.3) and survival difference was assessed by the Log-rank test. A cox regression model was conducted to report hazard ratios (HR) of marital status among 7 tumor sites. All analyses were carried out using SPSS, version 25.0. When $P<.05$ was regarded as statistical significance.

Results

Clinical characteristics

A total of 180009 patients were involved in this research. 64787 (36.0%) were younger than 60 years old and 115222 (64.0%) were older. There were 110245 (61.2%) males and 69764 (38.8%) females, with M: F ratio of 1.58:1. Seven SCC tumor sites mainly included 22383 cervix (12.4%), 8963 esophagus (5.0%), 24404 larynx (13.6%), 80935 lung (45.0%), 3090 nasopharynx (1.7), 17586 oropharynx (9.8%) and 22648 tongue (12.6%). Among 180009 patients, 93695 (52.1%) patients were married while 86314 (47.9%) patients were unmarried. Unmarried patients were subdivided into 37389 single (20.7%), 24322 divorced (13.5%), and 24603 widowed (13.6%). Other detailed clinical information was presented in Table 1. Results of Chi-square tests showed that significant differences were observed in the age, gender, race, stage, surgery, radiotherapy, and chemotherapy between married and unmarried groups. We also calculated the proportion of stage IV patients at the first diagnosis between two groups. The results showed that the ratio of distant metastases in the unmarried group was all higher than the married group in 7 sites. This phenomenon was particularly noticeable in the site of the larynx. Besides, rates of surgery, radiotherapy, and chemotherapy were computed in both two groups (Table 2). We observed that the married group had more therapeutic advantages than the unmarried group.

Propensity-score matching for married and unmarried groups

Baseline characteristics of 7 tumor sites between married and unmarried groups were different. So propensity-score matching analysis was performed to balance potential confounding factors between two groups. After matching, a total of 158880 patients matched pairs were enrolled, which including cervix (18620), esophagus (8142), larynx (22555), lung (73101), nasopharynx (2478), oropharynx (15024), and tongue (18960), respectively.

Survival analysis

Table 3 showed the median survival time (MST) of 4 marital status in 7 sites after propensity-score matching. The MST in the married group was always significantly better than that in the unmarried group (P<.001). Among 7 sites of SCC, head and neck and cervical SCC had more favorable survival. But the SCC of the esophagus and lung was associated with poor survival. The 5-year survival rate of the married and unmarried group was 27.3% and 19.8%, respectively.

Figure 1 displayed the survival differences between the two groups in 7 SCC sites by survival curves (P<.001). The curves showed the survival advantage of the married group intuitively. A cox regression analysis was used to compare 4 marital status related to OS (Table 4). The relative hazard of the unmarried group including single, divorced, and widowed was all higher than the married group. This was especially obvious for the site of the oropharynx. Single (HR 2.008), divorced (HR 1.856), and widowed (HR 3.078) group showed much higher risks than the married group.

Discussion

Several studies have indicated that there is a close relationship between marital status and survival of cancers [13–16]. But the correlation between marital status and SCC remained elusive. Seven high-prevalence sites of SCC were selected from the SEER database to address this issue. After propensity-score matching, marital status was confirmed to be significantly associated with the prognosis of SCC patients in all 7 sites. Moreover, the survival period of patients who were married was significantly longer than those who were single, divorced or widowed. Unmarried patients were more likely to have distant metastases and were less likely to undergo surgery, radiotherapy or chemotherapy. Besides, it is the first study to indicate that marriage has an independent beneficial effect on survival of SCC in seven common sites.

Previous studies had demonstrated that marital status was significantly related to superior prognosis of penis, oral cavity and tongue SCC[17–19]. Studies had shown that marriage was correlated with a reduction in cancer death ranging from 12–33%[20]. Some literature suggested that married people were more able to receive early screening and treatment due to the support of spouse[20–21]. Other potential advantages of being married included the increasing likelihood of having insurance coverage, good living habits, mental state or even social support[22]. The premise must be a benign marriage without adverse factors such as domestic violence. Also, the detailed classification of unmarried patients in our study exhibited that divorced and widowed patients had worse survival than those who were single. This may be attributed to psychological distress suffered by patients who were divorced or widowed. Furthermore, the poor prognosis of widowed patients may be also related to older age[23]. It was widely known that the association between tobacco smoking and the incidence of esophageal, lung, nasopharyngeal, head and neck SCC was well established[24–27]. Meanwhile, SCC often occurs in male smokers. The ratio of males to females in our study also supported this opinion. Previous researches had found that marriage reduced smoking and alcohol intake[28]. Males and black had a higher smoking-related mortality rate[29], so this type of patients may benefit more in survival time. In addition, being married meant earlier diagnosis and a superior prognosis for cervical cancer patients[30]. The possible reasons may come from the following two aspects: (1)Married women had higher cervical cancer screening rate than unmarried women[31]; (2)Married women may improve socioeconomic status through marriage and benefit from social support and private health insurance coverage[32–33]. This phenomenon reminded us to pay more attention to cancer screening and social welfare for unmarried women. Empirical evidence indicated that there was a positive correlation between economic status and health[34]. And married patients were more likely to get financial support from family. Apart from good living habits and financial support, maintaining a positive attitude is also an important factor in cancer treatment. A variety of literature had suggested that cancer

patients were in relation to the higher prevalence of depression and anxiety, especially for females[35]. Adverse psychological factors will significantly affect the prognosis. It is well-known that depression and anxiety can cause a host of physiological problems such as somatization disorders and low levels of the immune system[36–37]. Married patients can get comfort and encouragement from their spouses, as well as more active treatment based on their sense of family responsibility[38–39]. Thus, clinicians should pay more attention to assessing the mental status of unmarried patients and reduce the sense of loss of fighting disease alone. The company of family members may take the place of the role of spouse to some extent.

Our research can help clinicians notice the marital status of SCC patients. They should take it into consideration when judging prognosis and formulating therapeutic measures. If the patient is married, the clinician can inform the spouse of the precautions. The spouse can play the role of supervision and care. Community health services and family doctors can replace spouses to help remind unmarried people to check regularly. This measure may decrease the morbidity rate of unmarried patients and prolong survival time.

We acknowledge that several limitations exist in our study. First, only marital status at first diagnosis will be recorded in the SEER database. And the change of marital status after diagnosis may influence the final results of survival analysis. Meanwhile, the quality and duration of marriage are not included in the database, which is significant for the conclusion. Second, some crucial factors are not available in the SEER database, such as tobacco and alcohol use, income status, educational level, etc. High income and educational level are both favorable prognostic factors for cancers. Lack of these important factors may increase the likelihood of bias.

Conclusion

In conclusion, we have demonstrated that marital status is an independent prognostic factor of SCC patients. Married patients behaved more superior OS than unmarried patients of SCC in 7 sites. We tried to help unmarried patients minimize the survival gap by analyzing the reasons behind the longer survival time of married patients.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated during and/or analysed during the current study are available in the SEER database [https://seer.cancer.gov/].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Ji-li Xu: Methodology; Formal analysis and investigation; Writing-original draft preparation

Yong Guo:Conceptualization; Writing-review and editing; Funding acquisition; Supervision

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Tables

Table 1 Clinicopathological characteristics of 180009 patients in married and unmarried groups in 7 sites after propensity score matching

Variables	Total (n=180009)	Married (n=93695)	Unmarried (n=86314)	P value
Age				
<60y (%)	64787 (36.0)	32592 (34.8)	32195 (37.3)	P<.001
≥60y (%)	115222 (64.0)	61103 (65.2)	54119 (62.7)	
Gender				
Male	110245 (61.2)	65544 (59.5)	44701 (40.5)	P<.001
Female	69764 (38.8)	28151 (40.4)	41613 (59.6)	
Race				
White	144859 (80.5)	78805 (84.1)	66054 (76.5)	P<.001
Black	23413 (13.0)	7380 (7.9)	16033 (18.6)	
Other	11737 (6.5)	7510 (8.0)	4227 (4.9)	
Tumor location				
Cervix	22383 (12.4)	9310 (9.9)	13073 (15.1)	
Esophagus	8963 (5.0)	4176 (4.5)	4787 (5.5)	
Larynx	24404 (13.6)	13005 (13.9)	11399 (13.2)	
Lung	80935 (45.0)	42111 (44.9)	38824 (45.0)	P<.001
Nasopharynx	3090 (1.7)	1851 (2.0)	1239 (1.4)	
Oropharynx	17586 (9.8)	10074 (10.8)	7512 (8.7)	
Tongue	22648 (12.6)	13168 (14.1)	9480 (11.0)	
TNM staging				
I	46298 (25.7)	25176 (26.9)	21122 (24.5)	
II	20296 (11.3)	10586 (11.3)	9710 (11.2)	P<.001
III	46139 (25.6)	23737 (25.3)	22402 (26.0)	
IV	67276 (37.4)	34196 (36.5)	33080 (38.3)	
Surgery				
No	116553 (64.7)	57400 (61.3)	59153 (68.5)	P<.001
Yes	63456 (35.3)	36295 (38.7)	27161 (31.5)	
Radiation				
No/Unknown	71333 (39.6)	35713 (38.1)	35620 (41.3)	P<.001
Yes	108676 (60.4)	57982 (61.9)	50694 (58.7)	
Chemotherapy				
No/Unknown	92095 (51.2)	45859 (48.9)	46236 (53.6)	P<.001
Yes	87914 (48.8)	47836 (51.1)	40078 (46.4)	

Table 2 Comparison of distant metastasis rate and treatment rate between married and unmarried group in 7 sites

Variable	IV stage rate		Surgery rate		Radiotherapy rate		Chemotherapy rate	
	Married	Unmarried	Married	Unmarried	Married	Unmarried	Married	Unmarried
Cervix	12.1%	15.6%	59.1%	49.2%	57.4%	61.3%	50.4%	51.7%
Esophagus	32.0%	34.2%	21.9%	16.0%	68.7%	63.1%	69.7%	60.6%
Larynx	27.8%	36.9%	38.2%	34.5%	78.5%	76.3%	34.0%	39.3%
Lung	33.9%	35.3%	28.6%	23.1%	46.5%	45.2%	45.1%	38.3%
Nasopharynx	43.0%	45.9%	10.1%	9.9%	86.6%	82.8%	83.2%	80.4%
Oropharynx	70.5%	74.1%	46.8%	35.5%	86.8%	82.5%	71.0%	70.0%
Tongue	52.0%	55.7%	52.0%	47.7%	67.0%	63.5%	53.6%	50.5%

Table 3 Median survival time of 7 tumor sites in 4 marital status

Variable	Married	Single	Divorced	Widowed
Cervix	NA	NA	140.0 (NA)	53.0 (45.6-60.4)
Esophagus	11.0 (10.4-11.6)	8.0 (7.3-8.7)	9.0 (7.9-10.1)	7.0 (6.2-7.8)
Larynx	88.0 (84.7-91.3)	55.0 (50.7-59.3)	50.0 (45.9-54.1)	39.0 (35.5-42.5)
Lung	12.0 (11.7-12.3)	9.0 (8.7-9.3)	11.0 (10.6-11.4)	10.0 (9.6-10.3)
Nasopharynx	99.0 (83.5-114.5)	72.0 (49.5-94.5)	43.0 (27.1-58.9)	20.0 (12.3-27.7)
Oropharynx	NA	80.0 (72.0-88.0)	86.0 (75.8-96.2)	36.0 (29.2-42.8)
Tongue	142.0 (NA)	59.0 (52.7-65.3)	63.0 (56.1-69.9)	29.0 (25.0-33.0)

Table 4 Hazard ratio of 4 marital status in 7 sites

Variable	Married	Single (P value)	Divorced (P value)	Widowed (P value)
Cervix	reference	1.267 (P<.001)	1.487 (P<.001)	2.397 (P<.001)
Esophagus	reference	1.259 (P<.001)	1.191 (P<.001)	1.314 (P<.001)
Larynx	reference	1.410 (P<.001)	1.466 (P<.001)	1.865 (P<.001)
Lung	reference	1.191 (P<.001)	1.071 (P<.001)	1.176 (P<.001)
Nasopharynx	reference	1.119 (P=.101)	1.581 (P<.001)	2.237 (P<.001)
Oropharynx	reference	2.008 (P<.001)	1.856 (P<.001)	3.078 (P<.001)
Tongue	reference	1.743 (P<.001)	1.712 (P<.001)	2.593 (P<.001)

Figures

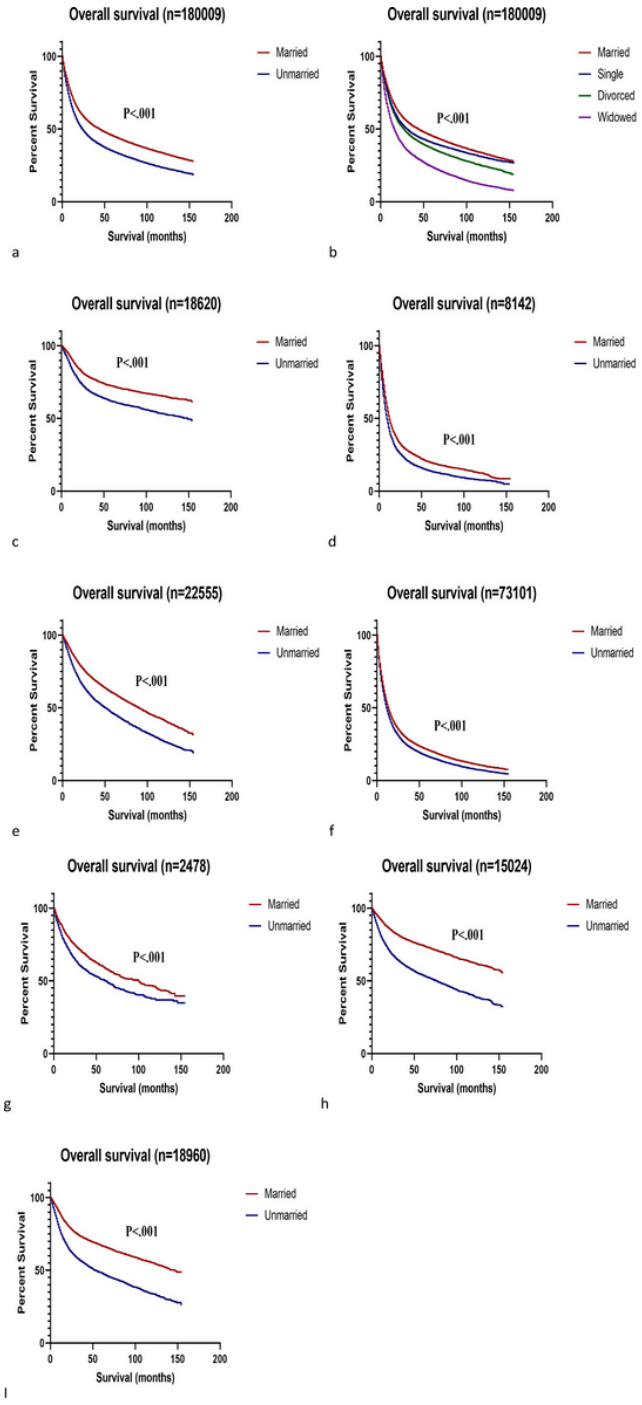

Figure 1

Overall survival of SCC patients in 7 sites according to different marital status a: Total (married, unmarried); b: Total (married, single, divorced, widowed); c: Cervix; d:Esophagus; e: Larynx; f: Lung; g: Nasopharynx; h: Oropharynx; l: tongue