


**ORIGINAL RESEARCH**

## **Relationship between Melanoma Stage at the Diagnosis and Survival During a period of 30 Years (1982-2011)**

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### **ABSTRACT**

Melanoma is a malignant tumor of melanocytes, and is a potentially aggressive cancer. The incidence of melanoma is rising at a greater rate than any other cancer in the U.S. The aim of this study was to examine the association between melanoma stage at the time of diagnosis and survival among U.S. adult melanoma patients during 1982-2011.

This was a secondary analysis of a non-concurrent cohort study conducted on 185219 U.S. adult patients who were diagnosed with primary cutaneous melanoma between 1982-2011. Chi-square, Kaplan-Meier, and Cox proportional hazards regression were used to analyze the data. Significance was assessed using p-value and 95% confidence interval.

Men had more cutaneous melanoma. Black non-Hispanic patients were diagnosed less frequently. Patients who were married or in a domestic partnership were most likely to be diagnosed. The adjusted HR for distant melanoma was 141-fold that of in situ (95% CI 126.38-157.19). The adjusted HR was the highest in the first decade of diagnosis (1.7; 95% CI 1.6-1.75).

In conclusion, survival is highly affected by melanoma stage at diagnosis. Black non-Hispanic patients had the lowest hazard ratio of all races. The sample size was large, which enhances the generalizability to the U.S. population.

**KEY WORDS:** Melanoma – Stage – Diagnosis – Survival – Saudi Arabia

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### **INTRODUCTION**

Melanoma or primary cutaneous melanoma is a malignant tumor of melanocytes, and is a potentially aggressive and unpredictable cancer.[1] Today, nearly 2-3% of people (1 in 55) in the United States are expected to have melanoma (National Cancer Institute), while it was 1 in every 1500 individuals back in 1930.[1] The incidence of melanoma is rising at a greater rate than any other cancer in the United States, and the increase in mortality is second only to lung cancer.[2] Melanoma incidence and mortality due to melanoma is a major public health concern. About 55,560 cases of melanoma in situ were expected to be diagnosed in 2012 in U.S.[3] This consistent increase in melanoma incidence has been accompanied by a rapid increase in mortality rates in men. Globally, New Zealand and Australia have the highest melanoma incidence.[4] The American Joint Committee on Cancer (AJCC) described the development of Melanoma into different stages involving the thickness/ulceration, the lymph node involvement and metastasis. The stages have been discussed in detail in several different studies. The AJCC staging system classifies tumor thickness as thin (<1mm), intermediate (1-4mm), and thick (>4mm).[5, 6, 7] The current AJCC N-category arranges patients according to

number of nodes involved as follows: 1 (N1) versus 2–3 (N2) versus 4 or more (N3) nodes.[5, 8]

In regards to survival rate, one study showed that among 528 patients in western Australia during the period of 1975-1976, the relative five-year survival rates of invasive malignant melanoma were 85% in men and 89% women while cases of pre-invasive melanoma of both sexes experienced 100% relative five-year survival.[9] To our knowledge, there were no studies about the association between melanoma stage at diagnosis and survival that cover a period of 30 years in the U.S. The objective of this study is to examine the relationship between melanoma stage at the time of diagnosis and survival among U.S. adult melanoma patients during a period of 30 years (1982-2011).

### **METHODS**

#### **Study Design**

This is a secondary analysis of a non-concurrent cohort study of US adult patients who were diagnosed with primary cutaneous melanoma between 1982-2011 to determine the relationship between melanoma stage at the time of diagnosis and survival.

Data were analyzed from the National Cancer Institute's Surveillance, Epidemiology, and End Result (SEER) program. SEER collects incidence and survival data for patients with malignant tumors through selected population-based cancer registries across the United States. Because these data are population-based, they have the advantage of not being influenced by selection biases associated with treatment and referral patterns.

The outcome of interest was survival, and the main independent variable was melanoma stage at diagnosis. Potential confounders included sex, age at diagnosis, decade of diagnosis, race/ethnicity, primary site, and marital status at diagnosis. Melanoma stage at diagnosis was categorized based on SEER codebook as follows: in situ, localized, regional, and distant. Age at diagnosis was categorized as follows: less than 30 years, 30-39, 40-49, 50-59, 60-69, and 70 years or older. In order to assess potential changes in survival due to decade of diagnosis, we divided the study period into three time periods: 1982-1991, 1992-2001, and 2002-2011. Race/ethnicity was categorized as follows: white non-Hispanic, black non-Hispanic, Hispanic, and Other (which includes Asian/Pacific Islander, American Indian/Alaska Native, and other/unspecified). Marital status at diagnosis was categorized into single, married/domestic partnership, and separated/divorced/widowed. The inclusion criteria were adult patients with primary cutaneous melanoma and year of diagnosis between 1982 and 2011. After excluding duplicate cases and cases that were missing survival information, a total sample size of 185219 was obtained.

#### Statistical Methods

The chi-square test was used to examine the association between categorical variables and melanoma stage at diagnosis (Table 1) and cause-specific vital status (Table 2). Survival time was defined as time from diagnosis of the primary melanoma to either date of death due to melanoma, or date of last follow up. Death due to a non-melanoma cause was considered censored. Kaplan-Meier method was used to estimate the overall survival curve (Figure 1), as well as survival curve per stage (Figure 2). Cox proportional hazards regression was used to calculate the unadjusted and adjusted hazard ratios (HR) and 95% confidence interval (CI) to assess the significance of the

results (Table 3). Collinearity was assessed using Pearson correlation. Statistical Package for the Social Sciences (SPSS) software version 22 (IBM) was used to analyze the data.

#### Ethical Review

The present study using secondary analysis of anonymous data was exempt from IRB review by the Florida International University (FIU) IRB under exemption category #4 ("Existing data, documents, and records specimens").

#### RESULTS

Table 1 shows the characteristics of US adult patients with primary cutaneous melanoma during the period of 1982-2011. It shows the characteristics of patients by different melanoma stages at the time of diagnosis. Males in general had more cutaneous melanoma than females. For example, males had two-thirds of the cases compared to females in distant melanoma (66.6% and 33.4%, respectively). As expected, as individuals age, the more frequently they are diagnosed with melanoma, except for those who have localized melanomas. Individuals diagnosed with localized melanoma are between 50-59 years old, which is unexpected when compared to individuals who are 60-60 years old at diagnosis (20.3% and 18.2 % respectively). When comparing decade of diagnosis, results showed that diagnosis with melanoma has increased from the first decade; this is best shown when comparing the number of in situ melanoma cases diagnosed in 1982-1991 to the number diagnosed in 2002-2011 (11.3% and 57.4% respectively). Black non-Hispanics were generally diagnosed less frequently from all stages of melanoma compared to White non-Hispanics, who were diagnosed most frequently for all stages of melanoma. In situ and distant melanomas were commonly diagnosed in the head and neck, while localized and regional melanomas were more likely to be diagnosed in the trunk. Distant stage melanoma diagnosed in the trunk occurred the least frequently. Individuals who were married or in domestic partnerships were most likely to be diagnosed with melanoma, especially in situ (74.1%). All associations were significant with a p-value less than 0.001.

Characteristics	Melanoma Stage				P-Value
	In situ 56179 (%)	Localized 94968 (%)	Regional 12613 (%)	Distant 3977 (%)	
<b>Gender</b>					< 0.001
Male	53.9	52.9	59.5	66.6	
Female	46.1	47.1	40.5	33.4	
<b>Age at diagnosis</b>					< 0.001
<30	3.5	6.9	6.4	2.8	
30-39	8.5	13.8	11	7.9	
40-49	15.4	19	16.1	14	
50-59	21.1	20.3	17.6	20	
60-69	22.4	18.2	18.1	21.6	
≥70	29	20.9	30.8	33.7	
<b>Decade of diagnosis</b>					< 0.001
1982-1991	11.3	22	21.7	23.5	
1992-2001	31.3	32.4	35	31.4	
2002-2011	57.4	45.7	43.3	45.1	
<b>Race/Ethnicity</b>					< 0.001
White (Non-Hispanic)	97.2	96.2	91.2	92.1	
Black (Non-Hispanic)	0.3	0.7	2.9	2.3	
Hispanic	1.7	2	3.1	3.1	
Other	0.8	1.1	2.8	2.5	
<b>Primary site</b>					< 0.001
Head and Neck	37.4	20	25.3	31.4	
Trunk	24.9	34.9	32.1	3.1	
Upper limb	23.2	24.9	21	17.2	
Lower limb	14.5	20.2	21.6	18.3	
<b>Marital status at diagnosis</b>					< 0.001
Single	12.6	15.4	16.9	15.9	
Married/Domestic Partner	74.1	71	63.3	61.2	
Separated/ Divorced/ Widowed	13.3	13.7	19.8	22.8	

**TABLE 1.** Characteristics of U.S. adult patients with primary cutaneous melanoma, 1982-2011 (n=185219)

Table 2 describes the unadjusted association between vital status and risk factors in U.S. adult patients with primary cutaneous melanoma during the period of 1982-2011. Its results were obtained using Chi-square test to examine the association between the vital status with other possible confounders. In regards to the association between vital status and melanoma stage at diagnosis, patients with in situ, localized, and regional survived or died due to other cause than melanoma (98.8, 92.9, 67.9% respectively) compared to those who died due to melanoma. However, patients with distant melanoma died because of the melanoma (76%). Results showed that a larger percentage of men died because of melanoma compared to women (17.1, 6.6% respectively). Patients of ages 50-59 years and 60-69 years either lived or died due to causes other than melanoma with a percentage of 90.7%, 90.1% respectively compared to other age groups. However, patients of ages 30-39 years died because of melanoma more than any

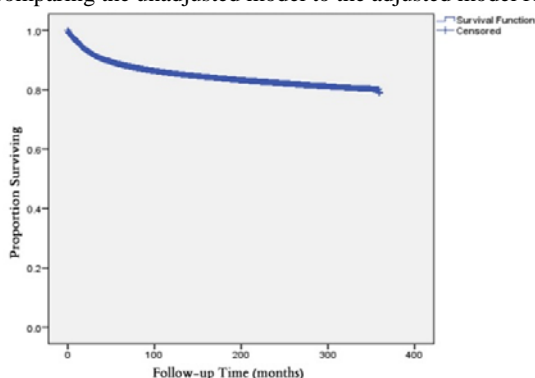
other age group (20.7%). Individuals survived more as time passed during the three decades. In the last decade, 2002-2011, individuals had a better survival than others (94.8%). However, patients diagnosed in the first decade (1982-1991) died more due to melanoma compared to others (25.7%). Results showed that White non-Hispanics survived better than other races/ethnicities (87.9%). On the other hand, Black non-Hispanics died more frequently compared to other races (40.1%). Interestingly, married individuals or those who were in domestic partnerships either lived or died due to causes other than melanoma more frequently than others (88.8%), while those who were single died more due to melanoma (32.1%). All associations were significant with a  $p < 0.001$ . The median follow up time was 81 months. The overall survival curve and the survival curves by stage at diagnosis were estimated using the Kaplan-Meier method and are shown in Figures 1 and 2, respectively.

Characteristics	Vital Status (Outcome)		P-Value
	Alive or dead of other cause 161785 (%)	Death due to melanoma 23434 (%)	
<b>Melanoma stage</b>			< 0.001
In situ	98.8	1.2	
Localized	92.9	7.1	
Regional	67.9	32.1	
Distant	24	76	
<b>Gender</b>			< 0.001
Male	82.9	17.1	
Female	93.2	6.8	
<b>Age at diagnosis</b>			< 0.001
<30	86.3	13.7	
30-39	79.3	20.7	
40-49	86.7	13.3	
50-59	90.7	9.3	
60-69	90.1	9.9	
≥70	87.9	12.1	
<b>Decade of diagnosis</b>			< 0.001
1982-1991	74.3	25.7	
1992-2001	85.1	14.9	
2002-2011	94.8	5.2	
<b>Race/Ethnicity</b>			< 0.001
White (Non-Hispanic)	87.9	12.1	
Black (Non-Hispanic)	59.9	40.1	
Hispanic	76.5	23.5	
Other	79.9	20.1	
<b>Primary site</b>			< 0.001
Head and Neck	91.1	8.9	
Trunk	90.6	9.4	
Upper limb	92.8	7.2	
Lower limb	89.4	10.6	
<b>Marital status at diagnosis</b>			< 0.001
Single	67.9	32.1	
Married/Domestic Partner	88.8	11.2	
Separated/ Divorced/ Widowed	81.3	18.7	

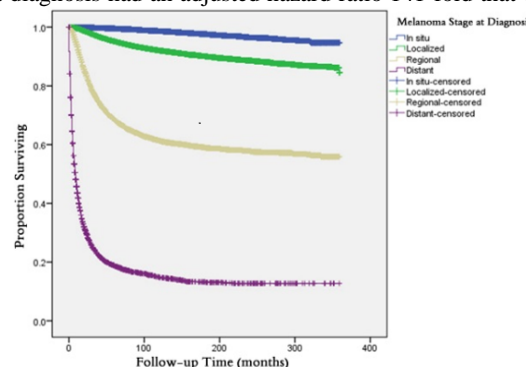
**TABLE 2.** Unadjusted association between vital status and risk factors among U.S. adult patients with primary cutaneous melanoma, 1982-2011

Table 3 describes the association between unadjusted and adjusted hazard ratios for primary cutaneous melanoma among U.S. adult patients during the period of 1982-2011. No collinearity was found between the variables. When comparing the unadjusted model to the adjusted model for

melanoma stage at diagnosis, the hazard ratio decreased for all stages except for the localized stage where the hazard ratio increased from 5.3 (95% CI 4.9-5.7) to 5.8 (95% CI 5.28-6.4). Also, patients with distant melanoma at diagnosis had an adjusted hazard ratio 141-fold that of



**Figure 1:** Kaplan Meier Curve of Overall Survival



**Figure 2:** Kaplan Meier Survival Curve by Melanoma Stage at Diagnosis

patients with melanoma in situ at diagnosis (95% CI 126.38-157.19). Females had a lower adjusted hazard ratio compared to males (0.6; 95% CI 0.57, 0.62). The hazard ratio increased from the unadjusted to the adjusted model for all age groups except for the age group 30-39, for which it decreased from 1.6 (95% CI 1.5-1.7) to 1.3 (95% CI 1.19-1.5). The age group of 40-49 had an unadjusted hazard ratio of 1 with 95% CI 0.96-1.08, but the adjusted hazard ratio increased to 1.7 (95% CI 1.5-1.9). The adjusted hazard ratios were higher in the first two decades of diagnosis (1982-1991 and 1992-2001). In all races/ethnicities, the hazard ratios decreased from the unadjusted to adjusted models, with hazard ratios for black non-Hispanics decreasing from 4.3 (95% CI 4.03-4.52) to 0.6 (95% CI 0.5-0.7). All adjusted hazard ratios of primary sites were statistically significant except for the adjusted hazard ratio of the lower limb (0.9; 95% CI 0.94, 1.06). Regarding marital status at diagnosis, all results were significant. The unadjusted hazard ratio for individuals who were separated/divorced/widowed increased from 0.6 (95% CI 0.54-0.58) to 1.2 (95% CI 1.12-1.28) in the adjusted model.

## DISCUSSION

The aim of this study was to determine if melanoma stage at the time of diagnosis affected survival among United States adult patients who were diagnosed during 1982-2011. Patients with distant melanoma at diagnosis had an adjusted hazard ratio 141-fold that of patients with melanoma in situ at diagnosis. Women had an adjusted hazard ratio of 0.6 (95% CI 0.57-0.62) compared to men. Increased age at diagnosis showed expected results: the older the patient, the higher the hazard of death. Diagnosis in 2002-2011 showed improvements in survival compared to earlier decades. This might be explained by improved healthcare quality, improved hospital facilities and technologies, advanced treatment, and medications. After adjusting for possible confounders, Black non-Hispanics had the lowest hazard ratio of all races with a hazard ratio of 0.6 (95% CI 0.5-0.7). This may biologically be reasonable due to melanin production being high in darker skins.[10, 11] Individuals with race/ethnicity of Hispanic and Other had an adjusted hazard ratio close to 1 with 95% CI 0.9-1.2 and 95% CI 0.78-1.05, respectively, which

indicates there was not much of a difference between these groups and the reference (White non-Hispanic).

In relation to primary site, the adjusted hazard ratio did not reveal any noticeable difference compared to the unadjusted model. It is worth mentioning that the hazard ratio for trunk was 1.1 compared to the head and neck, while the hazard of death for upper limb was almost 20% lower than that of the head and neck. The adjusted hazard ratio for the lower limb was not significant.

Patients who were married or in domestic partnerships at the time of diagnosis were the most likely to be diagnosed with melanoma, especially for in situ and localized stage at diagnosis. On the other hand, patients who were single, separated, divorced, or widowed were less likely to be diagnosed with melanoma. Also, the hazard of death for patients who were married or in domestic partnerships was 20% lower than patients who were single, separated, divorced, or widowed, indicating patients who were married or in domestic partnerships had slower progression of the disease.

Lemish et al conducted a study on melanoma survival in Western Australia.[9] They assessed the survival for 528 patients, of which 113 patients had pre-invasive melanoma and 415 patients had invasive malignant melanoma. These patients were diagnosed during 1975-1976 and they were followed up to 1980. The study showed that the 5-years survival in relation to clinical stage for both sexes was 91% in patients having localized disease, 54% in those with stage 2, and 13% for those with stage 3. These results are similar to the results in this study, in which survival decreases as the stage of diagnosis is more severe (Table 2). Karjalainen and Hakulinen conducted a regression analysis of relative survival rates based on nationwide cancer registry data.[12] It consisted of 4980 cases of melanoma of the skin diagnosed in Finland in 1953 to 1981. The study stated that the 5-year survival rates increased with time for both males and females. These results are similar to the results of this study when comparing survival by decade of diagnosis. Many other studies have showed that females had superior survival compared to men after adjusting for multiple confounding variables, including stage at diagnosis.[13]

Characteristics	Unadjusted		Adjusted	
	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>Melanoma stage</b>				
In situ	Ref.		Ref.	
Localized	5.3 (4.9, 5.75)	< 0.001	5.8 (5.28, 6.4)	< 0.001
Regional	31.3 (28.84, 33.92)	< 0.001	26.9 (24.36, 29.67)	< 0.001
Distant	202.4 (186.16, 220.09)	< 0.001	141 (126.38, 157.19)	< 0.001
<b>Gender</b>				
Male	Ref.		Ref.	
Female	0.4 (0.35, 0.37)	< 0.001	0.6 (0.57, 0.62)	< 0.001
<b>Age at diagnosis</b>				
<30	Ref.		Ref.	
30-39	1.6 (1.5, 1.7)	< 0.001	1.3 (1.19, 1.5)	< 0.001
40-49	1 (.96, 1.08)	0.475	1.7 (1.5, 1.9)	< 0.001
50-59	0.7 (0.69, 0.79)	< 0.001	2.1 (1.85, 2.32)	< 0.001
60-69	0.8 (0.76, 0.86)	< 0.001	2.5 (2.25, 2.82)	< 0.001
≥70	1.2 (1.095, 1.227)	< 0.001	3.6 (3.25, 4.05)	< 0.001
<b>Decade of diagnosis</b>				
1982-1991	3.5 (3.34, 3.59)	< 0.001	1.7 (1.6, 1.75)	< 0.001
1992-2001	2 (1.9, 2.06)	< 0.001	1.3 (1.2, 1.3)	< 0.001
2002-2011	Ref.		Ref.	
<b>Race/Ethnicity</b>				
White (Non-Hispanic)	Ref.		Ref.	
Black (Non-Hispanic)	4.3 (4.03, 4.52)	< 0.001	0.6 (0.5, 0.7)	< 0.001
Hispanic	2.2 (2.04, 2.31)	< 0.001	1.03 (0.9, 1.2)	0.664
Other	1.7 (1.62, 1.95)	< 0.001	0.9 (0.78, 1.05)	0.177
<b>Primary site</b>				
Head and Neck	Ref.		Ref.	
Trunk	1 (0.91, 0.9)	0.02	1.1 (1.02, 1.12)	0.01
Upper limb	0.8 (0.72, 0.79)	< 0.001	0.81 (.77, .86)	< 0.001
Lower limb	1.1 (1.03, 1.13)	0.001	0.9 (.94, 1.06)	0.983
<b>Marital status at diagnosis</b>				
Single	Ref.		Ref.	
Married/Domestic Partner	0.3 (0.28, 0.29)	< 0.001	0.8 (0.76, 0.86)	< 0.001
Separated/ Divorced/ Widowed	0.6 (0.54, 0.58)	< 0.001	1.2 (1.12, 1.28)	< 0.001

**TABLE 3.** Unadjusted and adjusted hazard ratios for primary cutaneous melanoma among U.S. adult patients, 1982-2011

Ortiz et al conducted a secondary analysis of SEER registries–Medicare–linked database (1991–1999) on 14,630 men and women 65 years old and older.[14] The study showed that widowed persons were at increased risk of death from melanoma with a hazard ratio of 1.23 (95% CI 1.06-1.44). This result supports our finding of a hazard ratio of 1.2 (95% CI 1.12-1.28) for widowed individuals, but it is important to mention that widowed was categorized with separated and divorced patients in our study.

One strength of this study is that it utilized the population-based, high-quality SEER database. This study analyzed a large sample size, and almost all results were significant. The study provides a comprehensive description of primary cutaneous melanoma survival by melanoma stage at diagnosis. This study could help tailor preventative measures and provide additional useful information in the diagnosis and treatment of melanoma. However, one weakness was that information related to survival was missing for more than 12% of the sample; this could represent systematic bias, but it should not affect this study since the analysis utilized a large sample size. Additionally, Breslow thickness, Clark's level, UV light exposure, socioeconomic status, and treatment status were not included as confounders in this study because they were not available in the SEER database. Finally, the follow up period was not equal for all three decades of diagnosis.

This study was the first, to our knowledge, to study the association between the melanoma stage at diagnosis and survival within a period of 30 years in U.S. It is noticeable that the number of patients increased with each decade. The public becoming more aware of the importance of diagnosis might explain this. Further research needs to be done to investigate this increase. It is also important to note that even though married individuals have better survival after diagnosis and a better adjusted hazard ratio, they are diagnosed more frequently. This might be explained by the fact that married individuals express more care and

concerns toward each other. Nevertheless, more research needs to be conducted to explain this association.

## CONCLUSION

In conclusion, survival is highly affected by melanoma stage at diagnosis. The more advanced the stage, the worse the survival. This study also found that Black non-Hispanics had the lowest hazard ratio of all races with a hazard ratio of 0.6 (95% CI 0.5-0.7), which is opposite to what is reported in the literature.[15] Further studies are needed to confirm this result. The sample size for this study was large, which enhances the generalizability of this study to the U.S. population.

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## AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the [Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals](#) of the [International Committee of Medical Journal Editors](#). Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

## SPONSORSHIP

Declared none.

## COMPETING INTERESTS

The authors declare no competing interests.

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