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Disparities in the occurrence of adverse health conditions following treatment among adolescent and young adult melanoma survivors

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Abstract

Background: Melanoma is the third most common cancer in the adolescent and young adult (AYA) population, however no studies have addressed the occurrence of adverse health conditions following melanoma treatment in these survivors.

Methods: Patients age 15-39 diagnosed with cutaneous melanoma from 1996-2012 and surviving ≥2 years were obtained from the California Cancer Registry and linked to statewide hospitalization data. The influence of age at diagnosis, sex, race/ethnicity, neighborhood socioeconomic status (SES), health insurance, and surgery on the development of adverse health conditions was evaluated using Cox proportional hazards regression models.

Results: Of 8,259 patients, 35.3% were male, 83.3% non-Hispanic white, 82.4% had private health insurance, and 60.5% were considered high SES. In Cox regression models, males had an increased risk of developing adverse health conditions across all systems, including cardiac [Hazard Ratio (HR):1.73, 95% Confidence Interval (CI) 1.47-2.03], lymphedema (HR:1.56, CI 1.37-1.77), hematologic disorders (HR:1.17, 95%CI 1.03-1.33), major infection/sepsis (HR:1.59, CI 1.39-1.82), and second cancers (HR:1.51, CI 1.31-1.74). Patients with public/no insurance (vs. private) had a greater risk of developing all studied adverse health conditions, including subsequent cancers (HR:2.34, CI 1.94-2.82). AYA patients residing in low SES neighborhoods had similar increased risk of developing adverse health conditions.

Conclusions: Of AYA melanoma survivors, males, those with public/no health insurance, and those living in low SES neighborhoods had a greater likelihood of developing of adverse health conditions.

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The authors declare that they have no conflict of interest. No competing financial interests exist.

Impact: Strategies to improve surveillance and secondary prevention of these adverse health conditions is needed among AYA melanoma survivors, specifically the at-risk populations identified.

Keywords

melanoma; survivorship; adolescent and young adult; adverse health conditions; disparities

Introduction:

Melanoma is the third most common cancer in the adolescent and young adult (AYA) population.[1-4] The AYA population is defined as all patients between the ages of 15 and 39 years.[5] Historically, as cancer is primarily a disease of the elderly and increasing age the #1 risk factor for cancer, adolescents and young adults with cancer have been an understudied population.[5-9] It was first noted in 1996 that cancer patients age 15-19 had not benefitted from available cancer therapies when compared to children age 0-14.[8] Follow-up studies found that patients age 15-39 did not demonstrate the improved outcomes seen in older adults age ≥40.[5, 6] In 2006, a large, multicenter effort led by the NCI, entitled the AYA Health Outcomes and Patient Experience (AYA HOPE) study, was the first national cohort study of patients aged 15-39, and found worse outcomes following standard cancer therapies when compared to children less than 14 and adults ≥ 40 years old.[5-9] However, long-term outcomes following the diagnosis of melanoma in the AYA population have yet to be explored.

Worldwide, the melanoma incidence in the AYA population appears to be increasing.[2, 10] Studies conducted throughout the United States, Brazil, the Netherlands and Germany demonstrate females are at higher risk of developing melanoma among AYAs.[2-5] However, non-Hispanic (NH) white males have been shown to have inferior survival compared to females, suggesting disparities exist among the AYA melanoma survivor population.[10, 11] Because of under-representation of AYAs in clinical trials, the approach to treatment and surveillance guidelines is the same as that of older adults.[1, 12]

The prognosis of early stage melanoma is favorable and younger age has been associated with improved survival in both node-positive and node-negative non-metastatic disease.[1, 2, 13, 14] The potential longevity following diagnosis raises the need for ongoing care and surveillance in this population. Young cancer survivors have been shown to have an elevated risk of adverse health conditions, or the development of medical conditions, when compared to those without cancer.[4, 15-18] A previous study of the Danish Patient Registry compared 33,555 AYA cancer survivors to 228,447 patient controls, which included 4093 patients with malignant melanoma. This study found a statistically significant increased risk for melanoma patients to develop a secondary cancer or adverse health conditions when compared to controls.[18] A separate study showed AYA melanoma survivors have a significantly higher incidence of cardiovascular disease (CVD) when compared to healthy controls.[17] A third study using the Behavioral Risk Factor Surveillance System (BRFSS) determined that AYA cancer survivors (including melanoma) had a higher prevalence of

chronic conditions, disability and poor physical health when compared to age-matched controls.[4]

It is well-established with robust data that AYA melanoma patients are at a higher risk for the development of adverse health conditions and secondary cancers when compared to healthy controls. However, no population-based studies have addressed if the occurrence of adverse health conditions following melanoma treatment differs by race/ethnicity, sex, neighborhood SES, or health insurance.

In this study, we sought to determine whether the development of medical conditions 2 years after diagnosis among AYA melanoma survivors (hereafter referred to as “adverse health conditions”) differed by sociodemographic factors. Using the population-based California Cancer Registry (CCR) data linked to hospitalization data from the Office of Statewide Health Planning and Development (OSHPD), we analyzed associations between sociodemographic factors and medical conditions among AYA melanoma patients surviving 2 years or more. The purpose of this study was to identify groups of patients at elevated risk of developing adverse health conditions in order to develop strategies to improve surveillance and long-term care for AYA melanoma survivors.

Materials and Methods:

Patients:

Patients eligible for the study were all persons age 15-39 years who resided in California when diagnosed with a primary, invasive cutaneous melanoma (International Classification of Diseases for Oncology, 3rd edition, topography codes C44.0-C44.9, histology codes 8720-8790) during the period of January 1, 1996 through December 31, 2012, reported to the CCR from all non-Veterans Administration facilities, and survived ≥2 years after diagnosis.[19] For each patient, we obtained CCR information routinely recorded in the medical record at diagnosis including age, sex, race/ethnicity, summary stage, initial treatment and census-block group of residence. In addition, we obtained follow-up time and vital status (routinely determined by the CCR through hospital follow-up and linkages to state and national vital status and other databases) as of December 2014.

Using a deterministic strategy based on social security number and gender, OSHPD staff linked the CCR data to OSHPD hospital discharge records. The OSHPD hospital data contain detailed information for each discharge from any non-Federal (e.g., not military or Veterans Administration) hospitals in California. Clinical variables recorded include a principal diagnosis and up to 24 other diagnoses and a principal procedure and up to 20 other procedures, including corresponding procedure dates. All diagnoses and procedures were coded using the International Classification of Diseases, 9th Revision, Clinical Modifications (ICD-9-CM). Serial records for an individual patient were identified using a record linkage number.

We grouped hospital discharge diagnoses present ≥ 2 years after diagnosis into lymphedema, hematologic disorders (anemia, leukopenia, thrombocytopenia, major bleeding), endocrine disorders (hypothyroidism, ovarian/testicular dysfunction), diabetes mellitus, cardiac disease

(hypertension, ischemia, heart disease, stroke), autoimmune disease, venous thromboembolism (VTE) and infection/sepsis (Supplemental Table S1). While only the first hospitalization relative to each type of adverse health condition was noted, an individual could have multiple adverse events for each system recorded. Second primary melanomas and other, non-melanoma second primary cancers as an adverse health condition were identified by the CCR. In order to examine the temporal relationship between melanoma diagnosis and medical conditions, we excluded pre-existing medical conditions present before melanoma diagnosis as outcomes.

From CCR information on the primary source of payment at initial diagnosis and/or treatment (health insurance), we created insurance categories of public (Medicaid and other government-assisted programs), private/military (health maintenance organizations, preferred provider organizations, and managed care not otherwise specified), none (self-pay) and unknown.[20] Consistent with prior observations that the small percentage of uninsured AYA cancer patients (8.5% in our study) may reflect retroactive enrollment in Medicaid at cancer diagnosis, we considered publicly insured and uninsured patients together in the analyses.[21]

We used a multi-component index of neighborhood SES based on patients' residential census-block group at diagnosis as geocoded by the CCR. The index is derived from 2000 U.S. Census (for cases diagnosed in 1996-2005) and 2006-2010 American Community Survey (for cases diagnosed in 2006-2007) data on education, occupation, unemployment, household income, poverty, rent, and house values.[22] The index is grouped into quintiles, based on the distribution of SES across all census block groups in California, and then into low (quintiles 1-3) and high SES (quintiles 4, 5).

The final study population included 8,259 AYA melanoma patients after exclusion of those who died within 2 years or had invalid survival time (n=1,101); with an unknown/invalid record linkage number (n=2,820); or with metastatic or unknown stage of disease (n=279). All study protocols were overseen by the Institutional Review Board of the University of California, Davis and by the California Committee for the Protection of Human Subjects.

Statistical Analyses:

The 10-year cumulative incidence and associated 95% confidence intervals (CIs) of developing a medical condition ≥2 years after diagnosis was calculated using nonparametric methods that account for death as a competing risk.[23] Person-years of observation were compiled from two years after melanoma diagnosis to date of first hospitalization with a medical condition, the date of last known contact, date of death or the study cut-off date (12/31/2014), whichever occurred first. Gray's K-sample test statistic was used to determine whether cumulative incidence of a medical condition differed by sociodemographic or clinical factors.[24]

To evaluate sociodemographic and clinical characteristics associated with the occurrence of each medical condition ≥2 years after diagnosis, we used multivariable Cox proportional hazards regression to calculate adjusted hazard ratios (HR) and 95% CIs. In all models, the proportional hazards assumption was assessed numerically based on cumulative sums of

Martingale residuals and visually based on inspection of the survival curves [log (-log) of the survival distribution function by log (months)]; variables that violated this assumption (summary stage, year of diagnosis, comorbidities) were included as stratifying variables to allow for differing baseline hazards associated with these variables. Models also included age, gender, race/ethnicity, health insurance, neighborhood SES and surgery. All analyses were conducted using SAS version 9.4 software (SAS institute Inc., Cary, NC, USA).

Results:

Our study consisted of 8,259 AYA patients diagnosed with a primary cutaneous invasive melanoma. As shown in Table 1, 83.3% were NH-white and 64.7% were female. Within the cohort, 60.5% of patients lived in a high SES neighborhood and 82.4% had private health insurance. Surgical treatment exclusively was documented in 96.1% of patients, whereas a cumulative 1.7% of patients had some form of systemic therapy. Of all patients, 8.4% were noted to have regional disease. In the cohort of patients surviving ≥ 2 years from diagnosis, the most commonly developed medical conditions were hematologic disorders (9.1%), cardiac disease (7.7%), and subsequent cancers (6.4%). Of these, the majority of subsequent cancers were a second melanoma (56.4%), followed by breast (11.8%), thyroid (6.7%) and prostate (2.3%) cancers. The locations of first and subsequent primary melanomas are presented in Supplemental Table S2. In total, 93.5% of patients were alive at the end of the study period, whereas 4.7% had died from melanoma.

Table 2 depicts the cumulative incidence of medical conditions at 10 years post-diagnosis by baseline characteristics. Patients presenting with regional disease at diagnosis (as opposed to localized disease) were more likely to develop several adverse health conditions, to include hematologic disorders (21.87% vs 7.86%), cardiac disease (12.17% vs 6.16%), lymphedema (2.67% vs 0.87%), VTE (2.68% vs. 0.61%), autoimmune disorders (6.29% vs 2.66%) and infection/sepsis (11.34% vs 4.73%). NH white patients (5.47%) had a higher incidence of subsequent cancer compared to patients of Hispanic (4.92%) and other race/ethnicity, including NH Black, Asian/Pacific Islander and other/unknown (3.03%). Males had a significantly higher incidence of cardiac disease (8.45% vs 5.76%) and infection/sepsis (6.17% vs 4.78%), while females had a higher rate of endocrine disorders (3.21% vs 1.07%).

Cumulative incidence of adverse health conditions at 10 years was also studied with respect to insurance status and neighborhood socioeconomic status (SES) (Table 2). Insurance was grouped as private versus public/no health insurance. In this category, patients with public/no health insurance had a significantly higher incidence of hematologic disorders (17.65% vs. 8.48%), cardiac disease (13.95% vs 6.10%), lymphedema (2.40% vs 0.93%), VTE (2.36% vs 0.67%), autoimmune disorders (6.20% vs 2.74%) and infection/sepsis (11.48% vs 4.76%). With respect to neighborhood SES, patients residing in low SES neighborhoods had a significantly higher incidence of hematologic disorders (10.58% vs 7.95%), cardiac disease (8.43% vs 5.56%), diabetes mellitus (2.06% vs 0.81%), autoimmune disorders (3.74% vs 2.44%) and infection/sepsis (6.23% vs. 4.63%).

In multivariable models (Table 3), Hispanics did not have a statistically significant increased risk for adverse health conditions compared to non-Hispanic whites, but significant differences were observed by gender, health insurance type and neighborhood SES.

Notably, males had an increased risk for every category of adverse health condition in this study. This included hematologic disorders (HR 1.17, CI 1.03-1.33), lymphedema (HR 1.73, CI 1.47-2.03), endocrine disorders (HR 1.27, CI 1.10-1.48), diabetes mellitus (HR 1.67, CI 1.43-1.95), cardiac disease (HR 1.56, CI 1.37-1.77), autoimmune disorders (HR 1.44, CI 1.25 – 1.67), VTE (HR 1.80, CI 1.54 – 2.12), and infection/sepsis (HR 1.59, CI 1.39-1.82). Males were also at increased risk for developing a subsequent melanoma (HR 1.53, CI 1.33-1.75) and subsequent cancer of another type (HR 1.51, CI 1.31 – 1.74).

AYAs with public/no insurance had significantly increased risk with respect to those with private health insurance by at least two-fold higher for all adverse health conditions studied. This included hematologic disorders (HR 2.30, CI 1.95-2.72), lymphedema (HR 2.87, CI 2.36-3.49), endocrine disorders (HR 2.60, CI 2.16-3.13), diabetes mellitus (HR 2.72, CI 2.25-3.29), cardiac disease (HR 2.22, CI 1.87-2.63), autoimmune disorders (HR 2.68, CI 2.23-3.22) VTE (HR 2.81, CI 2.31- 3.42), and infection/sepsis (HR 2.69, CI 2.27-3.19). This population was also at increased risk for development of subsequent melanoma (HR 2.41, CI 2.01 – 2.88) and other subsequent cancers (HR 2.34, CI 1.94 – 2.82). Similarly, residing in a low SES neighborhood was associated with a higher risk of several of the same conditions, including hematologic disorders, lymphedema, endocrine disorders, diabetes mellitus, cardiac disease, autoimmune disorders, VTE and infection/sepsis, although to a lesser degree (Table 3).

Discussion:

It is known that AYA cancer patients, and melanoma survivors specifically, are at higher risk for developing adverse health conditions and secondary cancer when compared to age-matched healthy controls.[4, 17, 18] In this large population-based study of over 8,200 2-year AYA melanoma survivors, we show that male patients, those with public/no insurance, and those residing in a low SES neighborhood were at a significantly higher long-term risk of developing a variety of adverse health conditions. This key finding demonstrates disparities among AYA melanoma survivors and suggests a need for increased surveillance during survivorship, targeted interventions, and possible development of alternative treatment strategies to improve outcomes for these higher risk populations. To our knowledge, we are the first to report significant differences in adverse health conditions among groups following melanoma diagnosis and treatment in the AYA population.

Although females in the AYA age range are known to have a higher risk of developing melanoma than males [2, 3, 10, 11], previous studies have shown that AYA males have worse survival after melanoma, [10, 11] consistent with our findings that males were also at statistically significant higher risk for developing most adverse health conditions considered, to include the alarming development of a second cancer. In particular, compared to females, a population-based study in the United States by Gamba et al[3] found melanoma-specific and all-cause survival to be worse and a Dutch study by Eggen, et al[4] found relative survival to

be worse in males. [5,6] As the disparity for males persisted for both melanoma and all-cause survival, it is reasonable to postulate that this could be partially attributed to adverse health conditions aside from the melanoma diagnosis. Additionally, previous studies have demonstrated an increased need for melanoma screening in uninsured, unmarried men, as this population was significantly more likely to present with late-stage disease.[25] Having a spouse or partner was found to be protective for men, lending credence to the theory that such relationships encourage improved health behaviors or screening in males, although possible biologic differences cannot be ruled out.[25, 26] It is unclear at this time whether this difference in adverse health conditions can be attributed to biological, behavioral or multifactorial differences between the sexes. Screening for adverse health conditions, subsequent cancers or second melanomas under a formal, targeted, long-term healthcare relationship for male survivors is likely to improve compliance and surveillance.

The sociodemographic differences in risk for adverse health conditions that we observed in our study may relate to differences in health behaviors. The Centers for Disease Control and Prevention (CDC) reports that cigarette use is higher in men, those with lower annual household incomes and among those with no insurance, Medicaid or public insurance (vs private insurance). [27] Among AYA cancer survivors, those with public/no insurance were more likely to report an obese BMI, low physical activity and current smoking than those with private insurance, associations that were also observed in the comparison group of non-cancer survivors.[28] Further, AYA cancer survivors more commonly reported adverse medical and behavioral characteristics, to include smoking and obesity when compared to respondents with no history of cancer. [4, 29] Kaul et al reported 21-33% of AYA cancer survivors engaged in unhealthy habits, including smoking and low physical activity, which were significantly higher than that of the aged-matched non-survivor cohort.[16, 28] Findings from these prior studies suggests the increased risk for adverse health conditions in our study may be a reflection of the combined risks of the sociodemographic and AYA cancer survivor population and highlights the need for targeted interventions in these subgroups.

AYA cancer survivors with public/no insurance may be at a disadvantage for developing adverse health conditions due to having poorer access to survivorship care.[1, 12] Among pediatric and adolescent cancer survivors, studies have demonstrated a pattern of “illness-driven care,” in which the patients seek episodic symptom management versus preventative long-term surveillance for adverse health conditions.[30] AYA survivors may have infrequent or no contact with a supervising physician familiar with the specific survivorship needs of this population, particularly if they have public/no insurance.[31, 32] AYA patients have been shown to lose health insurance following the conclusion of cancer treatment and this loss was associated with a barrier to post-treatment medical care.[33] This observation is particularly pertinent in a surgically treated cancer such as melanoma, wherein the termination of public health insurance can occur upon completion of definitive cancer treatment, which is relatively short-term.

Our study noted disparities in the development of adverse health conditions among persons living in low SES neighborhoods. The financial impact of cancer has been well-studied and the monetary, psychological and emotional effects cannot be overstated.[29, 30, 34-38]

Following treatment, AYA survivors are often faced with colossal medical bills and may have low work ability or be unemployed.[39] Their peers, on the other hand, are entering the workforce and becoming financially independent. Kirchhoff et al reported that AYA survivors are more likely to forego care due to cost barriers than the control population.[29] In a separate study, Yabaroff et al demonstrated higher psychological financial hardship among survivors in the working age population (ages 18-64).[34] These patterns are consistent with our study findings, as we noted an increased incidence of adverse health conditions in patients of lower SES, in whom the financial burden of survivorship likely precludes affordability of preventative medical care and routine surveillance.

As we eliminated patients with metastatic disease, the treatment of local and regional melanoma is primarily surgical. While surgery certainly is not benign, it does not carry the same systemic toxicities as prolonged chemotherapy regimens which have been associated with an increased risk of adverse health conditions and premature aging syndrome.[40] Surprisingly, the incidence of lymphedema, which can be attributed to surgical dissection, was much lower than other adverse health conditions studied, although we did note a significant difference between those with local vs regional disease ((0.87% vs 2.67%, $p < 0.001$). It is important to note that depending on size and location, the surgical removal of melanoma can result in disfigurement and impact functional status.[41] In our patient cohort, diagnosed from 1996-2012, patients with regional disease (stage III melanoma) may have been treated with adjuvant interferon or other systemic agent, which could explain the higher incidence of adverse health conditions. The current standard of care for locally advanced includes adjuvant immunotherapy with nivolumab or pembrolizumab, the long-term effects of which are as yet unstudied with regards to the AYA population.

Our study must be considered in light of its limitations. The CCR and OSPHD databases are well-maintained, but subject to the inherent biases applicable to retrospective database studies and any errors in coding. OSPHD captures hospitalization data and therefore only tracks adverse health conditions that are discharge diagnoses. Therefore, any pre-existing or chronic adverse health conditions that are managed solely as an outpatient are not contained in these data and medical conditions may be underestimated in our study population. Our study lacks granular data which may shed light on factors such as access to care and health behaviors, but have been explored in previous studies [4, 29] and thus should be taken in context of this existing literature. Finally, our study lacks individual levels of SES as SES is determined through a collection of neighborhood variables available in the CCR. Despite these limitations, our large, population-based study provides the first look at the disparities in adverse health conditions among AYA melanoma survivors that has not been previously shown.

Conclusions

Despite comprising the minority of the cohort, male patients, patients with public/no health insurance and patients living in low SES neighborhoods fared markedly worse in the development of adverse health conditions. Even in this primarily surgically-treated cancer, all patients will require lifelong surveillance as shown by our data. The reason for this is likely multifactorial in nature and can be partially attributed to inherent risk in these

populations due to health behaviors, access to care, health care patterns and financial burden. Strategies to improve surveillance and secondary prevention among AYA melanoma survivors, particularly the at-risk populations, are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Selected Characteristics and Late Effects Among 2-year Adolescent and Young Adult Cutaneous Melanoma Survivors (N=8,259), California, 1996-2012.

Characteristic	N (%)
Race/ethnicity	
NH White	6877 (83.3%)
NH Black	30 (0.4%)
Hispanic	670 (8.1%)
NH Asian/Pacific Islander	93 (1.1%)
Other/unknown	589 (7.1%)
Sex	
Male	2914 (35.3%)
Female	5345 (64.7%)
Year of diagnosis	
1996-2000	2526 (30.6%)
2001-2004	1976 (23.9%)
2005-2008	2194 (26.6%)
2009-2012	1563 (18.9%)
Stage at diagnosis	
Localized	7567 (91.6%)
Regional	692 (8.4%)
Neighborhood socioeconomic status (SES)	
Low SES	3266 (39.5%)
High SES	4993 (60.5%)
Health insurance	
Private	6809 (82.4%)
Public/none	686 (8.3%)
Unknown	764 (9.3%)
Treatment	
Surgery only	7939 (96.1%)
Surgery and chemotherapy	90 (1.1%)

Characteristic	N (%)
Surgery and radiation	22 (0.3%)
Surgery, chemotherapy and radiation	12 (0.2%)
Chemotherapy and radiation	8 (0.1%)
No treatment	188 (2.3%)
Late effect	
Subsequent cancers	525 (6.4%)
Hematologic (leukopenia/anemia/major bleeding/thrombocytopenia)	749 (9.1%)
Lymphedema	86 (1%)
Endocrine (hypothyroidism, ovarian/testicular dysfunction)	204 (2.5%)
Diabetes mellitus	135 (1.6%)
Cardiac (hypertension/ischemic/other heart diseases/stroke)	633 (7.7%)
Autoimmune disease	259 (3.1%)
Venous thromboembolism	76 (0.9%)
Infection and sepsis	458 (5.5%)
Cause of death	
Alive	7725 (93.5%)
Death from Melanoma	392 (4.7%)
Death from other cancer	53 (0.6%)
Death from heart/cerebrovascular	16 (0.2%)
Death from other cause	73 (0.9%)

Table 2:

Cumulative Incidence (with 95% Confidence Intervals) of Late Effects 10 Years after Diagnosis Among 2-year Adolescent and Young Adult Cutaneous Melanoma Survivors, California, 1996-2012

Variable	Hematologic Disorders	Cardiac Disease	Diabetes Mellitus	Endocrine Disorders	Lymphedema	VTE	Autoimmune Disorders	Infection/Sepsis	Subsequent Cancers
Race/ethnicity									
NH White	9.14% (8.39%, 9.94%)	6.86% (6.19%, 7.56%)	1.17% (0.91%, 1.48%)	2.35% (1.97%, 2.78%)	0.97% (0.74%, 1.26%)	0.76% (0.55% 1.03%)	2.90% (2.47%, 3.37%)	5.29% (4.72%, 5.91%)	5.47% (4.87%, 6.11%)
Hispanic	9.00% (6.79%, 11.57%)	7.72% (5.67%, 10.17%)	2.45% (1.40%, 3.99%)	3.79% (2.37%, 5.70%)	2.06% (1.09%, 3.58%)	0.99% (0.41%, 2.06%)	4.12% (2.67%, 6.03%)	5.83% (4.04%, 8.08%)	4.92% (3.25%, 7.09%)
Other/unknown[a]	7.55% (5.49%, 10.02%)	4.11% (2.72%, 5.92%)	1.56% (0.77%, 2.87%)	2.33% (1.25%, 3.96%)	0.53% (0.15%, 1.49%)	0.76% (0.25%, 1.89%)	2.47% (1.37%, 4.10%)	4.52% (2.94%, 6.60%)	3.03% (1.84%, 4.68%)
P value	*0.292*	*0.062*	*0.108*	*0.06*	*0.063*	*0.382*	*0.223*	*0.463*	*<0.0001*
Sex									
Female	9.10% (8.25%, 10.00%)	5.76% (5.08%, 6.50%)	1.19% (0.90%, 1.55%)	3.21% (2.70%, 3.78%)	1.00% (0.74%, 1.34%)	0.76% (0.53%, 1.07%)	3.32% (2.81%, 3.90%)	4.78% (4.17%, 5.46%)	5.37% (4.70%, 6.09%)
Male	8.80% (7.68%, 10.02%)	8.45% (7.34%, 9.65%)	1.53% (1.09%, 2.09%)	1.07% (0.70%, 1.56%)	1.05% (0.69%, 1.53%)	0.81% (0.51%, 1.23%)	2.28% (1.73%, 2.97%)	6.17% (5.22%, 7.23%)	4.95% (4.10%, 5.90%)
P value	*0.633*	*<0.0001*	*0.116*	<0.0001	0.661	0.417	*0.089*	*0.004*	*0.93*
Stage at diagnosis									
Localized	7.86% (7.18%,8.56%)	6.16% (5.56%, 6.81%)	2.36% (1.99%, 2.78%)	2.36% (1.99%, 2.78%)	0.87% (0.66%, 1.14%)	0.61% (0.43%, 0.84%)	2.66% (2.27%, 3.10%)	4.73% (4.21%, 5.29%)	5.31% (4.75%, 5.91%)
Regional	21.87% (18.47%, 25.45%)	12.71% (10.12%, 15.59%)	3.60% (2.28%, 5.36%)	3.60% (2.28%, 5.36%)	2.67% (1.59%, 4.22%)	2.68% (1.58%, 4.25%)	6.29% (4.44%, 8.56%)	11.34% (8.86%, 14.16%)	4.27% (2.73%, 6.31%)
P value	*<0.0001*	*<0.0001*	*0.063*	*0.063*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*0.06*
Health insurance									
Private	8.48% (7.74%, 9.25%)	6.10% (5.47%, 6.78%)	2.36% (1.98%, 2.81%)	2.36% (1.98%, 2.81%)	0.93% (0.70%, 1.21%)	0.67% (0.47%, 0.92%)	2.74% (2.32%, 3.21%)	4.76% (4.20%, 5.36%)	5.28% (4.70%, 5.92%)
Public/none	17.65% (14.58%, 20.96%)	13.95% (11.21%, 16.98%)	3.98% (2.55%, 5.87%)	3.98% (2.55%, 5.87%)	2.40% (1.37%, 3.91%)	2.36% (1.34%, 3.84%)	6.20% (4.39%, 8.42%)	11.48% (9.00%, 14.30%)	5.94% (4.16%, 8.15%)

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Variable	Hematologic Disorders	Cardiac Disease	Diabetes Mellitus	Endocrine Disorders	Lymphedema	VTE	Autoimmune Disorders	Infection/Sepsis	Subsequent Cancers
Unknown	6.00% (4.27%, 8.13%)	5.63% (3.98%, 7.67%)	2.00% (1.12%, 3.33%)	2.00% (1.12%, 3.33%)	0.65% (0.22%, 1.58%)	0.36% (0.07%, 1.27%)	2.06% (1.15%, 3.42%)	4.31% (2.88%, 6.17%)	4.08% (2.70%, 5.89%)
P value	*<0.0001*	*<0.0001*	*0.114*	*0.114*	*<0.0001*	*0.001*	*<0.0001*	*<0.0001*	*0.786*
Neighborhood SES									
Low SES	10.58% (9.42%, 11.82%)	8.43% (7.40%, 9.54%)	2.06% (1.57%, 2.66%)	3.02% (2.40%, 3.75%)	1.18% (0.82%, 1.64%)	0.97% (0.65%, 1.39%)	3.74% (3.05%, 4.53%)	6.23% (5.34%, 7.22%)	4.51% (3.74%, 5.37%)
High SES	7.95% (7.13%, 8.84%)	5.56% (4.86%, 6.32%)	0.81% (0.57%, 1.13%)	2.09% (1.67%, 2.57%)	0.92% (0.65%, 1.26%)	0.66% (0.43%, 0.96%)	2.44% (1.99%, 2.97%)	4.63% (4.00%, 5.32%)	5.69% (4.98%, 6.46%)
P value	*<0.0001*	*<0.0001*	*<0.0001*	*0.093*	*0.053*	*0.042*	*0.001*	*0.004*	*0.016*
Surgery									
Yes	9.00% (8.31%, 9.72%)	6.71% (6.10%, 7.35%)	1.29% (1.04%, 1.59%)	2.45% (2.09%, 2.86%)	1.03% (0.80%, 1.30%)	0.80% (0.60%, 1.04%)	2.91% (2.52%, 3.35%)	5.26% (4.73%, 5.83%)	5.19% (4.66%, 5.76%)
No/unknown	9.18% (4.78%, 15.33%)	6.16% (2.98%, 10.97%)	2.23% (0.58%, 6.02%)	2.62% (0.85%, 6.22%)	0.69% (0.06%, 3.50%)	0.00% (0.00%, 0.00%)	5.31% (2.28%, 10.23%)	5.88% (2.48%, 11.38%)	7.16% (3.26%, 13.13%)
P value	*0.603*	*0.68*	*0.299*	*0.916*	*0.605*	*0.234*	*0.128*	*0.868*	*0.197*

NH=non=Hispanic; SES=socioeconomic status; VTE= venous thromboembolism

[a]Other/unknown race/ethnicity includes non-Hispanic Black, non-Hispanic Asian/Pacific Islander and other/unknown

Table 3:

Cox proportional hazard regression model. Multivariable adjusted[a] hazard ratios (HR) and associated 95% confidence intervals (95% CI) of late effect among 2-year adolescent and young adult cutaneous melanoma survivors, California, 1996-2012

Variable	Hematologic Disorders HR (95% CI)	Cardiac Disease HR (95% CI)	Diabetes Mellitus HR (95% CI)	Endocrine Disorders HR (95% CI)	Lymphedema HR (95% CI)	VTE HR (95% CI)	Autoimmune Disorders HR (95% CI)	Infection/ Sepsis HR (95% CI)	Subsequent Melanoma HR (95% CI)	Subsequent Cancer(Other[b]) HR (95% CI)
Age										
15-24	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
25-29	0.85 (0.68, 1.05)	0.82 (0.61, 1.10)	0.90 (0.68, 1.18)	0.88 (0.66, 1.18)	0.94 (0.72, 1.21)	0.81 (0.62, 1.06)	0.84 (0.62, 1.13)	0.87 (0.68, 1.11)	0.98 (0.75, 1.28)	0.83 (0.62, 1.10)
30-34	0.87 (0.71, 1.07)	0.95 (0.73, 1.24)	1.02 (0.80, 1.31)	1.11 (0.86, 1.45)	1.28 (1.02, 1.60)	0.99 (0.78, 1.26)	0.98 (0.75, 1.29)	0.94 (0.75, 1.17)	1.17 (0.92, 1.48)	1.04 (0.82, 1.33
35-39	1.01 (0.84, 1.21)	1.15 (0.90, 1.46)	1.19 (0.95, 1.49)	1.35 (1.06, 1.72)	1.67 (1.36, 2.06)	1.17 (0.94, 1.46)	1.17 (0.92, 1.50)	1.12 (0.92, 1.37)	1.33 (1.07, 1.65)	1.27 (1.02, 1.59)
Race/ethnicity										
NH White	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Hispanic	0.88 (0.70, 1.10)	0.89 (0.67, 1.19)	0.97 (0.76, 1.26)	0.96 (0.73, 1.26)	0.97 (0.78, 1.22)	0.99 (0.77, 1.28)	0.90 (0.68, 1.21)	0.90 (0.71, 1.15)	0.82 (0.63, 1.06)	1.03 (0.81, 1.33)
Other/unknown[c]	0.79 (0.60, 1.03)	0.70 (0.48, 1.02)	0.78 (0.56, 1.07)	0.77 (0.54, 1.08)	0.78 (0.59, 1.02)	0.77 (0.55, 1.06)	0.76 (0.52, 1.09)	0.91 (0.69, 1.19)	0.62 (0.45, 0.86)	0.58 (0.41, 0.83)
Sex										
Female	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Male	1.17 (1.03, 1.33)	1.73 (1.47, 2.03)	1.27 (1.10, 1.48)	1.67 (1.43, 1.95)	1.56 (1.37, 1.77)	1.44 (1.25, 1.67)	1.80 (1.54, 2.12)	1.59 (1.39, 1.82)	1.53 (1.33, 1.75)	1.51 (1.31, 1.74)
Neighborhood SES										
High SES	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Low SES	1.29 (1.14, 1.47)	1.31 (1.11, 1.54)	1.27 (1.09, 1.47)	1.38 (1.18, 1.61)	1.36 (1.20, 1.55)	1.33 (1.15, 1.54)	1.29 (1.10, 1.52)	1.28 (1.12, 1.46)	1.08 (0.94, 1.24)	1.14 (0.99, 1.32)
Health insurance										
Private	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Public/none	2.30 (1.95, 2.72)	2.87 (2.36, 3.49)	2.60 (2.16, 3.13)	2.72 (2.25, 3.29)	2.22 (1.87, 2.63)	2.68 (2.23, 3.22)	2.81 (2.31, 3.42)	2.69 (2.27, 3.19)	2.41 (2.01, 2.88)	2.34 (1.94, 2.82)

Variable	Hematologic Disorders HR (95% CI)	Cardiac Disease HR (95% CI)	Diabetes Mellitus HR (95% CI)	Endocrine Disorders HR (95% CI)	Lymphedema HR (95% CI)	VTE HR (95% CI)	Autoimmune Disorders HR (95% CI)	Infection/ Sepsis HR (95% CI)	Subsequent Melanoma HR (95% CI)	Subsequent Cancer(Other[b]) HR (95% CI)
Unknown	0.88 (0.69, 1.13)	0.73 (0.51, 1.05)	0.78 (0.57, 1.06)	0.80 (0.58, 1.10)	0.82 (0.64, 1.05)	0.75 (0.55, 1.03)	0.67 (0.46, 0.97)	0.76 (0.58, 1.00)	0.70 (0.52, 0.95)	0.84 (0.63, 1.12)
Surgery										
Yes	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
No/unknown	1.04 (0.67, 1.61)	0.56 (0.26, 1.19)	0.73 (0.40, 1.33)	0.78 (0.43, 1.44)	0.78 (0.46, 1.30)	0.93 (0.55, 1.60)	0.56 (0.26, 1.19)	0.79 (0.46, 1.34)	0.81 (0.47, 1.42)	0.97 (0.57, 1.66)

NH= Non-Hispanic; SES= socioeconomic status; VTE= venous thromboembolism

[a]Models adjusted for all variables in the table and stratified by stage at diagnosis and year of diagnosis

[b]Includes all subsequent primary cancers, except subsequent melanomas

[c]Other/unknown race/ethnicity includes non-Hispanic Black, non-Hispanic Asian/Pacific Islander and other/unknown