Disparities in the Occurrence of Late Effects 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: Data for patients ages 15 to 39 years diagnosed with cutaneous melanoma from 1996 to 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% were 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 [HR, 1.73, 95% confidence interval (CI), 1.47–2.03], lymphedema (HR, 1.56; 95% CI, 1.37–1.77), hematologic disorders (HR, 1.17; 95% CI, 1.03–1.33), major infection/sepsis (HR, 1.59; 95% CI, 1.39–1.82), and second cancers (HR, 1.51; 95% 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; 95% 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 adverse health conditions.

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

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 is the number one risk factor for cancer, AYAs with cancer have been an understudied population (5–9). It was first noted in 1996 that patients with cancer ages 15 to 19 years had not benefitted from available cancer therapies when compared with children ages 0 to 14 years (8). Follow-up studies found that patients ages 15 to 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 Study, was the first national cohort study of patients ages 15 to 39, and found worse outcomes following standard cancer therapies when compared with 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 with females, suggesting disparities exist among the AYA melanoma survivor population (10, 11). Because of underrepresentation 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 nonmetastatic 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 with those without cancer (4, 15–18). A previous study of the Danish Patient Registry compared 33,555 AYA cancer survivors with 228,447 patient controls, which included 4,093 patients with malignant melanoma. This study found a statistically significant increased risk for patients with melanoma to develop a secondary cancer or adverse health conditions when compared with controls (18). A separate study showed AYA melanoma survivors have a significantly higher incidence of cardiovascular disease when compared with healthy controls (17). A third study, using the

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Behavioral Risk Factor Surveillance System determined that AYA cancer survivors (including melanoma) had a higher prevalence of chronic conditions, disability, and poor physical health when compared with age-matched controls (4).

It is well established with robust data that AYA patients with melanoma are at a higher risk for the development of adverse health conditions and secondary cancers when compared with healthy controls. However, no population-based studies have addressed whether the occurrence of adverse health conditions following melanoma treatment differs by race/ethnicity, sex, neighborhood socioeconomic status (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 patients with melanoma surviving 2 years or more. The purpose of this study was to identify groups of patients at elevated risk of developing adverse health conditions 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 ages 15 to 39 years who resided in California when diagnosed with a primary, invasive cutaneous melanoma [International Classification of Diseases (ICD) 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 ICD, 9th Revision, Clinical Modifications. 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, and major bleeding), endocrine disorders (hypothyroidism, and ovarian/testicular dysfunction), diabetes mellitus, cardiac disease (hypertension, ischemia, heart disease, and stroke), autoimmune disease, venous thromboembolism (VTE), and infection/sepsis (Supplementary 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, nonmelanoma second primary cancers as an adverse health condition were identified by the CCR. To examine the temporal relationship between melanoma diagnosis and medical conditions, we excluded preexisting 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 patients with cancer (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 multicomponent index of neighborhood SES based on patients' residential census-block group at diagnosis as geocoded by the CCR. The index was 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 was 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 and 5).

The final study population included 8,259 AYA patients with melanoma 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 (Sacramento, CA) and by the California Committee for the Protection of Human Subjects.

Statistical analyses

The 10-year cumulative incidence and associated 95% confidence intervals (CI) of developing a medical condition ≥2 years after diagnosis were calculated using nonparametric methods that account for death as a competing risk (23). Person-years of observation were compiled from 2 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 cutoff date (December 31, 2014), whichever occurred first. Gray 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 HRs 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, and 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.).

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 Supplementary 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 1. Selected characteristics and late effects among 2-year AYA cutaneous melanoma survivors ($N = 8,259$), California, 1996–2012.

Characteristic	*N* (%)
Race/ethnicity	
NH White	6,877 (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	2,914 (35.3%)
Female	5,345 (64.7%)
Year of diagnosis	
1996–2000	2,526 (30.6%)
2001–2004	1,976 (23.9%)
2005–2008	2,194 (26.6%)
2009–2012	1,563 (18.9%)
Stage at diagnosis	
Localized	7,567 (91.6%)
Regional	692 (8.4%)
Neighborhood SES	
Low SES	3,266 (39.5%)
High SES	4,993 (60.5%)
Health insurance	
Private	6,809 (82.4%)
Public/none	686 (8.3%)
Unknown	764 (9.3%)
Treatment	
Surgery only	7,939 (96.1%)
Surgery and chemotherapy	90 (1.1%)
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%)
VTE	76 (0.9%)
Infection and sepsis	458 (5.5%)
Cause of death	
Alive	7,725 (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 depicts the cumulative incidence of medical conditions at 10 years postdiagnosis 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 with 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 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 with NH 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; 95% CI, 1.03–1.33), lymphedema (HR, 1.73; 95% CI, 1.47–2.03), endocrine disorders (HR, 1.27; 95% CI, 1.10–1.48), diabetes mellitus (HR, 1.67; 95% CI, 1.43–1.95), cardiac disease (HR, 1.56; 95% CI, 1.37–1.77), autoimmune disorders (HR, 1.44; 95% CI, 1.25–1.67), VTE (HR, 1.80; 95% CI, 1.54–2.12), and infection/sepsis (HR, 1.59; 95% CI, 1.39–1.82). Males were also at an increased risk for developing a subsequent melanoma (HR, 1.53; 95% CI, 1.33–1.75) and subsequent cancer of another type (HR, 1.51; 95% 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 2-fold for all adverse health conditions studied. This included hematologic disorders (HR, 2.30; 95% CI, 1.95–2.72), lymphedema (HR, 2.87; 95% CI, 2.36–3.49), endocrine disorders (HR, 2.60; 95% CI, 2.16–3.13), diabetes mellitus (HR, 2.72; 95% CI, 2.25–3.29), cardiac disease (HR, 2.22; 95% CI, 1.87–2.63), autoimmune disorders (HR, 2.68; 95% CI, 2.23–3.22), VTE (HR, 2.81; 95% CI, 2.31–3.42), and infection/sepsis (HR, 2.69; 95% CI, 2.27–3.19). This population was also at an increased risk

Table 2. Cumulative incidence (with 95% CIs) of late effects 10 years after diagnosis among 2-year AYA 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	*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	*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	*<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%)
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	*<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	*<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	*0.603*	*0.68*	*0.299*	*0.916*	*0.605*	*0.234*	*0.128*	*0.868*	*0.197*

Note: *P* values are italicized.

[a]Other/unknown race/ethnicity includes NH Black, NH Asian/Pacific Islander, and other/unknown.

Table 3. Cox proportional hazard regression model.

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[a]) 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[b]	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)
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)

Note: Multivariable-adjusted[c] HR and associated 95% CIs of late effect among 2-year AYA cutaneous melanoma survivors, California, 1996–2012.

[a]Includes all subsequent primary cancers except subsequent melanomas.

[b]Other/unknown race/ethnicity includes NH Black, NH Asian/Pacific Islander, and other/unknown.

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

for development of subsequent melanoma (HR, 2.41; 95% CI, 2.01–2.88) and other subsequent cancers (HR, 2.34; 95% 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 patients with cancer, and specifically melanoma survivors, are at higher risk for developing adverse health conditions and secondary cancer when compared with age-matched healthy controls (4, 17, 18). In this large population-based study of more than 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 for 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 with females, a population-based study in the United States by Gamba and colleagues (11) found melanoma-specific and all-cause survival to be worse and a Dutch study by Eggen and colleagues (10) 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. In addition, 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 health care 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 reports that cigarette use is higher in men, among those with lower annual household incomes, and among those with no insurance, Medicaid, or public insurance (vs. private insurance; ref. 27). Among AYA cancer survivors, those with public/no insurance were more likely to report an obese body mass index, low physical activity, and current smoking than those with private insurance, associations that were also observed in the comparison group of noncancer survivors (28). Furthermore, AYA cancer survivors more commonly reported adverse medical and behavioral characteristics, to include smoking and obesity, when compared with respondents with no history of cancer (4, 29). Kaul and colleagues reported 21% to 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 nonsurvivor cohort (16, 28). Findings from these prior studies suggest 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 highlight the need for targeted interventions in these subgroups.

AYA cancer survivors with public/no insurance may be are 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 posttreatment 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, psychologic 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 and colleagues reported that AYA survivors are more likely to forego care due to cost barriers than the control population (29). In a separate study, Yabaroff and colleagues demonstrated higher psychologic financial hardship among survivors in the working age population (ages 18–64; ref. 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 versus 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 to 2012, patients with regional disease (stage III melanoma) may have been treated with adjuvant IFN or other systemic agent, which could explain the higher incidence of adverse health conditions. The current standard of care for locally advanced disease

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 preexisting 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 have 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.

Disclosure of Potential Conflicts of Interest

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Disclaimer

The ideas and opinions expressed herein are those of the author(s) and do not necessarily reflect the opinions of the State of California, Department of Public Health, NCI, and Centers for Disease Control and Prevention or their contractors and subcontractors.

Authors' Contributions

A.A. Gingrich: Investigation, writing–original draft, writing–review and editing. **C.A.M. Sauder:** Investigation, writing–review and editing. **M. Goldfarb:** Conceptualization, writing–review and editing. **Q. Li:** Data curation, formal analysis, investigation, methodology. **T. Wun:** Conceptualization, methodology, writing–review and editing. **T.H.M. Keegan:** Conceptualization, resources, data curation, supervision, funding acquisition, investigation, writing–review and editing.

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