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Red meat and fruit intake is prognostic among patients with localized cutaneous melanomas more than 1 mm thick

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Abstract

Background—As the 10-year mortality for localized cutaneous melanoma more than 1.00 mm thick approaches 40% following complete resection, non-therapeutic interventions that can supplement recommended active surveillance are needed. Although guidelines recommending

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nutrition, physical activity and tobacco cessation for cancer survivors have been published, data describing their associations with melanoma survivorship are lacking.

Methods—Analysis of modifiable lifestyle behaviors collected on the 249 cases with melanomas more than 1.00 mm thick enrolled in the Connecticut Case-Control Study of Skin Self-Examination study was conducted. Independent associations with melanoma-specific survival were evaluated through Cox proportional hazards modeling adjusting for age, gender, Breslow thickness, ulceration and the presence of microsatellites. Independently significant variables were then combined into a single model and backwards elimination was employed until all remaining variables were significant at $p<0.05$.

Results—Following adjustment for age, Breslow thickness and anatomic site of the index melanoma, daily fruit consumption was associated with improved melanoma-specific survival (HR=0.54; 95% CI: 0.34–0.86) whereas at least weekly red meat consumption was associated with worse outcomes (HR=1.84; 95% CI: 1.02–3.30). Natural red (HR=0.44; 95% CI: 0.22–0.88) or blond (HR=0.52; 95% CI: 0.29–0.94) hair were also favorably prognostic. Higher fish consumption was of borderline significance for improved survival only when considered independently (HR=0.65; 95% CI: 0.40–1.05); no association was seen following adjustment for red meat and fruit consumption ($p>0.10$).

Conclusions—Dietary choices at the time of diagnosis are associated with melanoma-specific survival in patients with melanomas more than 1.00 mm thick. Further validation of our findings in larger cohorts with repeated post-diagnostic measures is warranted to further evaluate whether dietary modification during the survivorship period can improve melanoma-specific survival.

Keywords

Cutaneous Melanoma; Prognosis; Mortality; Red meat; Fruit; Hair color; Alcohol use; Fish; Smoking; Body mass index

1. Introduction

The 10-year mortality for localized cutaneous melanomas >1.00 mm thick is 30–60% following curative intent resection [1]. Yet, due to the morbidity associated with approved interferon-based adjuvant therapy, active surveillance is the recommended standard-of-care for the majority of these patients with active treatments commencing only after metastatic disease is confirmed [2]. Consequently, “fear of recurrence”, a spectrum of symptoms that range from mild depression and irritability to debilitating anxiety manifested during the follow-up period [3], is highly prevalent among melanoma survivors [4–6].

Heightened fear of recurrence can convert the cancer diagnosis into a teachable moment for promoting lifestyle behaviors with potential prognostic benefit [7]. Lifestyle interventions display a survival benefit across multiple malignancies. For example, smoking cessation improves outcomes in lung [8, 9] and oropharyngeal cancers [9, 10], abstinence from alcohol improves head and neck cancer survival [11] and regulation of energy balance through weight management and/or physical activity has a positive prognostic influence on most hormonally-regulated and gastrointestinal cancers [12–15].

Nonetheless, the study of modifiable lifestyle factors with respect to melanoma prognosis is still sparse and has largely been restricted towards describing patterns of post-diagnosis ultraviolet light (UV) exposure and the associated risk of developing second primary melanomas [6, 16–19]. Even fewer published studies describe the association between modifiable lifestyle factors and recurrence of the index melanoma. Two large cohort studies, the US-based Cancer Prevention Study II (CPS-II) and the British Million Women Study, have evaluated the effects of body mass index (BMI) captured at the time of diagnosis on melanoma-specific survival and both studies reported a null association [20, 21]. The CPS-II also considered cigarette smoking. Cigarette smoking was assessed only at the time of enrollment prior to any cancer diagnosis and showed fewer accrued deaths due to melanoma after 24 years of follow-up among those who smoked at the time of enrollment compared with never-smokers [22]. However, absence of a dose-response relationship across pack-years smoked weakens their evidence for causation. By contrast, the Roswell Park Cancer Institute hospital-based cohort study reported a null association between cigarette smoking, captured as a single measurement at the time of diagnosis, and melanoma-specific survival [9]. To the best of our knowledge, neither alcohol nor dietary preferences have been evaluated in the context of melanoma prognosis.

Here, we evaluate the association between lifestyle factors using a single measurement taken at diagnosis and melanoma specific survival for patients from the Connecticut Skin Self-Examination Case Control Study (1987–1989) with melanomas >1.00 mm thick. Significant associations can identify the set of lifestyle choices with potential relevance to melanoma outcomes suitable for further analysis, including longitudinal assessment in survival cohorts, with the goal of identifying those with prognostic potential in the setting of active surveillance.

2. Methods

2.1. Study Population

The Connecticut Skin Self-Examination Case-Control Study (1987–1989) was initially conducted among Caucasian Connecticut residents to evaluate the association between skin self-examination and melanoma mortality. Study design and recruitment strategies, approved by the Yale Human Investigations Committee to comply with the principles embodied in the Declaration of Helsinki, have been previously described elsewhere [23, 24]. Briefly, cases included Connecticut residents diagnosed with localized cutaneous malignant melanoma during January 15, 1987, and May 15, 1989, and were identified through the Connecticut Tumor Registry Rapid Case Ascertainment System. Following primary physician approval, eligible participants were contacted by trained nurse-interviewers to obtain informed consent. 650 cases were enrolled, representing 75% of all potentially eligible individuals.

2.2. Assessment of Demographic and Lifestyle Variables

Demographic and lifestyle variables were assessed by self-report at time of enrollment through a structured interview administered in-person by a trained nurse-interviewer. Height (inches) and weight (pounds) were captured as continuous variables with participants stating

their current height and weight at 1-year prior to the interview. Hair color, defined as natural (uncolored or bleached) color at age 20, was categorized into eight levels: blonde, dishwater blonde, light brown, medium brown, reddish-blonde, red-brown, dark brown, or black. Hair samples were provided to aid participant selections. Eye color was selected from eight choices guided by colored pictorials: blue, blue-gray, gray, green, blue-green, hazel, medium-brown, or dark-brown. Tobacco use was evaluated by first defining lifetime ever-smokers as any participant who smoked at least one cigarette per day for 3 or more months. Then, among ever smokers, current smoking status, average packs/day, age at initiation and, if relevant, at quitting were collected. Alcohol consumption was captured as a 5-level variable with available categories: no consumption, less than 1 drink/week, 1–5 drinks/week, 1–2 drinks/day, 3–4 drinks/day and more than 5 drinks/day. Dietary preference for red meat, fish, green salad, and fruit at the time of the interview were assessed as a 4-level scale with categories for daily, greater than once/week, once per week or less or no consumption. Regular use of vitamin/mineral supplements was coded as yes, no or occasional. Marital status groupings included married, widowed, currently separated, currently divorced and never married. Highest educational level attained was described as less than seventh grade, junior high school, partial high school, high school graduate, partial college, Bachelor's degree and Graduate degree.

2.3. Assessment of Pathologic Variables

For each case, the hematoxylin and eosin-stained slides of the index melanoma were re-annotated by a single dermatopathologist (RLB). Breslow thickness (millimeters), Clark level of invasion (I–V) and mitotic index (number of mitoses/high-powered field), were recorded as continuous variables. Ulceration, regression, microsatellites and solar elastosis were each coded as binary variables noting the presence or absence of each. Histologic subtype was classified as superficial spreading, nodular, lentigo malignant melanoma and other. Degree of tumor-infiltrating lymphocytes (TIL) was noted as absent, non-brisk or brisk. Anatomic site was captured from the original surgical report, corroborated with the patient interview and grouped according to head and neck, upper limb, lower limb and trunk [25]. If assessment of a parameter was not possible from the provided slides, then values recorded on the diagnostic hospital pathology report were used, if available.

2.4. Follow-up and Vital Status Ascertainment

Participants and their referring physicians were re-contacted biannually by mail and/or telephone through 2004. Ascertainment of death was through the Connecticut Tumor Registry and Connecticut Department of Public Health State Vital Records Office. Cause of death was determined from the Death Certificate. The median follow-up was 16 years with 80% followed for more than 5 years and 67% followed for 10 or more years.

2.5. Data Analysis

T stage according to the AJCC 7th Edition criteria [1] was determined for all participants using Breslow thickness, ulceration status and, where necessary, mitotic index. Breslow thickness was categorized according to T stage cutpoints (1.00 or less, 1.01–2.00 and 2.01–4.00 and more than 4.00) and mitotic index was reclassified as 0, 1–6 and more than 6 mitoses/high-powered field. Age at diagnosis was dichtomized, dividing individuals as 65

years or younger versus more than 65 years at diagnosis. BMI was calculated from the reported height and weight as $[(\text{weight}/2.2)/(\text{height}*0.0254)]^2$ and categorized according to NHANES cutpoints for obese (BMI of 30.0 or more), overweight (BMI of 25.0–29.9) and normal/underweight (BMI less than 25.0) [26]. Tobacco use captured both smoking status at the time of diagnosis (never, former and current) and, among ever-smokers, total pack-years smoked to yield a 5-level variable describing never smokers, and two categories each for former and current smokers based on having smoked less than or more than 20 pack-years at the time of diagnosis. Alcohol consumption was grouped semi-quantitatively as never-drinkers, less than 1 drink/week, 1–5 drinks/week and 1 drink a day or more. Dietary covariates were dichotomized as 'weekly or more' or 'less than weekly' except for fruit consumption which was dichotomized as daily versus less than daily. Vitamin use was dichotomized into never- and ever- users. Hair, eye color, marital status and education categories were also simplified. Hair color was reduced to three categories: blondes and dishwater blondes were included as *blonde*, reddish-blonde and red-brown were grouped as *red* and the remaining four levels combined as *brunette/black*. Eye color was dichotomized with individuals reporting dark or light brown eyes included as *brown/black* and those individuals reporting hazel, blue, green or grey eyes grouped as *blue/green*. Education levels were grouped as less than high school, high school diploma, some college, Bachelor's degree and Graduate degree. Marital status was simplified by combining 'currently separated' and 'currently divorced' into a single category. For all variables, missing values were not imputed and individuals with a missing value were censored from analyses where variables for which missingness occurred were included.

Univariate distributions for each demographic, pathologic and lifestyle variable were obtained and bivariate associations with Breslow thickness were calculated using a chi-square analysis. Univariate and multivariate survival analyses for lifestyle variables, the latter adjusting for established clinicopathologic prognostic factors, were performed using the Cox Proportional Hazards regression with hazard ratios (HRs) and 95% confidence intervals (95% CIs) reported. Overall P-values for proportional hazards models were calculated using the likelihood ratio test. All statistical analyses were performed using SAS version 9.3 or statistical platform (SAS Institute, Cary, NC).

3. Results

Among the 650 cases included in the parent study, re-staging according the AJCC 7th edition criteria [1] was possible for 577 individuals of which 113 (19.6%) died of melanoma during the follow-up period. Because of the high (94%) melanoma-specific survival among T_1 melanomas, this study is limited to the subset of 249 individuals with melanomas more than 1.00 mm thick who accrued 92 (83.2%) of the observed melanoma-specific deaths. Bivariate associations between the demographic, pathologic and lifestyle variables and Breslow thickness are shown (Table 1). Consistent with published data [1], increasing tumor thickness was significantly associated with presence of ulceration ($p<0.001$), higher mitotic indices ($p<0.001$), increasing Clark level ($p<0.001$), presence of microsatellitosis ($p=0.017$) and absence of regression ($p=0.005$), indicating that our sample is representative. We also observed an increase of nodular melanomas and a corresponding decrease in superficial spreading tumors among the thicker lesions ($p<0.001$). As this cohort was accrued prior to

sentinel lymph node biopsy adoption [27], the presence and distribution of nodal micrometastases is not available. Breslow thickness was not associated with any demographic or lifestyle variable.

Table 2 presents the individual crude and multivariable HRs for all demographic, lifestyle and pathologic variables, the latter adjusted for Breslow thickness, age, sex, ulceration and microsatellitosis – established prognostic factors in early-stage melanoma [28]. Of the 18 variables evaluated, only red meat consumption, hair color and anatomic site yielded significant independent multivariable-adjusted associations with melanoma survival. More frequent red meat consumption yielded poorer survival, (adjusted HR=1.93 (95% CI: 1.08–3.45); p=0.018). By contrast, either blonde (adjusted HR=0.63 (95% CI: 0.36–1.10)) or red hair (adjusted HR=0.50 (95% CI: 0.25–0.99)) conferred a survival advantage (overall p=0.048). Similarly, compared with the survival observed for head and neck melanomas, melanomas occurring on the trunk (adjusted HR=0.47 (95% CI: 0.26–0.84)), upper extremities (adjusted HR=0.37 (95% CI: 0.16–0.85)) or lower extremities (adjusted HR=0.29 (95% CI: 0.13–0.69)) demonstrated improved survival (overall p=0.018). More frequent fruit (adjusted HR=0.65 (95% CI: 0.42–1.02); p=0.06) and fish (adjusted HR=0.66 (95% CI: 0.41–1.06); p=0.08) consumption were of borderline statistical significance. We also observed that, following adjustment for clinicopathologic parameters, individuals who were current heavy smokers had borderline significant worse survival outcomes compared to the never-smoking reference group (adjusted HR=2.01 (95% CI: 0.99–4.07), Wald p=0.054). However as this group represented only a small portion of the study sample (n=23, 9.58%), the overall likelihood ratio p-value was not significant (overall p=0.251). A larger sample is required to characterize melanoma survival among current heavy smokers.

To assess combined effects, we included each of the variables independently that had an adjusted p-value <0.10 into a single multivariable model that also included the 5 baseline clinicopathologic covariates and conducted backwards elimination until all retained covariates were significant at p<0.05. As all non-head and neck anatomic sites conferred a similar survival advantage, this variable was dichotomized accordingly. Fruit consumption, red meat consumption, hair color and anatomic site each remained significant following adjustment for age at diagnosis and Breslow thickness (Table 3).

4. Discussion

Although 30%–70% of patients with intermediate-thickness or thick localized melanomas will die of their disease despite complete resection, active surveillance is standard for the majority of these patients. Consequently, melanoma survivors would be interested in pursuing lifestyle choices with the potential to reduce their risk of recurrence. Melanoma survivors already reduce overall UV exposure to prevent second primary melanomas [29–31]. Yet, data regarding the association between other modifiable lifestyle behaviors and melanoma survival is sparse and encouraging their modification in melanoma survivorship clinics is premature. Here, we evaluated the survival benefit of BMI, smoking, alcohol use and dietary preferences as recorded at the time of diagnosis to identify the subset associated with improved melanoma-specific survival.

In our final model that adjusted for age, Breslow thickness, anatomic location of the primary tumor, hair color and fruit consumption, significantly poorer outcomes were observed among individuals who consumed red meat once or more per week. Red meat consumption is prognostic for colorectal cancer where higher consumption before and after diagnosis are associated with increased disease-specific mortality [32, 33]. Here, putative mechanisms include direct exposure of the colorectal mucosa to fatty acid [34] or heme iron [35]-induced oxidative damage, inflammation and vascular dysfunction [36] and chromosomal damage from polyaromatic hydrocarbons and heterocyclic amines generated during processing and cooking [37, 38]. Consumption of extensively grilled, but not rare, red meat was also associated with increased risk of aggressive prostate cancer [38], supporting the relevance of red meat-associated exposures for target organs outside the gastrointestinal tract. As melanoma evasion of the host immune system contributes to metastatic progression, recent research describing metabolic reprogramming of the immune system posits a complementary hypothesis. One mechanism promoting immune evasion is a relative excess of CD4+ regulatory T lymphocytes (T_{reg}) within the TIL population [39]. Tumor microenvironments rich in free fatty acids, via signal transduction through the phosphatidyl-inositol-3-kinase/mTOR cascade, promote the differentiation of naïve T-cells into T_{reg} subpopulations [40]. As regular consumption of red meat correlates with elevated serum triglyceride levels [41], it is possible that diets high in red meat can trigger an immunosuppressive T_{reg} excess. Validation in appropriate model systems is required.

Following similar multivariable adjustment, we also report improved survival with daily fruit consumption at the time of diagnosis. Five or more daily fruit servings have been shown to decrease the risk for diverse chronic diseases including cardiovascular diseases, cancer, dementia, osteoporosis and rheumatoid arthritis [42, 43] with pharmacodynamic studies of whole-fruit extracts [44, 45] or of specific components including resveratrol [46] and lycopene [47] supporting increased intake of anti-oxidative phytochemicals as the underlying mechanism. Nonetheless, the impact of fruit consumption on cancer-specific survival is still emerging. While a statistically-significant inverse association between overall survival and increased fruit consumption was observed among women enrolled in the US-based Multi-Ethnic Cohort (MEC) study (HR for more than 4.8 servings/day=0.82; 95% CI: 0.69–0.92), null results were obtained in both the European Prospective Investigation into Cancer and Nutrition (EPIC) study (HR=0.96; 95% CI: 0.90–1.03) and among MEC men (HR=0.96; 95% CI: 0.84–1.09) [48, 49]. Both these studies, however, enrolled healthy individuals who were cancer-free at the time of their dietary assessment compared to our population who had already received their cancer diagnosis at the time of study enrollment and interview. Moreover, as breakdown by cancer subtypes was not done in either study, melanoma-specific survival could not be evaluated.

The remaining lifestyle variables were not associated with melanoma survival. Our data for BMI are consistent with the two large studies previously reporting null associations with melanoma-specific survival [20, 21]. For smoking, while we observed significantly worse survival among current heavy smokers, this group contained few individuals and the overall effect of our smoking variable was null consistent with the null results reported by Warren *et al.* [9]. Although our data are discordant with the protective effects of smoking noted in

CPS-II, the lack of dose-response across pack-years in that study questions the validity of that result [22].

Among clinicopathologic variables, we observed improved survival among individuals with red or blonde hair. Our findings on the survival benefit associated with red and blonde hair color is consistent with the survival benefit observed among individuals who carry blond or red hair-conferring melanocortin-1 receptor variants [50]. We also noted worse outcomes for head and neck melanomas, consistent with prior reports [51].

Our study notes several strengths. We are the first to consider the association of dietary factors with melanoma outcomes. Next, we restricted our cohort to individuals with advanced localized disease who have the most to benefit from non-therapeutic treatment alternatives. We also recognize several important weaknesses in our study. First, our measurement of lifestyle behaviors was based upon a single measurement taken at the time of diagnosis which carries the now-proven false assumption that subjects maintain their pre-diagnostic behaviors throughout the follow-up period [52], creating nondifferential misclassification of lifestyle exposures and bias towards the null. Additionally, for post-diagnosis behavior changes that would be predicated on the pre-diagnosis behavior (e.g., rates of smoking cessation among current smokers versus new-onset smoking among never-smokers), differential misclassification can occur. Validation of all our results in prospective longitudinal studies with repeated post-diagnosis lifestyle measurements is necessary. Next, due to our small sample size we cannot rule out false negative results. We did not detect an association with green salad, a dietary choice equally rich in phytochemicals, and our trend towards significance for fish consumption disappeared when included in a multivariable model with fruit. Third, as “daily” was the highest consumption level coded for fruit intake, we could not further refine our analysis discriminate among individuals with at least daily fruit consumption those who adhered to the “5-a-day” recommendations [43, 52] from those who did not. Lastly, our food group categories and their semi-quantitative measurements did not support reclassification into dietary subtypes, the preferred method for analyzing food-based exposures as they not only parallel the 2010 Dietary Guidelines for Americans [53] but they also account for the strong correlations between certain individual food choices, acknowledging that the effect size for single dietary constituents might be too small to measure [54].

In conclusion, we report significant associations between red meat or fruit consumption at the time of diagnosis with melanoma-specific survival, in patients with localized melanomas more than 1.00 mm thick, a group where recurrence following curative resection is not uncommon but in whom active surveillance is standard. Further validation of our findings is warranted to further evaluate whether their modification during the survivorship period can improve melanoma-specific survival. We not only propose examining patterns of red meat and fruit consumption in larger cohorts of Stage II patients where repeated post-diagnostic measures are captured but also promote exploring their relevance to the survival from Stage I melanomas, a population subset that includes over 70% of newly-diagnosed cases but where the observed 10-year melanoma-specific survival exceeds 90% [55].

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HIGHLIGHTS

- 249 patients with localized melanomas ≥1.00 mm thick were followed for 15 years.
- Smoking, dietary preferences, BMI and alcohol use were measured at diagnosis.
- After adjustment for tumor thickness, age, lesion location and hair color:
  - Eating red meat at least weekly was associated with poorer survival.
  - Eating fruit at least daily was associated with better survival.

Table 1

Characteristics of the study sample according to Breslow thickness

	1.01–2.00 mm (*N*=123)		2.01–4.00 mm (*N*=83)		>4.00 mm (*N*=43)		
	N	**%**	***N***	**%**	***N***	**%**	***P* values**
Demographic Parameters							
Age at diagnosis							
65 years or less	83	67.5	53	63.9	22	51.2	0.160
More than 65 years	40	32.5	30	36.1	21	48.8	
Sex							
Male	66	53.7	46	55.4	29	67.4	0.281
Female	57	46.3	37	44.6	14	32.6	
Education level							
Some high school	18	14.6	14	16.9	11	25.6	
High school diploma	37	30.1	19	22.9	13	30.2	
Some college	22	17.9	29	34.9	8	18.6	0.100
Bachelor’s degree	23	18.7	11	13.3	7	16.3	
Graduate degree	23	18.7	10	12.1	4	9.3	
Marital status							
Married	89	72.4	61	73.5	29	67.4	
Separated/divorced	9	7.3	3	3.6	3	7.0	0.898
Widowed	12	9.8	11	13.3	6	14.0	
Never married	13	10.6	8	9.6	5	11.6	
Hair color							
Brown or black	73	59.4	50	60.2	23	53.4	
Blonde	33	26.8	14	16.9	14	32.6	0.177
Red	17	13.8	19	22.9	6	14.0	
Eye color							
Brown or black	26	21.1	15	18.1	8	18.6	0.847
Blue or green	97	78.9	68	81.9	35	81.4	
Pathologic Parameters							
Ulceration							**<0.001**

	1.01–2.00 mm (*N*=123)		2.01–4.00 mm (*N*=83)		>4.00 mm (*N*=43)		
	N	**%**	***N***	**%**	***N***	**%**	***P* values**
Absent	111	90.2	50	60.2	19	44.2	
Present	12	9.8	33	39.8	24	55.8	
Mitotic index							
0 mitoses/mm^2	13	10.6	1	1.2	0	0.0	
1–6 mitoses/mm^2	92	74.8	33	39.8	19	44.2	**<0.001**
More than 6 mitoses/mm^2	18	14.6	49	59.0	24	55.8	
Clark level							
II–III	47	38.8	15	18.8	2	5.0	**<0.001**
IV–V	74	61.2	65	81.3	38	95.0	
Anatomic site							
Head and neck	13	10.9	15	18.8	5	11.9	
Trunk	70	58.8	36	45.0	22	52.4	0.594
Upper extremities	17	14.3	14	17.5	7	16.7	
Lower extremities	19	16.0	15	18.8	8	19.1	
Tumor-infiltrating lymphocytes							
None	57	46.3	41	49.4	20	47.6	
Non-brisk	48	39.0	37	44.6	19	45.2	0.327
Brisk	18	14.6	5	6.0	3	7.1	
Microsatellitosis							
Absent	116	94.3	70	92.1	31	79.5	**0.017**
Present	7	5.7	6	7.9	8	20.5	
Histologic subtype							
Superficial spreading	78	64.5	36	43.9	12	28.6	
Nodular	11	9.1	23	28.1	17	40.5	**<0.001**
Lentigo maligna	14	11.6	7	8.5	4	9.5	
Other	18	14.9	16	19.5	9	21.4	
Solar elastosis							
Absent	87	70.7	63	75.9	33	76.7	0.618
Present	36	29.3	20	24.1	10	23.3	
Regression							

	1.01–2.00 mm (*N*=123)		2.01–4.00 mm (*N*=83)		>4.00 mm (*N*=43)		
	N	**%**	***N***	**%**	***N***	**%**	***P* values**
Absent	61	49.6	58	71.6	27	65.9	**0.005**
Present	62	50.4	23	28.4	14	34.2	
Lifestyle Parameters							
Body mass index							
Less than 25 kg/m^2	58	47.2	36	43.4	13	31.0	0.081
25–29.9 kg/m^2	51	4.5	30	36.1	17	40.5	
30 kg/m^2 or more	14	11.4	17	20.5	12	28.6	
Tobacco use							
Never	50	42.0	31	38.8	13	31.7	0.078
Former, ≤20 pack-years	23	19.3	18	22.5	4	9.8	
Former, >20 pack-years	29	24.4	22	27.5	10	24.4	
Current, ≤20 pack-years	9	7.6	3	3.8	5	12.2	
Current, >20 pack-years	8	6.7	6	7.5	9	22.0	
Alcohol consumption							
Never	29	23.6	18	21.7	14	32.6	0.222
Less than 1 drink/week	42	34.2	31	37.4	8	18.6	
1–5 drinks/week	33	26.8	21	25.3	9	20.9	
More than 5 drinks/week	19	15.5	13	15.7	12	27.9	
Vitamin use							
None	61	49.6	43	51.8	21	48.8	0.934
Any	62	50.4	40	48.2	22	51.2	
Fruit consumption							
Less than daily	40	32.5	30	36.1	21	48.8	0.160
Daily or more	83	67.5	53	63.9	22	51.2	
Green salad consumption							
Less than weekly	23	18.7	16	19.3	13	30.2	0.252
Weekly or more	100	81.3	67	80.7	30	69.8	
Red meat consumption							
Less than weekly	33	26.8	22	26.5	10	23.3	0.895
Weekly or more	90	73.2	61	73.5	33	76.7	

	1.01–2.00 mm (*N*=123)		2.01–4.00 mm (*N*=83)		>4.00 mm (*N*=43)		
	N	**%**	***N***	**%**	***N***	**%**	***P* values**
Fish consumption							
Less than weekly	70	56.9	55	66.3	29	67.4	0.283
Weekly or more	53	43.1	28	33.7	14	32.6	

[a]Rows may not sum to total due to missing values; percents may not sum to 100% due to rounding

Table 2

Crude and covariate-adjusted[a] melanoma-specific survival Cox regression model results for demographic, pathologic and lifestyle variables

	Univariate Hazard Ratio (95% CI)	*P* value	Multivariable[a] Hazard Ratio (95% CI)	*P* value
Demographic Parameters				
Education level				
Some high school	1.00		1.00	
High school diploma	0.77 (0.42–1.41)		1.03 (0.51–2.08)	
Some college	0.55 (0.29–1.07)	0.332	0.71 (0.34–1.51)	0.630
Bachelor's degree	0.51 (0.24–1.07)		0.66 (0.27–1.61)	
Graduate degree	0.71 (0.36–1.42)		0.98 (0.44–2.17)	
Marital status				
Married	1.00		1.00	
Separated/divorced	0.48 (0.15–1.53)	0.327	0.74 (0.23–2.39)	0.475
Widowed	1.15 (0.60–2.25)		1.21 (0.59–2.47)	
Never married	1.39 (0.75–2.58)		1.75 (0.84–3.65)	
Hair color				
Brown or black	1.00		1.00	
Blonde	0.72 (0.43–1.19)	0.012	0.63 (0.36–1.10)	**0.048**
Red	0.57 (0.30–1.08)		0.50 (0.25–0.99)	
Eye color				
Brown or black	1.00	0.298	1.00	0.634
Blue or green	1.32 (0.77–2.26)		1.14 (0.65–2.03)	
Pathologic Parameters				
Mitotic index				
0 mitoses/mm^2	1.00		1.00	
1–6 mitoses/mm^2	1.78 (0.56–5.72)	0.054	1.09 (0.33–3.59)	0.991
More than 6 mitoses/mm^2	2.71 (0.84–8.77)		1.09 (0.31–3.85)	
Anatomic Site				
Head and neck	1.00		1.00	
Trunk	0.52 (0.31–0.89)	**0.020**	0.47 (0.26–0.84)	**0.018**
Upper extremities	0.41 (0.19–0.87)		0.37 (0.16–0.85)	
Lower extremities	0.33 (0.16–0.70)		0.29 (0.13–0.69)	
Tumor-infiltrating lymphocytes				
None	1.00		1.00	
Non-brisk	0.94 (0.62–1.44)	0.051	0.93 (0.59–1.45)	0.111
Brisk	0.34 (0.12–0.95)		0.38 (0.13–1.07)	
Histologic subtype				
Superficial spreading	1.00		1.00	
Nodular	2.08 (1.21–3.57)	**0.001**	1.33 (0.73–2.44)	0.151
Lentigo maligna	2.26 (1.11–4.60)		1.87 (0.88–4.01)	

	Univariate Hazard Ratio (95% CI)	*P* value	Multivariable[a] Hazard Ratio (95% CI)	*P* value
Other	2.61 (1.54–4.41)		1.90 (1.04–3.48)	
Solar elastosis				
Absent	1.00	0.520	1.00	0.749
Present	1.17 (0.73–1.86)		1.09 (0.65–1.82)	
Regression				
Absent	1.00	0.132	1.00	0.151
Present	0.72 (0.47–1.11)		0.71 (0.44–1.14)	
Lifestyle Parameters				
Body mass index (BMI)				
Less than 25.0 kg/m^2	1.00		1.00	
25.0–29.9 kg/m^2	1.09 (0.70–1.70)	0.931	0.80 (0.49–1.33)	0.554
30.0 kg/m^2 or more	1.02 (0.56–1.84)		0.74 (0.40–1.37)	
Tobacco use				
Never	1.00		1.00	
Former, ≤20 pack-years	0.90 (0.49–1.67)		0.85 (0.44–1.64)	
Former, >20 pack-years	1.04 (0.59–1.81)	0.104	0.90 (0.49–1.64)	0.251
Current, ≤20 pack-years	1.29 (0.59–2.80)		1.41 (0.62–3.21)	
Current, >20 pack-years	2.31 (1.25–4.27)		2.01 (0.99–4.07)	
Alcohol consumption				
Never	1.00		1.00	
Less than 1 drink/week	0.64 (0.36–1.14)	0.202	0.59 (0.32–1.10)	0.327
1–5 drinks/week	0.94 (0.54–1.65)		0.93 (0.51–1.70)	
More than 5 drinks/week	1.18 (0.65–2.15)		0.90 (0.47–1.73)	
Vitamin use at diagnosis				
None	1.00	0.997	1.00	0.989
Any	1.00 (0.66–1.50)		1.00 (0.65–1.55)	
Fruit consumption at diagnosis				
Less than daily	1.00	0.062	1.00	0.074
At least daily	0.67 (0.45–1.02)		0.66 (0.42–1.04)	
Green salad consumption at diagnosis				
Less than weekly	1.00	0.485	1.00	0.583
Weekly or more	0.84 (0.52–1.37)		0.87 (0.52–1.44)	
Red meat consumption at diagnosis				
Less than weekly	1.00	**0.008**	1.00	**0.018**
Weekly or more	1.97 (1.15–3.38)		1.93 (1.08–3.45)	
Fish consumption at diagnosis				
Less than weekly	1.00	0.100	1.00	0.072
Weekly or more	0.70 (0.45–1.08)		0.65 (0.40–1.05)	

[a] Adjusted for Breslow thickness, age at diagnosis, sex, ulceration and microsatellitosis

Table 3

Combined multivariable Cox models for the independently-significant lifestyle factors, adjusting for clinicopathologic covariates

	Multivariate HR (95% CI)	*P* value
Age at diagnosis		
65 years or less	1.00	**0.012**
Greater than 65 years	1.86 (1.16–3.01)	
Breslow thickness		
1.01–2.00 mm	1.00	
2.01–4.00 mm	1.65 (0.97–2.81)	**0.003**
4.01 mm or more	2.81 (1.58–4.99)	
Anatomic location		
Head and neck	1.00	**0.002**
Trunk or limbs	0.39 (0.22–0.68)	
Hair color		
Brown or black	1.00	
Blonde	0.52 (0.29–0.94)	**0.009**
Red	0.44 (0.22–0.88)	
Fruit consumption at diagnosis		
Less than daily	1.00	**0.010**
At least daily	0.54 (0.34–0.86)	
Red meat consumption at diagnosis		
Less than weekly	1.00	**0.030**
Weekly or more	1.84 (1.02–3.30)	