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 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.

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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 toward 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