

ORIGINAL ARTICLE

Diet quality is associated with primary melanoma thickness

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Abstract

Background Patients' diets can influence the outcome of several common cancers, but the effect on melanoma prognosis is unknown.**Objective** To assess the association between quality of melanoma patients' prediagnosis diets and primary tumour thickness, the main prognostic indicator for melanoma.**Methods** We used baseline data from patients newly diagnosed with tumour stage Ib to IV cutaneous melanoma, with completed questionnaires about food intake in the past year and other factors. Diet quality was measured by the Healthy Eating Index (HEI) and melanoma thickness was extracted from histopathology reports. We estimated prevalence ratios (PR_{adj}) and 95% confidence intervals (CIs) adjusted for confounding factors using Poisson regression models to assess associations between HEI scores and melanoma thickness.**Results** Of 634 study patients, 238 (38%) had melanomas >2 mm thick at diagnosis. Patients with the highest HEI scores were significantly less likely to be diagnosed with thick melanoma than patients with lowest HEI scores (PR_{adj} 0.93, 95% CI 0.86–0.99) ($P_{\text{trend}} = 0.03$). There was no evidence of effect modification by age, sex, previous melanoma or comorbidities.**Conclusions** Melanoma thickness at diagnosis is significantly associated with quality of patients' diets before diagnosis.

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Conflict of interest

None declared.

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Introduction

The content of people's diets can affect their long-term health including risk of developing or dying from various cancers.^{1–4} A low-fat, high-fibre diet and low bodyweight may protect against progression of breast, prostate and colorectal cancers.^{5,6} Cutaneous melanoma, a relatively common cancer in white populations, can be fatal if diagnosed as a thick tumour.⁷ Whether diet quality affects disease course in melanoma survivors is unknown. One human study has assessed the association between melanoma patients' consumption of specific foods and their prognosis.⁸ It reported improved survival in patients eating fruit daily (hazard ratio, 0.54), and worse survival with eating red meat daily (hazard ratio, 1.84), but no effect of high intakes of fish or salad greens.⁸ No studies have assessed overall diet in relation to melanoma progression.

One reason for the dearth of such studies is the generally high survival of today's melanoma patients who tend to be diagnosed with thin tumours with excellent prognosis.⁹ However, despite these trends, melanoma mortality continues to rise in many countries¹⁰ due to older adults presenting with thick rapidly growing primary melanomas of nodular subtype.^{11,12} In the absence of prospective studies of diet with melanoma mortality as outcome, measured tumour thickness at diagnosis can serve as a surrogate for risk of mortality. Evidence of discretionary dietary factors that might modify the rapid growth of thick melanomas would be an important addition to clinical knowledge for public health benefit.

In a cohort of high-risk primary melanoma patients in Australia, we earlier reported the influence of dietary intake of long-chain omega-3 vs. omega-6 fatty acids on melanoma thickness at

diagnosis.¹³ Omega-3 fatty acids promote apoptosis and inhibit angiogenesis¹⁴ and can reduce invasiveness of melanoma cells *in vitro*,¹⁵ while omega-6 fatty acids may increase tumour invasiveness.¹⁶ We found that people with high intakes of meat, fish and fat – who thus consumed relatively high amounts of omega-3 and omega-6 fatty acids – were more likely to be diagnosed with thick rather than thin primary melanomas.¹³

We have now extended this study to assess the possible influence of the overall quality of patients' diets, measured by the Healthy Eating Index (HEI), on thickness of melanoma at diagnosis. The HEI measures how well habitual food and drink intakes adhere to the regularly updated Dietary Guidelines for Americans.¹⁷ Using the HEI allows the complex synergistic and cumulative effects of foods and their nutrient components to be studied,¹⁸ and since its introduction in 1995,¹⁹ many links between diet quality and reduced risk of chronic diseases have been shown across age and ethnic groups in the USA^{20–22} and elsewhere.^{23–26} Here, we hypothesized that melanoma patients who consume a recommended dietary pattern up to time of diagnosis present with thinner melanomas than those consuming less healthy diets.

Materials and methods

We used baseline data from a prospective study of patients in Queensland, Australia, newly diagnosed with tumour stage Ib to IV cutaneous melanoma, 2010–2014, ascertained from specialist public hospitals, private surgical clinics and pathology services, as detailed elsewhere.²⁷ In all, 1254 eligible patients (aged >16 years with no clinical signs of nodal spread at presentation) were invited to participate; 825 (66%) provided written, informed consent. We excluded 36 participants who were later found to have loco-regional disease at the time of diagnosis and 89 were deemed ineligible in the American Joint Committee on Cancer melanoma staging's 8th edition,²⁸ leaving 700 participants. At recruitment, participants completed a questionnaire regarding *inter alia*, age, sex, level of education, height and weight, frequency of skin checks, personal and family histories of melanoma and serious comorbidities (heart disease, diabetes and non-cutaneous cancer). Body mass index (BMI) was calculated (weight divided by height-squared). This study was approved by the Human Research Ethics Committees of the Metro South Hospital and Health Service (HREC/11/QPAH/470) and the QIMR Berghofer Medical Research Institute (P1305). All participants provided written informed consent.

Outcome

Tumour thickness (mm) of primary melanoma, tumour site (head or neck, trunk, upper limb, lower limb), presence of ulceration (yes, no), mitotic rate (per mm²) and melanoma subtype (superficial spreading melanoma, nodular, other, not classified) were extracted from histopathology reports.

Dietary assessment

At recruitment (on average 36 days (\pm 26) after diagnosis), patients also completed a 142-item semi-quantitative food frequency questionnaire (FFQ) adapted from the Nurses' Health Study^{29,30} and validated in an Australian population.^{31–33} They reported usual intakes of set amounts of each food item using nine categories, from 'never' to '4+ per day'. Additional information included intakes of specific breakfast cereals, cooking oils, butters, margarines, spreads and dietary supplements; frequency of eating fried food at home, in restaurants or fried take-away foods; and consumption of sugar and visible fat on meat. Average food intake (grams per day) was estimated by multiplying consumption frequencies (proportions of daily use) by the specified portion size in the FFQ. Average daily intakes of foods and nutrients were estimated using the Food Patterns Equivalents Database 2015–2016³⁴ and Australian food composition data, NUTTAB 2010,³⁵ respectively.

Calculation of the modified healthy eating index-2015

We used the HEI version aligned with the 2015–2020 Dietary Guidelines for Americans¹⁷ whose components correspond to key recommendations of the 2013 Australian Dietary Guidelines.³⁶ The HEI comprises nine recommended foods receiving high scores for consumption, and four foods to be consumed sparingly that receive high scores for low consumption.³⁷ The total of component scores ranges from 0 indicating non-adherence to 100 indicating perfect adherence to dietary guidelines. For each patient, we calculated scores for each HEI component (except sodium) following published methods^{17,37,38} and applying SAS codes (SAS Institute Inc., Cary, NC, USA) for FFQs from the National Cancer Institute³⁹ to the guideline-based food and nutrient intake data. As we did not ask about discretionary use of salt, we followed the approach used by Xie *et al* in scoring dietary sodium and based the scores on sex-specific deciles of sodium intake,⁴⁰ assigning lowest score to highest decile intake and highest score to the lowest. Finally, scores for each HEI component were summed to derive the modified HEI-2015 score (*modHEI-2015*), henceforth called the healthy eating index score (Table S1).

Statistical analysis

Thickness of primary melanomas was classified as 'thick' (>2 mm in depth) and 'thin to moderately thick' (\leq 2 mm). HEI scores were divided into tertiles, with adherence to dietary guidelines increasing from lowest (reference group) to highest. Chi-squared tests for nominal variables and ANOVA for continuous variables were used to assess associations between patient characteristics and melanoma thickness. We estimated prevalence ratios (and 95% confidence intervals) using unadjusted and adjusted Poisson regression models with robust error variance⁴¹ to demonstrate the association between HEI score and melanoma thickness. To test for linear trends, we assigned an

ordinal number from 1 (lowest) to 3 (highest tertile) and modelled this as a continuous variable. Our adjusted model included age (<55, 55–60 and >70), sex, frequency of skin checks (known to be associated with melanoma thickness,⁴² sun protection practices⁴³ and diet⁴⁴), socio-economic indicators (education and health sector where patient first presented) and energy intake (continuous).

In addition, we examined age, sex, past history of melanoma and serious comorbidities as potential effect modifiers by including a multiplicative term (tertiles of HEI score by these factors). We conducted sensitivity analyses with five additional multivariate models adjusting for the core factors listed above but replacing the two socio-economic indicators in each iteration with: number of sun protection measures usually practised; times spent outdoors, weekdays and weekends; lifestyle indicators (BMI, smoking and alcohol intake); personal and family history of melanoma and tumour characteristics (melanoma subtype, ulceration and mitotic rate). We repeated multivariate analysis excluding 74 patients who reported changing their diets within

2 years of index melanoma diagnosis. Finally, we identified dietary guideline components that were least and most complied with, by calculating component adherence scores (dividing patients' achieved score by maximum score and multiplying by 100 for each component). The median component per cent adherence was calculated for the lowest and highest healthy eating index score groups. Analyses were conducted in SAS v9.4.

Results

Of the 700 patients for study, we excluded 37 who did not complete a diet questionnaire, 18 with extreme energy intake values and 11 who answered <90% of the FFQ food items, leaving a final sample of 634. Median age was 65 years (range 22–89), 373 (59%) were male and 238 (38%) had melanomas >2 mm thick at diagnosis (Table 1). Compared with those with melanomas ≤2 mm, those with thicker tumours were significantly ($P < 0.05$) older, and more likely to be: male, treated in the public health sector and to have serious co-morbidity, but there was no difference in the frequency of skin checks (Table 1). As

Table 1 Patient and tumour characteristics by thickness of the primary melanoma

Patient and tumour characteristics	Total N = 634	Thickness		P-value†
		≤2 mm (%) N = 396	>2 mm (%) N = 238	
Patient characteristics				
Age at diagnosis, mean (±SD)	62 (±13)	61 (±13)	64 (±13)	0.002
Body mass index, mean (±SD)	28.3 (±5.4)	28.4 (±5.5)	28.1 (5.2)	0.65
Male sex, n (%)	373 (59)	213 (54)	160 (67)	0.0009
University or college degree, n (%)	129 (20)	82 (21)	47 (20)	0.27
Private health sector, n (%)	353 (56)	233 (59)	120 (50)	0.039
Skin checks by doctor ≥1/year, n (%)	311 (49)	194 (49)	117 (49)	0.58
Comorbidity‡, n (%)	301 (47)	175 (44)	126 (53)	0.033
Tumour characteristics				
Site of melanoma, n (%)				
Head and neck	134 (21)	72 (18)	62 (26)	0.061
Trunk	227 (36)	147 (37)	80 (34)	
Upper limb	132 (21)	91 (23)	41 (17)	
Lower limb	141 (22)	86 (22)	55 (23)	
Ulceration, n (%)	178 (28)	83 (21)	95 (40)	<0.0001
Mitotic rate >3 mm ² , n (%)	269 (43)	119 (31)	150 (63)	<0.0001
Subtype, n (%)				
SSM	253 (40)	191 (48)	62 (26)	<0.0001
Nodular	152 (24)	59 (15)	93 (39)	
Other§	106 (17)	67 (17)	39 (16)	
Not classified¶	123 (19)	79 (20)	44 (18)	
Median daily intake				
Ethanol (g), mean (±SD)	10.9 (±15.5)	10.2 (±14.5)	12.0 (±17.0)	0.172
Total energy intake (MJ), mean (±SD)	9.2 (±2.8)	9.0 (±2.6)	9.6 (±2.9)	0.011

†Chi-squared tests (categorical variables) and ANOVA (continuous).

‡Ever diagnosis of heart disease, diabetes, hypertension/stroke or cancers other than skin.

§Other: lentigo maligna (17.8%), desmoplastic (34.0%), nevoid (22.6%), spitzoid (4.7%), lentiginous (1.9%), acral lentiginous (7.6%) and mixed (11.3%).

¶Not classified: unable to classify (12.2%), not stated (87.0%) and other (0.8%).

Table 2 Prevalence ratios (and 95% CI) of thick melanomas (>2 mm) by tertile of modified Healthy Eating Index-2015 (*modHEI-2015*) scores

	Tertile 1 N = 212	Tertile 2 N = 214	Tertile 3 N = 208	P _{trend}
Mean <i>modHEI-2015</i> score, mean (sd)	53.3 (5.9)	66.1 (2.7)	77.1 (4.7)	
N (%) with thick (>2 mm) melanoma	95 (40)	75 (32)	68 (29)	
Unadjusted	1.00	0.93 (0.87, 0.99)	0.92 (0.86, 0.98)	0.011
Adjusted†	1.00	0.94 (0.88, 1.00)	0.93 (0.86, 0.99)	0.030

†Adjusted for age, sex, skin examination habits, education, health sector and energy intake.

expected, thicker melanomas had significantly more ulceration and mitoses, and were more likely of nodular subtype (Table 1).

Median HEI score among study patients was 65.7 (range 33.7–90.4). Scores increased with age and were higher among females and those treated in the private sector (all $P < 0.001$), with no difference according to skin examination frequency or presence of co-morbidity (Table S2). Melanoma thickness decreased significantly with increasingly healthy dietary patterns after adjustment for confounding factors including frequency of skin examinations, such that those patients with the highest HEI scores were significantly less likely to be diagnosed with a thick (>2 mm) melanoma than the third of patients with the lowest scores (PR_{adj} 0.93 (95% CI 0.86, 0.99) (P_{trend} = 0.03) (Table 2). There was no evidence of effect modification by age, sex, previous melanoma or comorbidities. Results remained unchanged after several sensitivity multivariate analyses replacing socioeconomic indicators with other potential confounders and after excluding those who changed their diet within 2 years of completing the FFQ.

On comparing the range of adherence for specific dietary components between those in lowest and highest tertiles of HEI score (Table 3), the median per cent adherence of melanoma patients in the lowest tertile was low ($\leq 50\%$ of maximum score) for the recommended components of Total Fruit, Greens and Beans, Whole Grains and Fatty Acids, and for Sodium and Saturated fats as components to eat sparingly. In contrast, among melanoma patients in the highest HEI tertile, median adherence was low ($< 50\%$ of maximum scores) for Fatty Acids only; moderate (50% to $< 80\%$) for Greens and Beans, Whole Grains, Dairy and Sodium; and high ($\geq 80\%$) for all other components. All study patients achieved maximum scores for Total Protein Foods and Refined Grains.

Discussion

We have assessed the relation between melanoma patients' diet quality before diagnosis and the thickness of their primary

Table 3 Median component per cent adherence, lowest vs. highest tertile

Component	Tertile 1 Median = 53%	Tertile 3 Median = 77%
Adequacy		
Total vegetables	78%	100%
Greens and beans	19%	51%
Total fruits	46%	100%
Whole fruits	74%	100%
Whole grain	30%	65%
Dairy	55%	69%
Total protein foods	100%	100%
Seafood and plant proteins	67%	100%
Fatty acids	2%	34%
Moderation		
Sodium	30%	70%
Refined grains	100%	100%
Saturated fats	32%	82%
Added sugars	82%	100%

tumour as a way of addressing the larger issue of influence of patients' diets on melanoma outcome. We used dietary patterns to capture the complexity of nutrients in patients' overall diets, and measured these patterns with an index that positively weights high consumption of foods recommended in a healthy diet, and low consumption of foods to be consumed sparingly.³⁷ We found that diet quality prediagnosis was inversely associated with thickness of melanoma at diagnosis, with the patients in the top tier of diet quality being 7% less likely than those in the lowest tier to be diagnosed with melanoma > 2 mm thick vs. ≤ 2 mm, after accounting for known confounders. Notably, we adjusted for frequency of skin checks (both by doctor and self) because frequent skin checks are associated with thinner melanomas, as well as higher education and other positive health-related behaviours like not smoking and sun protection/avoidance, all of which are associated with eating habits.

On assessing compliance with dietary components, we found that those with poorer diets had lower intakes of recommended foods, namely Total Fruits, Greens and Beans, Whole Grains, Seafood and Plant Proteins, and higher intakes of Sodium and Saturated Fats that should be eaten sparingly. All patients had low compliance (below 50%) for the Fatty Acids component but full compliance (100%) for Total Protein Foods, consistent with a National Health Survey in 2011 showing almost all Australians (99%) meet recommended protein intake,⁴⁵ likely from animal-based foods such as red meat and poultry that are highly consumed^{146,47} but not fish (also a source of omega-3 fatty acids), as previously noted.¹³ Thus, all patients in this study, particularly those with the poorest diet quality, could benefit by substituting fish, as well as beans, legumes, nuts and seeds (sources of mono- and polyunsaturated fats) for some of the highly consumed red

meat and poultry (sources of saturated fat), in order to improve compliance with the Saturated Fat and Fatty Acid components while adhering to the Total Protein Foods component.

Our findings broadly agree with those of the previous US study of specific foods and melanoma prognosis showing better survival in patients who, at diagnosis, ate fruit every day, and worse survival in patients eating red meat every day.⁸ However, the previous study's dietary assessment was extremely limited: patients were asked only about consumption of red meat, fish, green salad and fruit on a 4-level scale, daily to never, because the primary aim was to examine modifiable lifestyle factors and melanoma survivorship.⁸ Thus, our study substantially extends knowledge in this field, presenting detailed assessment of the whole of patients' diets at time of diagnosis, and adjusting for an extensive list of possible confounding factors. Our results suggest that eating a healthy diet including seafood, plant proteins, green vegetables, all with well-established anticarcinogenic actions such as anti-inflammatory and antioxidant effects,^{1–4} together with low intakes of less healthy nutritional components, especially sodium and saturated fats, likely played a role in healthy-eating patients' decreased melanoma thickness at diagnosis.

One of our greatest limitations was the use of melanoma thickness in lieu of melanoma survival as the prognostic outcome in order to gain sufficient statistical power to assess the effects of diet quality in melanoma survivors. We also acknowledge the limitations in using self-reported dietary information with its attendant potential misclassification of patients' intakes, but we note that this misclassification would be non-differential and reduce power to detect difference and would not introduce bias to results. We are unable to infer causality because prediagnosis diet patterns and thickness were measured at the same time. On the other hand, our study has many strengths including novelty; extensive analyses to minimize the effect of other possible explanatory factors like frequent skin checks and our demonstration that the findings were not affected by patients changing their diets. As well, our detailed investigation of dietary components of a healthy diet allows dermatologists and others to give practical advice to high-risk patients in similar settings, with the caveat that our results may not apply to patients in countries with different dietary patterns. Our assessment of the level of compliance with recommended intakes also shows that people at risk of melanoma who have poorer quality diets could be particularly encouraged to increase their consumption of green vegetables, whole grain foods and foods rich in fatty acids such as fish and nuts.

In conclusion, we have shown that melanoma patients who were consuming healthy diets in the year before diagnosis were less likely to present with thick (>2 mm) melanomas than patients whose diet was of poor quality, independent of their frequency of skin checks and of other beneficial behaviours. Large longitudinal studies in other settings could confirm and advance

these results by assessing the association of diet quality before diagnosis with recurrence-free survival rather than tumour thickness, while accounting for disease stage and management and socioeconomic factors.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Components and scoring criteria for the modified Healthy Eating Index-2015 (*modHEI*-2015)

Table S2. Patient and tumour characteristics at baseline by tertile of modified Healthy Eating Index-2015 (*modHEI*-2015) scores