British Journal of Nutrition, page 1 of 7
doi:10.1017/S000711451700006X

Glycaemic index, glycaemic load and risk of cutaneous melanoma in a population-based, case–control study

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(Submitted 6 October 2016 – Final revision received 16 December 2016 – Accepted 2 January 2017)

Abstract

Glycaemic index (GI) and glycaemic load (GL) are indicators of dietary carbohydrate quantity and quality and have been associated with increased risk of certain cancers and type 2 diabetes. Insulin resistance has been associated with increased melanoma risk. However, GI and GL have not been investigated for melanoma. We present the first study to examine the possible association of GI and GL with melanoma risk. We carried out a population-based, case–control study involving 380 incident cases of cutaneous melanoma and 719 age- and sex-matched controls in a northern Italian region. Dietary GI and GL were computed for each subject using data from a self-administered, semi-quantitative food frequency questionnaire. We computed the odds ratio (OR) for melanoma according to quintiles of distribution of GL and GL among controls. A direct association between melanoma risk and GL emerged in females (OR 2·38; 95 % CI 1·25, 4·52 for the highest *v.* the lowest quintile of GL score, $P_{\text{for trend}}$ 0·070) but not in males. The association in females persisted in the multivariable analysis after adjusting for several potential confounders. There was no evidence of an association between GI and melanoma risk. GL might be associated with melanoma risk in females.

Key words: **Glycaemic index: Glycaemic load: Melanoma: Case–control studies: Epidemiology**

The dietary glycaemic index (GI) of a carbohydrate-containing food is an indicator of its effect on postprandial blood glucose response, compared with the response elicited by administration of glucose with equivalent carbohydrate content. Epidemiological studies suggest a possible role of dietary GI in increasing the risk of cancer at some sites[1–3], and there appears to be a biological plausibility for such an association[4–6]. GI has been found to modulate insulin sensitivity[7]. Low-GI diets compared with high-GI diets may improve glycaemic control, leading to lower insulin output and inflammatory responses and possibly a lower risk of several chronic diseases, including cancer[2,8,9]. GI varies considerably for different foods depending on several factors such as the amounts and types of carbohydrates and the cooking method. The product of a food's GI and its total carbohydrate content is represented by another indicator called the glycaemic load (GL). GL accounts not only for carbohydrate quality but also for quantity[10]. Findings from the Italian component (European Prospective Investigation into Cancer and Nutrition (EPIC)-Italy) of the EPIC initiative have suggested that GL and carbohydrate intake are positively associated with breast cancer and colon cancer risk[3,11].

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; GI, glycaemic index; GL, glycaemic load; SFA; saturated fatty acids; FFQ, food frequency questionnaire; OR, odds ratio; CI, confidence interval.

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The risk of malignant melanoma, which has been associated with ultraviolet exposure, atypical nevi and genetic factors, has also been found to be linked to dietary factors[12–14]. In a previous study, we found an association between carbohydrate intake and melanoma risk[15], and insulin resistance has been suggested to occur in melanoma patients[16]. However, no study appears to have evaluated the association between GI and GL and risk of melanoma. We sought to address this question using a population-based, case–control study in an Italian community.

Methods

Details of our case–control study on dietary risk factors for cutaneous melanoma in the population of five provinces of the Emilia Romagna region, northern Italy (population about 3 000 000), have been provided elsewhere[17–19]. In brief, during 2005–2006, we attempted to recruit all patients with newly diagnosed cutaneous malignant melanoma residing in the provinces of Bologna, Ferrara, Modena, Parma and Reggio Emilia and attending the local dermatological clinics. Inclusion criteria were a histologically based recent diagnosis of cutaneous melanoma without clinical evidence of metastasis. A total of 572 eligible patients were contacted by their dermatologists to participate in the study, and 394 (68·9 %) agreed to participate. In these subjects, the melanomas had a median Breslow's thickness of 0·61 mm, with no substantial differences between males and females (0·179 by non-parametric *K*-sample test on the equality of medians). All patients had undergone only surgical treatment for the disease. Each subject was administered lifestyle and food frequency questionnaire (FFQ) (see below) during a routine visit at the beginning of follow-up for their disease. The questionnaires could be returned at the following visit or sent back to the Research Center for Environmental, Genetic and Nutritional Epidemiology of Modena and Reggio Emilia University. We randomly selected 2825 potential controls matched to cases for sex, year of birth (±5 years) and province of residence from the Emilia Romagna region National Health Service directory (mandatory for all Italian residents), and we mailed lifestyle and FFQ, a description of the study and a pre-paid return envelope to them. A total of 747 (26·4 %) potential controls agreed to participate in the present study and returned the questionnaires. In all, fourteen cases and twenty-eight controls were excluded from subsequent analysis because of incompleteness of data or extreme values (ratio of total energy intake:calculated basal metabolic rate lower than the 0·5th percentile or higher than the 99·5th percentile) derived from the FFQ. All participants gave their written informed consent before enrolment.

Dietary assessment

We investigated subjects' usual diet during the past 12 months with a validated, semi-quantitative FFQ designed to capture eating behaviours in Italy, specifically developed as part of the EPIC study for the northern Italian population[20,21]. The EPIC questionnaire was designed to be self-administered, and was checked by trained personnel after compilation. Participants were asked to respond to 248 questions about 188 different food items, including seasonal foodstuffs, and to indicate the number of times a given item was consumed (per day, week, month or year), from which the absolute frequency of consumption of each item was calculated. The quantity of food consumed was assessed by selecting an image of a food portion or by selecting a predefined standard portion when no image was available. The food items were then linked, using specially designed software[20], to the Italian Food Tables[21] to obtain estimates of daily intake of macronutrients and micronutrients plus energy. GI of food items containing available carbohydrates were obtained from the Italian Glycemic Index Table (managed by the Department of Food Sciences, University of Parma, based on direct analysis of main carbohydrate food sources in Italy), which contains about 150 food products covering >90 % of the carbohydrate intake of people living in Italy. When a food consumed was not present in the table, we used the GI value published elsewhere (GI international tables[22] and www.glycemicindex.com[23]). We computed the daily average dietary GI for each participant as the sum of the GI of each food item consumed, multiplied by the average daily amount consumed and the percentage of carbohydrate content, all divided by the total daily carbohydrate intake. The daily average dietary GL was calculated similarly except that there was no division by total carbohydrate intake. Total carbohydrate intake (g/d) was calculated using the Food Composition Database for Epidemiologic Research in Italy published by the European Oncology Institute[24].

Additional variables

Each participant provided information on demographic characteristics (place and date of birth, province of residence, marital status, education), weight and height, phenotypic characteristics (eye, hair and skin colour), sunburn history (never, first before 18 years of age, first after 18 years of age) and skin reaction to sunlight exposure (speed of tan and tendency to burn). We classified eye colour into light (blue/green), light brown and dark (brown/black) categories. Hair colour was classified as blond, red, light brown or dark brown/black at 20 years, and skin colour was classified as white, light brown, brown/olive or dark brown/ebony. On the basis of these categories, each subject was assigned to a phototype using the Fitzpatrick phototyping scale[25]. We computed BMI as weight/height^2 (kg/m^2) and categorised subjects as normal weight, overweight or obese according to commonly used definitions[26].

Statistical analysis

Analyses were conducted overall and stratified by sex. We computed the odds ratio (OR) for melanoma according to quintiles of distribution (among controls) of GI, GL and total carbohydrates, sugars and starch after adjusting for energy intake using the Willett nutrient residual method[27]. OR and 95 % CI were computed using conditional logistic regression analysis, adjusting for education (four categories), BMI (continuous), phototype (four categories), skin sensitivity to sun exposure (five categories), sunburns history (three categories) and dietary intake of total energy (continuous), vitamin C (continuous), vitamin D (continuous), saturated fatty acids (SFA) (continuous) and fibre (continuous). Trends

in the associations between GI and GL scores and risk were assessed by computing *P* values based on their values as continuous variables in conditional logistic regression models[28]. Finally, we modelled the association between GI and GL scores and risk of cutaneous melanoma using restricted cubic splines, computed with mkspline and xblc commands of Stata 14 statistical software (StataCorp LP, 2015)[29]. We selected the optimal number of knots according to Akaike's information criterion and used the knot-placement method recommended by Harrell[30], which led us to place three knots, at the 10th, 50th and 90th percentiles.

Results

A total of 380 cases (175 men and 205 women, aged 58 ± 16 and 53 ± 15 years, respectively) and 719 age-, sex- and province of residence-matched controls were included in the analysis. Demographic and clinical characteristics of cases and controls are reported in Table 1. Educational attainment and marital status were similar in cases and controls, whereas cases tended to have more fair skin types, high tendency to burn and were more likely to report a history of sunburns, ever and particularly after 18 years. Dietary characteristics related to the amount of carbohydrates, summarised in Table 2, showed that cases tended to have slightly higher GI and slightly lower total sugar intakes compared with controls and a higher intakes of starch. GI and GL were positively correlated (*r* 0·44; 95 % CI 0·39, 0·48).

Table 3 presents the unadjusted and adjusted OR for melanoma and corresponding 95 % CI according to quintiles of GI, GL and other dietary carbohydrates for the overall sample. The results suggest a positive association between GL and melanoma risk with OR 1·53 (95 % CI 1·02, 2·30) after comparison between the highest (Q5) and the lowest (Q1) quintiles in the unadjusted model, which was attenuated and less precise in the adjusted model (OR 1·35; 95 % CI 0·80, 2·27, Q5 *v.* Q1). No positive association emerged between GI and melanoma risk. The results also suggest that a higher risk of melanoma is associated with higher intakes of starch (adjusted OR 1·88; 95 % CI 1·05, 3·40, Q5 *v.* Q1).

Table 4 summarises analyses stratified by sex, adjusting for all covariates or only for energy and two dietary factors previously found to be associated with disease risk in our study population, vitamins C and D. The association between GL and melanoma

Table 1. Characteristics of the study participants by case–control status (Numbers and percentages)

	Cases		Controls		
	n	%	*n*	%	*P**
Subjects	380	34·6	719	65·4	
Sex					
Male	175	46·1	319	44·4	
Female	205	53·9	400	55·6	
Age (years)					
<50	146	38·4	272	37·8	
≥50	234	61·6	447	62·2	
Education					
Elementary or less	91	24·1	170	23·8	
Middle school	95	25·1	176	24·6	
High school	136	36·0	266	37·2	
College or more	56	14·8	103	14·4	0·983
Marital status					
Married	257	67·6	493	68·7	
Unmarried/single	68	17·9	103	14·3	
Divorced	23	6·0	48	6·6	
Widowed	31	8·2	74	10·3	
Unknown	1	0·3	1	0·1	0·461
BMI (kg/m^2)					
<25	195	51·3	351	48·8	
≥25 to <30	133	35·0	287	39·9	
≥30	52	13·7	81	11·3	0·307
Phototype†					
I	105	27·6	109	15·2	
II	136	35·8	238	33·1	
III	122	32·1	312	43·4	
IV	17	4·5	60	8·3	<0·001
Sunburn history					
Never	182	47·9	452	62·9	
Before 18 years	108	28·4	164	22·8	
After 18 years	90	23·7	103	14·3	<0·001
Skin sensitivity to sun exposure					
High tendency to burn and never tan	21	5·5	22	3·1	
High tendency to burn and moderate tan	117	30·8	131	18·2	
Moderate tendency to burn and gradual tan	160	42·1	357	49·7	
No tendency to burn and golden tan	65	17·1	149	20·7	
No tendency to burn and intense tan	17	4·5	60	8·3	<0·001

* *P* values from χ^2 tests.

† Phototype I, eyes/hair/skin light, high tendency to burn and never/moderate tan; phototype II, eyes/hair/skin light, moderate tendency to burn and gradual tan, or eyes/hair/skin brown high tendency to burn and moderate tan; phototype III, eyes/hair/skin brown, moderate/no tendency to burn and gradual/golden tan; phototype IV, no tendency to burn and intense tan.

Table 2. Dietary characteristics of the study participants by case–control status (Mean values and standard deviations)

	Cases		Controls		
	Mean*	SD	Mean*	SD	*P*†
Glycaemic index	52·0	3·2	51·7	3·2	0·069
Glycaemic load	124·9	24·1	122·1	24·1	0·389
Total carbohydrates (g/d)	239·7	95·0	235·5	96·1	0·483
Total sugars (g/d)	98·4	45·4	103·9	53·1	0·088
Starch (g/d)	141·1	69·6	131·4	65·3	0·022

* Daily dietary average.
† *P* values from two sample *t* tests.

Table 3. Overall OR for cutaneous melanoma according to quintiles of daily average of glycaemic load, glycaemic index and total carbohydrates, total sugars and starch intakes†
(Odds ratios and 95% confidence intervals; cases/controls, medians)

	Quintiles								
	Q1	Q2		Q3		Q4		Q5	
All subjects (380/719 cases/controls)	OR	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}*
Glycaemic load										
Cases/controls	61/144	69/144		76/144		80/144		94/143		
Median	92·0	112·9		122·0		132·1		149·7		
OR‡	1·00	1·19	0·79, 1·80	1·28	0·84, 1·95	1·40	0·93, 2·12	1·53	1·02, 2·30	0·074
OR§	1·00	1·16	0·74, 1·83	1·26	0·78, 2·02	1·28	0·79, 2·07	1·35	0·80, 2·27	0·450
Glycaemic index										
Cases/controls	71/144	68/144		74/144		80/144		87/144		
Median	47·7	50·1		51·7		53·2		55·7		
OR‡	1·00	0·90	0·60, 1·36	0·97	0·65, 1·45	1·08	0·72, 1·62	1·16	0·77, 1·76	0·127
OR§	1·00	0·78	0·51, 1·22	0·85	0·55, 1·31	0·88	0·56, 1·37	0·88	0·55, 1·42	0·802
Total carbohydrates (g/d)										
Cases/controls	63/144	67/144		80/144		80/144		90/143		
Median (g/d)	185·5	219·6		236·9		253·8		281·7		
OR‡	1·00	1·09	0·71, 1·68	1·32	0·87, 1·99	1·31	0·86, 1·99	1·43	0·95, 2·15	0·090
OR§	1·00	1·04	0·66, 1·64	1·26	0·80, 1·99	1·28	0·80, 2·03	1·26	0·77, 2·07	0·319
Total sugars (g/d)										
Cases/controls	81/144	83/144		89/144		72/144		55/143		
Median (g/d)	62·4	83·6		101·0		118·0		147·7		
OR‡	1·00	1·01	0·68, 1·50	1·09	0·73, 1·62	0·89	0·59, 1·35	0·67	0·43, 1·03	0·021
OR§	1·00	1·06	0·70, 1·62	1·29	0·83, 1·99	0·99	0·62, 1·59	0·76	0·47, 1·25	0·180
Starch (g/d)										
Cases/controls	55/144	65/144		60/144		97/144		103/143		
Median (g/d)	80·4	112·1		131·0		149·9		181·5		
OR‡	1·00	1·17	0·75, 1·84	1·11	0·70, 1·73	1·75	1·14, 2·69	1·93	1·26, 2·97	<0·001
OR§	1·00	1·21	0·73, 2·00	1·08	0·64, 1·81	1·69	0·99, 2·87	1·88	1·05, 3·40	0·008

* *P* for linear trend based on continuous values of intake.
† Lowest quintile (Q1) as the referent category.
‡ Unadjusted analysis.
§ Adjusted for intakes of SFA, vitamin C, vitamin D, fibre and total energy, phototype, skin sensitivity to sun exposure, sunburns history, BMI and education.

risk was observed among females only (fully adjusted OR 2·40; 95 % CI 1·23, 4·70, Q5 *v.* Q1), although the OR across the GL quintiles did not increase linearly. No evidence of any association with GI emerged in either sex. Total carbohydrate intake was also associated with melanoma risk only in females (fully adjusted OR 2·18; 95 % CI 1·16, 4·10, Q5 *v.* Q1), whereas the inverse association with sugar intake was observed only in men (OR 0·37; 95 % CI 0·17, 0·80, Q5 *v.* Q1). There was suggestion of a positive association of melanoma risk with starch intake for men (OR 1·99; 95 % CI 1·04, 3·80, Q5 *v.* Q1) and for women (OR 2·00; 95 % CI 1·11, 3·61, Q5 *v.* Q1), although these OR were attenuated and less precise in fully adjusted analyses. Stratified analyses for BMI, age and phototype did not reveal differences (data not shown).

Plots estimating the association between odds of being a case and GI and GL values, produced using regression spline analysis, appeared to confirm a direct association between GL and melanoma risk in females (Fig. 1).

Discussion

Although cutaneous melanoma has generally not been attributed to lifestyle factors apart from recreational or occupational ultraviolet exposure, our study is in line with growing epidemiological

Table 4. Adjusted OR for melanoma in sex-stratified analysis†
(Adjusted odds ratios and 95 % confidence intervals)

	Quintiles									
	Q1	Q2		Q3		Q4		Q5		
	OR	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}*
Glycaemic load										
Males										
Cases/controls	41/78		34/75		33/55		31/54		36/57	
OR‡	1·00	0·90	0·53, 1·53	1·13	0·63, 2·04	1·20	0·67, 2·15	1·11	0·64, 1·93	0·485
OR§	1·00	0·82	0·47, 1·42	1·07	0·58, 1·97	1·05	0·57, 1·93	0·86	0·47, 1·57	0·808
Females										
Cases/controls	20/66		35/69		43/89		49/90		58/86	
OR‡	1·00	1·88	0·96, 3·66	1·67	0·88, 3·14	1·91	1·02, 3·59	2·38	1·25, 4·52	0·070
OR§	1·00	2·08	1·04, 4·14	1·77	0·92, 3·40	1·91	0·99, 3·66	2·40	1·23, 4·70	0·111
Glycaemic index										
Males										
Cases/controls	34/72		32/62		36/65		35/64		38/56	
OR‡	1·00	1·03	0·56, 1·92	1·02	0·57, 1·84	1·16	0·64, 2·10	1·31	0·70, 2·47	0·493
OR§	1·00	1·02	0·54, 1·93	0·91	0·50, 1·66	1·02	0·56, 1·88	1·11	0·58, 2·14	0·967
Females										
Cases/controls	37/72		36/82		38/79		45/80		49/87	
OR‡	1·00	0·81	0·46, 1·41	0·92	0·53, 1·61	1·00	0·57, 1·75	1·06	0·62, 1·84	0·154
OR§	1·00	0·79	0·45, 1·40	0·86	0·49, 1·51	0·93	0·53, 1·65	0·88	0·49, 1·56	0·428
Total carbohydrates (g/d)										
Males										
Cases/controls	81/40		67/34		66/36		43/36		62/29	
OR‡	1·00	1·04	0·58, 1·86	1·10	0·63, 1·92	1·67	0·93, 3·00	0·89	0·50, 1·60	0·554
OR§	1·00	0·97	0·53, 1·77	1·00	0·56, 1·78	1·52	0·83, 2·81	0·71	0·38, 1·32	0·868
Females										
Cases/controls	63/23		77/33		78/44		101/44		81/61	
OR‡	1·00	1·20	0·63, 2·29	1·67	0·89, 3·13	1·24	0·66, 2·33	2·13	1·16, 3·91	0·069
OR§	1·00	1·21	0·63, 2·35	1·68	0·88, 3·23	1·24	0·65, 2·39	2·18	1·16, 4·10	0·073
Total sugars (g/d)										
Males										
Cases/controls	102/61		65/36		52/37		51/29		49/12	
OR‡	1·00	0·91	0·54, 1·54	1·12	0·66, 1·92	0·91	0·51, 1·62	0·39	0·19, 0·79	0·036
OR§	1·00	0·88	0·51, 1·50	1·16	0·66, 2·05	0·93	0·49, 1·74	0·37	0·17, 0·80	0·051
Females										
Cases/controls	42/20		79/47		92/52		93/43		94/43	
OR‡	1·00	1·23	0·64, 2·36	1·21	0·63, 2·32	1·02	0·52, 2·00	0·95	0·50, 1·83	0·227
OR§	1·00	1·33	0·68, 2·58	1·36	0·70, 2·65	1·26	0·62, 2·55	1·27	0·63, 2·54	0·897
Starch (g/d)										
Males										
Cases/controls	61/23		63/31		62/21		55/44		78/56	
OR‡	1·00	1·42	0·69, 2·91	0·94	0·45, 21·94	2·25	1·14, 4·43	1·99	1·04, 3·80	0·020
OR§	1·00	1·29	0·62, 2·69	0·80	0·37, 1·73	1·85	0·89, 3·81	1·60	0·79, 3·24	0·173
Females										
Cases/controls	83/32		81/34		82/39		89/53		65/47	
OR‡	1·00	1·05	0·58, 1·87	1·23	0·69, 2·18	1·48	0·85, 2·57	2·00	1·11, 3·61	0·005
OR§	1·00	0·95	0·52, 1·72	1·07	0·59, 1·94	1·27	0·71, 2·27	1·63	0·86, 3·12	0·052

* *P* for linear trend based on continuous values of intake.
† Lowest quintile (Q1) as the referent.
‡ Adjusted for vitamin C, vitamin D and total energy intakes.
§ Adjusted for intakes of SFA, vitamin C, vitamin D, fibre and total energy, phototype, skin sensitivity to sun exposure, sunburns history, BMI and education.

evidence suggesting a role of dietary factors in disease aetiology[12–15,17–19,31–34]. In the present investigation, apparently the first to evaluate an association of melanoma with GI and GL, we identified an association of GL with disease risk, although only in females and not always with a consistent trend. The observation of an association between dietary factors and melanoma risk only in females is not a new finding, as it has already been observed in all previous studies carried out in this study population[15,19,32] except one[18]. In interpreting these results, it must be considered that GL but not GI takes into account the amount of carbohydrate consumed in addition to qualitative factors such the concomitant intake of carbohydrates, fats and proteins, the processing of foods, meal preparation and serving temperature. Therefore, dietary GL is a more sensitive measure of postprandial glycaemia and insulin demand than dietary GI[35,36]. If melanoma risk is related to the overall insulin demand, it could be expected to be more strongly related to dietary GL than to dietary GI, consistent with what we observed. Our findings can be interpreted in light of previous studies that have found an association between GL, GI and risk of different cancers[2,3,37,38]. Some studies have found the association with disease risk to be stronger for, or exclusive to, GL compared with GI[39–41].

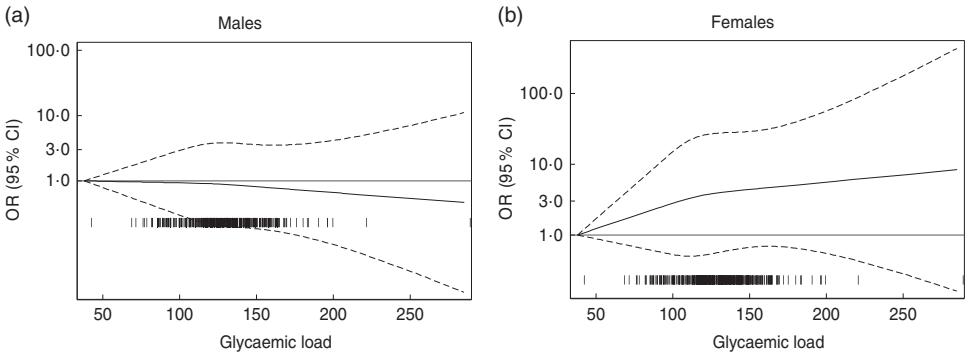

Fig. 1. Restricted cubic spline regression analysis of the odds of being a case according to the glycaemic load score, adjusting for SFA, vitamin C, vitamin D, fibre and total energy intakes, phototype, skin sensitivity to sun exposure, sunburns history, BMI and education. – – – –, 95 % confidence limits. Reference line at 1·0.

The pathophysiological mechanism that would link GI or GL to the aetiology of melanoma is still unknown. Gogas *et al.*[42] suggested a possible role of leptin in melanoma development. Leptin levels are directly associated with obesity, insulin levels and female sex[43,44], which may explain our findings of an increased risk of melanoma in females only. This sex-specific effect was also not unexpected on the basis of previous results in this study sample, as diet quality and vitamin C intake had shown an inverse association with disease risk that was largely restricted to females[19,32], already suggesting a potential effect modification by sex.

There is growing evidence supporting an association of dietary indices such as GL and GI with cancer risk at some sites[1,2,37,45,46]. The observation of a possible association of the disease with metabolic syndrome and altered insulin sensitivity[16] and, in our study population, of an inverse association between soluble carbohydrate intake and melanoma risk, particularly in females[15], add some plausibility to an association of GI and/or GL with melanoma risk.

Our study has certain limitations. The FFQ was not originally designed to estimate dietary GI and GL, although it carefully assessed total carbohydrate and energy intakes. In particular, GI and GL estimated through the EPIC FFQ may not accurately reflect the glycaemic effects of consuming mixed dishes as compared with individual food items. Another study limitation is the reduced statistical precision of the risk estimates for some subgroups, as shown by the wide CI. We also recognised that the study findings should be further assessed in studies with cohort designs to overcome the general limitations of case–control investigations.

The study also has strengths. Both selection and recall bias are unlikely, as diet was not generally regarded as a risk factor for melanoma, and we controlled for many potential confounders in the analyses. We also note that in our population the GI score distribution was comparable with that observed in other surveys conducted in the Italian population, whereas the GL score distribution was slightly lower[47].

In conclusion, we observed an association between GL and melanoma risk in an Italian population that was limited to females, although the possibility of unmeasured confounding cannot be ruled out. Further studies are warranted to fully elucidate the role of GL and related dietary factors in predicting risk of melanoma in humans, as well as to identify the reasons limiting this association to females.

Acknowledgements

Financial support for this study was provided by the Local Health Unit of Reggio Emilia – Italy (M. V.), the Italian League against Cancer – LILT Reggio Emilia Section (M. V.), Modena Policlinico Hospital and Modena Local Health Unit (M. V. and G. P.), and the US National Institute of Health (C. M. C., grant no. NIH-CA16042). All these funders had no role in the design, analysis or writing of this article.

M. V., C. M. and G. P. designed the original study; M. M., C. M. C., F. B., S. S. and C. A. analysed and interpreted the data and drafted the article. C. M. and M. V. recruited controls and collected their data. F. B., C. A., S. S. and V. K. prepared the FFQ and the associated nutrient and energy database and computed the glycaemic index of food items. C. F., F. F., C. L., C. R., G. A., A. L., L. V., A. V., C. P., C. F., P. A. F., E. D. and G. P. enrolled melanoma patients and collected their clinical, lifestyle and dietary data. All the authors read and approved the final version of the manuscript.

The authors declare that there are no conflicts of interest.

References

1. Melkonian SC, Daniel CR, Ye Y, *et al.* (2016) Glycemic index, glycemic load, and lung cancer risk in non-Hispanic whites. *Cancer Epidemiol Biomarkers Prev* **25**, 532–539.
2. Mullie P, Koechlin A, Boniol M, *et al.* (2016) Relation between breast cancer and high glycemic index or glycemic load: a meta-analysis of prospective cohort studies. *Crit Rev Food Sci Nutr* **56**, 152–159.
3. Sieri S, Krogh V, Agnoli C, *et al.* (2015) Dietary glycemic index and glycemic load and risk of colorectal cancer: results from the EPIC-Italy study. *Int J Cancer* **136**, 2923–2931.
4. McKeown-Eyssen G (1994) Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiol Biomarkers Prev* **3**, 687–695.
5. Fuchs MA, Sato K, Niedzwiecki D, *et al.* (2014) Sugar-sweetened beverage intake and cancer recurrence and survival in CALGB 89803 (Alliance). *PLOS ONE* **9**, e99816.
6. Aranceta Bartrina J & Perez Rodrigo C (2013) [Association between sucrose intake and cancer: a review of the evidence]. *Nutr Hosp* **28**, Suppl. 4, 95–105.
7. Jenkins DJ, Wolever TM, Taylor RH, *et al.* (1981) Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr* **34**, 362–366.

8. Barclay AW, Petocz P, McMillan-Price J, *et al.* (2008) Glycemic index, glycemic load, and chronic disease risk – a meta-analysis of observational studies. *Am J Clin Nutr* **87**, 627–637.
9. Choi Y, Giovannucci E & Lee JE (2012) Glycaemic index and glycaemic load in relation to risk of diabetes-related cancers: a meta-analysis. *Br J Nutr* **108**, 1934–1947.
10. Foster-Powell K, Holt SH & Brand-Miller JC (2002) International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr* **76**, 5–56.
11. Romieu I, Ferrari P, Rinaldi S, *et al.* (2012) Dietary glycemic index and glycemic load and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Am J Clin Nutr* **96**, 345–355.
12. Murzaku EC, Bronsnick T & Rao BK (2014) Diet in dermatology: part II. Melanoma, chronic urticaria, and psoriasis. *J Am Acad Dermatol* **71**, 1053 e1–1053 e16.
13. de Waure C, Quaranta G, Gualano MR, *et al.* (2015) Systematic review of studies investigating the association between dietary habits and cutaneous malignant melanoma. *Public Health* **129**, 1099–1113.
14. Miura K & Green AC (2015) Dietary antioxidants and melanoma: evidence from cohort and intervention studies. *Nutr Cancer* **67**, 867–876.
15. Vinceti M, Pellacani G, Malagoli C, *et al.* (2005) A population-based case-control study of diet and melanoma risk in northern Italy. *Public Health Nutr* **8**, 1307–1314.
16. Antoniadis AG, Petridou ET, Antonopoulos CN, *et al.* (2011) Insulin resistance in relation to melanoma risk. *Melanoma Res* **21**, 541–546.
17. Vinceti M, Malagoli C, Iacuzio L, *et al.* (2013) Serum fatty acids and risk of cutaneous melanoma: a population-based case-control study. *Dermatol Res Pract* **2013**, 659394.
18. Vinceti M, Malagoli C, Fiorentini C, *et al.* (2011) Inverse association between dietary vitamin D and risk of cutaneous melanoma in a northern Italy population. *Nutr Cancer* **63**, 506–513.
19. Malagoli C, Malavolti M, Agnoli C, *et al.* (2015) Diet quality and risk of melanoma in an Italian population. *J Nutr* **145**, 1800–1807.
20. Pala V, Sieri C, Palli D, *et al.* (2003) Diet in the Italian EPIC cohorts: presentation of data and methodological issues. *Tumori* **89**, 594–607.
21. Salvini S, Parpinel M & Gnagnarella P (1998) *Banca dati di composizione degli alimenti per studi epidemiologici in Italia (Food Composition Database for Epidemiological Study in Italy)*. 269th ed. Milan: European Institute of Oncology.
22. Atkinson FS, Foster-Powell K & Brand-Miller JC (2008) International tables of glycemic index and glycemic load values: 2008. *Diabetes Care* **31**, 2281–2283.
23. Sieri S, Krogh V, Berrino F, *et al.* (2010) Dietary glycemic load and index and risk of coronary heart disease in a large Italian cohort: the EPICOR study. *Arch Intern Med* **170**, 640–647.
24. European Institute of Oncology (2015) *Banca dati di composizione degli alimenti per studi epidemiologici in Italia*. http://www.bda-ieo.it/wordpress/
25. Fitzpatrick TB (1988) The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol* **124**, 869–871.
26. World Health Organization (2006) *WHO Global Database on Body Mass Index*. Geneva: World Health Organization. http://www.who.int/bmi/index.jsp
27. Willett W & Stampfer MJ (1986) Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* **124**, 17–27.
28. Rothman KJ, Greenland S & Lash TL (2013) *Modern Epidemiology*, 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins.
29. Orsini N & Greenland S (2011) A procedure to tabulate and plot results after flexible modeling of a quantitative covariate. *Stata J* **11**, 1–29.
30. Harrell FE (2001) *Regression Modeling Strategies*. New York: Springer-Verlag.
31. Vinceti M, Bonvicini F, Pellacani G, *et al.* (2008) Food intake and risk of cutaneous melanoma in an Italian population. *Eur J Clin Nutr* **62**, 1351–1354.
32. Malavolti M, Malagoli C, Fiorentini C, *et al.* (2013) Association between dietary vitamin C and risk of cutaneous melanoma in a population of northern Italy. *Int J Vitam Nutr Res* **83**, 291–298.
33. Wu H, Reeves KW, Qian J, *et al.* (2015) Coffee, tea, and melanoma risk among postmenopausal women. *Eur J Cancer Prev* **24**, 347–352.
34. Loftfield E, Freedman ND, Graubard BI, *et al.* (2015) Coffee drinking and cutaneous melanoma risk in the NIH-AARP Diet and Health Study. *J Natl Cancer Inst* **107**, dju421.
35. Bao J, Atkinson F, Petocz P, *et al.* (2011) Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: glycemic load compared with carbohydrate content alone. *Am J Clin Nutr* **93**, 984–996.
36. Roberts CK & Liu S (2009) Effects of glycemic load on metabolic health and type 2 diabetes mellitus. *J Diabetes Sci Technol* **3**, 697–704.
37. Turati F, Galeone C, Gandini S, *et al.* (2015) High glycemic index and glycemic load are associated with moderately increased cancer risk. *Mol Nutr Food Res* **59**, 1384–1394.
38. Woo HD, Park KS, Shin A, *et al.* (2013) Glycemic index and glycemic load dietary patterns and the associated risk of breast cancer: a case-control study. *Asian Pac J Cancer Prev* **14**, 5193–5198.
39. Oba S, Nanri A, Kurotani K, *et al.* (2013) Dietary glycemic index, glycemic load and incidence of type 2 diabetes in Japanese men and women: the Japan Public Health Center-based Prospective Study. *Nutr J* **12**, 165.
40. Limkunakul C, Sundell MB, Pouliot B, *et al.* (2014) Glycemic load is associated with oxidative stress among prevalent maintenance hemodialysis patients. *Nephrol Dial Transplant* **29**, 1047–1053.
41. Arikawa AY, Jakits HE, Flood A, *et al.* (2015) Consumption of a high glycemic load but not a high glycemic index diet is marginally associated with oxidative stress in young women. *Nutr Res* **35**, 7–13.
42. Gogas H, Trakatelli M, Dessypris N, *et al.* (2008) Melanoma risk in association with serum leptin levels and lifestyle parameters: a case-control study. *Ann Oncol* **19**, 384–389.
43. Havel PJ, Kasim-Karakas S, Dubuc GR, *et al.* (1996) Gender differences in plasma leptin concentrations. *Nat Med* **2**, 949–950.
44. Thomas T, Burguera B, Melton LJ 3rd, *et al.* (2000) Relationship of serum leptin levels with body composition and sex steroid and insulin levels in men and women. *Metabolism* **49**, 1278–1284.
45. Qin B, Moorman PG, Alberg AJ, *et al.* (2016) Dietary carbohydrate intake, glycaemic load, glycaemic index and ovarian cancer risk in African-American women. *Br J Nutr* **115**, 694–702.
46. Amadou A, Degoul J, Hainaut P, *et al.* (2015) Dietary carbohydrate, glycemic index, glycemic load, and breast cancer risk among Mexican women. *Epidemiology* **26**, 917–924.
47. Sieri S, Brighenti F, Agnoli C, *et al.* (2013) Dietary glycemic load and glycemic index and risk of cerebrovascular disease in the EPICOR cohort. *PLOS ONE* **8**, e62625.