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Trace elements and melanoma

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Abstract

Melanoma incidence has been steadily increasing in recent years in most western countries, thus suggesting a role of environmental risk factors. Among these determinants, it has been hypothesized that some trace elements of nutritional and toxicological interest may be implicated in the etiology of the disease.

We examined patients with newly diagnosed melanoma of the skin and population controls from the Modena province northern Italy. Clinical and dietary data were collected through questionnaires, and toenails were sampled for trace element determination. Levels of cadmium, chromium, lead, selenium, zinc, copper and iron in toenails were measured by inductively coupled plasma optical emission spectrometry and by neutron activation analysis.

Data obtained from 58 cases and 58 controls indicated higher levels of copper and lower concentrations of iron in melanoma patients, whilst no other differences were seen for the remaining elements. Patterns of correlations of zinc and copper with the estimated intake of some dietary factors were different between cases and controls.

Results of the present study suggest that abnormal intake or metabolism of copper and of iron might be implicated in the etiology of melanoma, whilst they do not indicate an involvement of exposure to cadmium, chromium, lead, selenium and zinc in this disease.

Keywords: Trace elements; Melanoma; Toenails; Case-control study

Introduction

Over the last 20 years melanoma incidence has rapidly risen in white populations throughout the world, but the reasons for such an increase are partly unknown [1]. It is well documented that genetic susceptibility and host factors (such as hair and eye colour, melanocytic nevi, extent of freakling and skin-type) are associated with a higher risk of melanoma, while sunlight exposure is considered the major environmental risk factor. It has also been suggested that other determinants, as dietary habits, may play a role in the etiology of cutaneous melanoma; among nutritional factors, the intake of polyunsaturated fats and alcohol might increase the risk of melanoma, whereas retinoids and vitamins C and E seem to protect the skin against the carcinogenic effects of ultraviolet radiation [2,3].

Recently it has been suggested that some trace elements of nutritional and toxicological interest may

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be involved in melanoma occurrence. Selenium has been linked to both decreased and excess risk of melanoma in some studies, and zinc and copper levels have been found to be modified among patients in some clinical and epidemiological studies, also depending on the stage of the disease [4].

The present study was carried out in order to elucidate the possible involvement of some trace elements in melanoma etiology; in particular, our aim was to examine melanoma patients and a control population for the distribution of toenail levels of cadmium, chromium, lead, selenium, copper, zinc and iron, and a possible imbalance of these trace elements, as well as to estimate the influence of some life-style habits and dietary factors on the levels of these trace elements.

Material and methods

Study design

A case–control study was carried out in the population of the Modena province (around 650,000 inhabitants), in Northern Italy. Cases were recruited among all newly diagnosed patients with cutaneous melanoma attending the Dermatologic Clinic of Modena University Hospital. Inclusion criteria were residence in Modena with histologically based diagnosis of cutaneous melanoma without clinical evidence of metastasis. Controls were randomly selected from the Modena population, matched for age (± 5 years) and sex.

Informed written consent was obtained from cases, and reference subjects consented to being part of the control group after having been informed about the protocol and the aims of the study. The study protocol included sampling of toenails, a dermatological examination and administration of life-style and dietary questionnaires. Dietary habits were assessed using a food frequency questionnaire developed by the Milan National Cancer Institute [5], including 248 questions on frequency of consumption of 188 foodstuffs. The questionnaires were read using software providing an estimate of consumption frequency and daily quantities of each food item, as well as the intake of dietary factors using the Italian Food Composition Table as reference database [6].

Element determination

Specimens of toenails were washed using a Triton X-100 solution for 15 min in an ultrasonic sonicator. The samples where digested in 2.5 ml nitric acid + 7.5 ml deionized water in a Perkin-Elmer Multiwave microwave digestion system using PTFE/TFM vessels and operating conditions of 170 °C and 15 bar.

Cadmium, lead and copper content in the samples was determined by inductively coupled plasma optical emission spectrometry (ICP-OES), using a Perkin-Elmer Optima 3000 XL spectrometer equipped with a Perkin-Elmer AS91 autosampler and a CETAC U-5000T + Ultrasonic Nebulizer. For quality control human hair GBW 09101 was used as reference material. The wavelenghts (λ as nm) for the ICP-OES measurements were 214.438, 220.353 and 324.754 for cadmium, lead and copper, respectively, and the corresponding limits of detection, as defined by the analytical method, were 0.18, 1.21 and 0.91 μg/l. The accuracy of the element determination in the reference material (GBW 09101) is shown in Table 1.

Chromium, selenium, zinc and iron concentrations in the toenails were determined by instrumental neutron activation. The cleaned samples, transferred into silica ampoules, were irradiated in the BERII reactor of the Hahn-Meitner Institute Berlin at a thermal flux density of 2×1014 neutrons/cm^2 s for 44 h. For quality control bovine liver NIST 1577b was used as reference material. All measurements were carried out by simultaneous analysis of the matched sets, i.e. a case with the corresponding control, in the same batch.

Statistical analysis

We used the statistical package STATA-8 for data analysis. Differences between cases and controls were analysed by the non-parametric Mann-Whitney test, because of the non-normal distribution of the data. We

Table 1. Accuracy of analytical determination of cadmium, lead and copper in GBW 09101 reference material

	Cadmium		Lead		Copper	
	Value found	Certified value	Value found	Certified value	Value found	Certified value
GBW 09101 trace element concentrations (μg/g, mean value ±SD)	0.0880 ± 0.0004	0.0950 ± 0.0012	8.12 ± 0.21	7.20 ± 0.70	23.0 ± 1.4	23.1 ± 0.4

also calculated Spearman rank correlation coefficients to examine the relation of copper, zinc and iron with the dietary intake of selected factors and total energy intake.

Results

As shown in Table 2, no significant differences were observed between cases and controls for cadmium, chromium, lead, selenium and zinc content in toenail, whereas toenail copper levels were significantly higher and iron concentrations were lower in patients. Copper and iron were also found to have different distributions in patients and controls (Fig. 1).

Once the dietary intake of selected factors had been estimated through the food frequency questionnaire, the intake was then analyzed in relation to toenail trace element concentrations. We observed some different patterns between cases and controls, as can be seen in Table 3. Iron was inversely related to cholesterol, animal protein and fats only in controls. Zinc was directly correlated with dietary riboflavin and retinol only in the control population, while no correlation was found in patients, as outlined also in Fig. 2. Copper was directly related to cholesterol and vitamin D only in patients.

Discussion and conclusions

Very few studies have so far examined the possible relation between trace elements and risk of melanoma, and no previous study has investigated the possible relation between melanoma and trace element status using toenails as biological indicator, which appear to reflect the mid-term exposure/intake of these elements.

The very diverse distribution of different elements (zinc, copper and iron) in melanoma cases and in controls found in our study suggests that the disease might be associated with an imbalance of these elements, as evaluated through their concentrations in toenails.

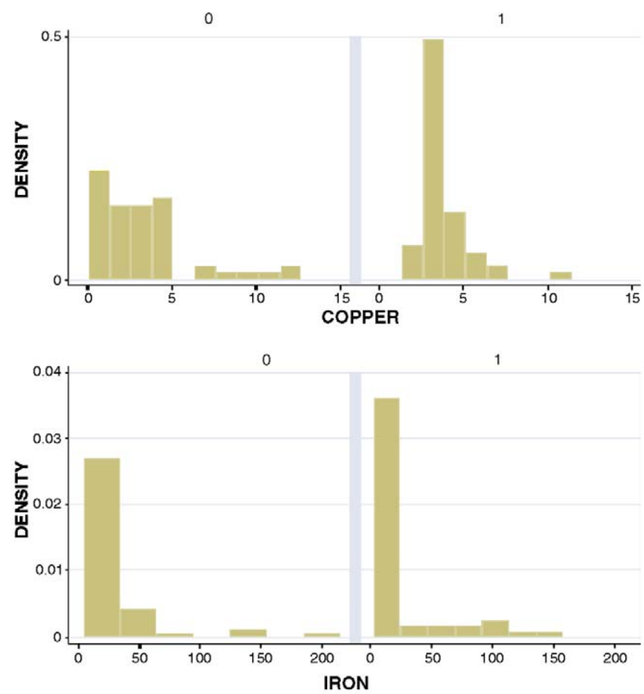

Fig. 1. Frequency distribution of toenail copper and iron levels in controls (0) and patients (1).

Table 2. Descriptive statistics of toenail trace elements concentration (μg/g) in 58 patients and 58 controls and comparison between the groups by Mann-Whitney test

Elements	Group	Mean	Median	SD	Min.	Max.	*Z*	*P*
Cadmium	Controls	0.041	0.022	0.099	0.00	0.77	1.795	0.073
	Cases	0.023	0.018	0.019	0.00	0.12		
Chromium	Controls	3.23	1.40	5.27	0.05	34.65	0.859	0.391
	Cases	2.66	1.20	3.64	0.10	17.00		
Lead	Controls	0.74	0.45	0.81	0.03	5.01	1.850	0.065
	Cases	0.62	0.28	1.02	0.01	7.02		
Selenium	Controls	0.66	0.65	0.12	0.39	1.03	0.903	0.367
	Cases	0.63	0.64	0.11	0.30	0.89		
Zinc	Controls	119	112	28.2	80	266	−0.134	0.893
	Cases	117	116	20.9	76	199		
Copper	Controls	3.20	2.80	2.84	0.09	12.71	−2.640	0.008
	Cases	3.82	3.51	1.48	1.95	11.27		
Iron	Controls	32.4	23	34.9	5	215	3.852	0.000
	Cases	26.0	13	33.6	3	159		

Table 3. Correlations (Spearman) between toenail trace element levels and intake of selected dietary factors

Parameters correlated		Controls		Patients	
		r	*p*	*r*	*p*
Cholesterol	Cu	0.064	0.635	0.269	0.041
	Zn	0.257	0.053	0.018	0.896
	Fe	−0.288	0.029	0.105	0.446
Animal protein	Zn	0.257	0.054	−0.078	0.574
	Fe	−0.301	0.023	0.154	0.261
Animal fats	Fe	−0.307	0.020	0.125	0.365
Riboflavin	Zn	0.248	0.063	−0.102	0.460
Retinol	Zn	0.375	0.004	−0.070	0.614
Vitamin D	Cu	−0.067	0.621	0.254	0.054
Calcium	Cu	0.236	0.077	0.006	0.962
	Zn	0.361	0.006	−0.054	0.697

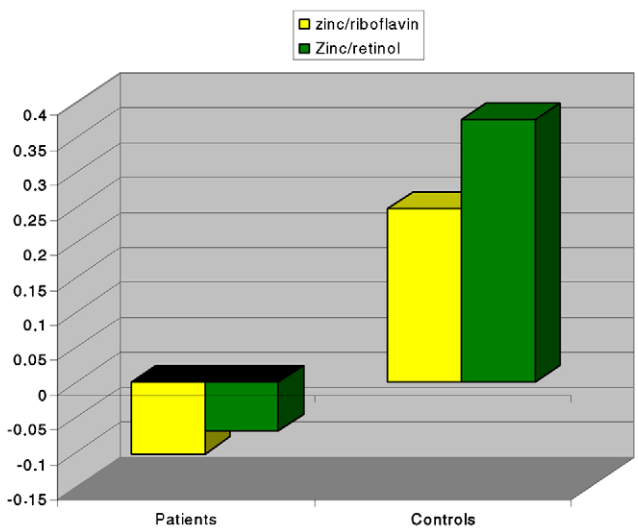

Fig. 2. Correlations between toenail zinc and dietary intake of riboflavin and retinol in patients and in controls.

In agreement with the findings of other authors, we have observed higher levels of copper in melanoma patients, even in absence of metastatic disease [7]. This finding might suggest the hypothetical involvement of this metal in the disease etiology, possibly related to its pro-oxidant action. Increasing literature data indicate that oxidative stress is involved in the etiopathogenesis and in the progression of malignant melanoma [8], as also suggested by the significant overexpression of anti-oxidant enzymes in those patients. Alternatively, the elevated copper content in patients might be associated with an abnormal metabolism of copper-containing proteins in the disease status.

We did not observe differences in the level of zinc between cases and controls, whereas both decreased and increased zinc concentrations have been found in the literature [4,9]. Therefore, our results do not suggest an involvement of zinc intake in melanoma etiology. However, the lack of correlation found in our study between zinc and some dietary factors such as retinol may indicate a disturbance of the metabolism of this vitamin and of zinc in patients, as already hypothesized by others [10]. It should also be noted that zinc is considered to be an important factor of mobilization of retinol reserves, and it seems to be necessary for the conversion of beta-carotene to retinol [10].

The lower level of iron in melanoma patients is an interesting finding, in good agreement with the observations of previous studies, which reported an inverse relation between dietary intake of this metal and melanoma risk [11]. The decrease we observed might be of etiologic interest but might also indicate a tendency of the neoplastic tissue to concentrate this element [12], a fact which might induce reduced iron concentrations in peripheral tissues.

Even if the reasons underlying the different relations between some dietary factors and trace element content in toenails in patients and in controls are difficult to explain, it can be hypothesized that the intake/absorption of nutrients such as cholesterol, animal protein and fats is different in the two groups and that such different dietary habits might influence the intake of iron, copper and zinc. However, we cannot exclude that these patterns may not be causally determined, being due to confounders.

We recognize that this study has limitations that have to be carefully considered. Firstly, the study size was associated with a limited statistical power of this investigation, a fact that hampers the evaluation of our data and suggests the need for further research. Larger studies are required to better elucidate the possible relation between zinc, copper and iron exposure and melanoma risk, as well as the biological mechanisms involved. Moreover, further research is needed to validate the use of toenails as biological indicator of mid-term or long-term exposure to trace elements, with the exception of selenium [13].

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