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Dietary cadmium intake and risk of cutaneous melanoma: An Italian population-based case-control study

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ABSTRACT

Introduction: Exposure to the heavy metal cadmium has been associated with many adverse health effects, such as atherosclerosis, diabetes, and cancer, possibly melanoma. In non-occupationally exposed individuals, food intake is a major source of cadmium exposure, after smoking. We aimed to assess the risk of melanoma in relation to dietary cadmium intake.
Methods: Using a population-based case-control study design, we recruited 380 incident cases of newly-diagnosed cutaneous melanoma and 719 matched controls in the Emilia-Romagna Region, Northern Italy in the years 2005-2006. We evaluated dietary intake using a semi-quantitative food frequency questionnaire. We used conditional logistic regression to compute odds ratios (ORs) and 95% confidence intervals (CIs) for melanoma according to quintiles of dietary cadmium intake, adjusting for several potential confounders, and we modeled the association non-parametrically, using restricted cubic splines.
Results: Median energy-adjusted intake of cadmium was 6.11 μg/day (interquartile range 5.38–6.91) among cases and 5.97 μg/day (5.15–6.79) among controls. For each 1 μg/day-increase in cadmium intake, the OR for melanoma was 1.11 (95% CI 1.00–1.24). Melanoma risk generally increased with increasing quintile of cadmium exposure, with ORs of 1.55 (95% CI 0.99–2.42), 1.54 (95% CI 0.99-2-40), 1.75 (95% CI 1.12–2.75), and 1.65 (95% CI 1.05–2.61) for the second through fifth quintiles, compared with the lowest quintile. Sex-stratified analysis showed ORs per 1 μg/day-increase in cadmium intake of 1.10 (95% CI 0.93-1-29) among men and 1.15 (95% CI 0.99–1.33) among women. Using spline regression analysis, we observed a generally linear increase in melanoma risk up to 6 μg/day of cadmium intake, after which the risk appeared to plateau.
Conclusions: We observed a positive non-linear association between dietary cadmium intake and risk of cutaneous melanoma in a Northern Italy population. However, further studies are needed to elucidate this association, due to concerns about exposure misclassification, unmeasured confounding, and the limited and conflicting evidence from epidemiological findings.

1. Introduction

Cadmium, a heavy metal, is toxic to humans [1,2]. It demonstrates both carcinogenic and non-carcinogenic adverse effects [3–6]. Cadmium may increase lung and prostate cancer risk [7–9], and potentially other cancer sites such as kidney, and perhaps also bladder, breast, endometrium and finally skin cancer [10–12].

Only two previous epidemiological studies have examined the relation between cadmium exposure risk of melanoma [13], with one using toenail cadmium levels not supporting a role of cadmium in the pathogenesis of cutaneous melanoma [14]. However, other findings suggested that overexpression of metallothionein following heavy metal exposure in primary melanoma is associated with disease progression [15]. None of previous studies assessed melanoma risk in relation to dietary cadmium exposure. Despite few epidemiological investigations in humans, mechanisms for cadmium carcinogenic effects, particularly in melanoma cells, have been reported [16,17]. Possible mechanisms include indirect genotoxic activity through generation of reactive oxygen species and epigenetic alteration such as DNA methylation, histone modifications and altered expression of non-coding RNA

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[18,19].

Biomonitoring of metal level is generally considered a valid method for assessment of exposure, with differences depending on the time frame to be evaluated, the accumulation pattern in target organs, or their invasiveness [20,21]. In addition to biomarkers, dietary questionnaires for the evaluation of dietary intake of cadmium has been frequently used [22,23], and dietary intake is often used as a surrogate indicator of cadmium exposure, especially in non-smokers and in non-occupationally exposed subjects [2,24]. Evaluation of dietary intake is also important for the risk assessment of cadmium in foods [25–27]. The aim of this study is to examine the risk of cutaneous melanoma in relation to dietary intake of cadmium in a Northern Italy population.

2. Methods

2.1. Assessment of dietary habits

We assessed intake of foods and nutrients using the validated European Prospective Investigation into Cancer and Nutrition (EPIC) semi-quantitative food frequency questionnaire (FFQ) in the version specifically developed for the Central-Northern Italy population [28,29]. The EPIC-FFQ was designed to estimate frequency and amount of consumption of 188 food items over the previous year, also using photos of serving sizes to help increase accuracy of reporting. We checked the completeness and the quality of data of the EPIC-FFQ by computing the ratio of total energy intake:calculated basal metabolic rate excluding subjects reporting energy intake < 0.5th or > 99.5th [30]. We assessed dietary cadmium intake by combining the analytical results of cadmium determination in foods and of the dietary assessment performed with the EPIC FFQ [22]. Finally, for each subject, we computed the Greek variant of Mediterranean diet Index (GMI) score for the *a priori* defined diet quality index ranking from 0 (lowest adherence) to 9 (highest adherence) [31].

2.2. Study population

Details about study participants have been previously reported [32,33]. To summarize, we recruited cutaneous melanoma cases from Dermatology Units of five provinces of Emilia Romagna region (Bologna, Ferrara, Modena, Parma and Reggio Emilia) among the newly-diagnosed cases in the period 2005-2006. The referent population was identified by accessing directories of the National Health Service, randomly selecting six referents matched to each case for sex, year of birth (± 5 years) and province of residence. We invited controls to participate by sending a participation kit to their home address using post mail. The kit included study information leaf-sheet, lifestyle and food frequency questionnaires, written informed consent, and pre-stamped return envelope to hand back material in case of acceptance. In particular, we collected information on possible confounders, particularly phototype (eye, hair and skin color; and skin sun reactions, i.e. tendency to burn and tan), sunburn history, education, and body mass index (BMI, kg/m^2). Overall, 394 melanoma cases and 747 population controls agreed to participate to the study. After checking the completeness and quality of data of the FFQ, we included in the present analysis 380 (96.4% of those eligible, 175 men and 205 women) cases and 719 (96.3% of those eligible, 319 men and 400 women) controls (Fig. 1). In particular, the final analytic sample comprised participants aged 18–87 years with median (interquartile range (IQR)) age of 57 years (IQR 42–67) in overall subjects, and 60 years (47–69) in men, and 53 years (41–67) in women, respectively.

2.3. Statistical analysis

For comparison between cases and controls, we used chi-squared test to evaluate difference in distribution of categorical characteristics and the nonparametric equality-of-medians test to compare cadmium intake median levels. We categorized daily cadmium dietary intake into quintiles based on the distribution of energy-adjusted residuals in the overall control group [34]. We performed multivariate conditional logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of cutaneous melanoma for increasing quintiles of intake, using the lowest category as reference. We included in the multivariable model the subsequent variables: age, education, phototype, sunburn history, education, BMI, and non-alcohol energy intake. Additionally, we performed sensitivity analyses considering the following factors as possible confounders or effect modifiers, also based on previous findings from this population: Greek-Mediterranean diet Index adherence score [35], the daily average values for dietary glycemic load or dietary glycemic index [32], intake of vitamin C [36], dietary vitamin D [33], fiber [37] or iron [37,38].

We also stratified analyses by sex and age. Finally, we modeled the relation between dietary cadmium intake and melanoma risk using restricted cubic splines, computed with the ‘mkspline’ and ‘xblc’ routines of the Stata-15.1 statistical package (Stata Corp., TX 2017) [39,40], by selecting the cutpoints adopted for categorical analysis, namely 20th, 40th, 60th and 80th percentiles in overall control population. Alternatively, we selected the optimal number of five knots according to Akaike’s information criterion and we used the Harrell’ knot automatic placement method [41]. In further sensitivity analyses, we switched from daily energy-adjusted residuals (in μg/day) to weight-adjusted residuals of cadmium intake (in μg/day) or to weekly weight-divided intake (in μg per kilogram (kg) of body weight (bw) per week), taking into account parameters used by international food safety authorities [25,26].

3. Results

Detailed information regarding identification and recruitment of study participants is shown in Fig. 1. Characteristics of included participants are reported in Table 1. Most variables showed substantially similar distributions between cases and controls, except for a slightly higher proportion of phototype I subjects in cases and phototype IV in controls, and consequently a higher proportion of subjects reporting sunburn history in the cases than controls. Median non-alcoholic energy intake was 1810 kcal/day (IQR: 1443-2293) in all subjects, with higher values in men (1880 kcal/day, IQR: 1517-2395) than women (1754 kcal/day, IQR: 1402-2188), but comparable values between cases (1831 kcal/day, IQR: 1412-2301) and controls (1798 kcal/day, IQR: 1455-2292).

In Table 2 we present the distribution of energy-adjusted residual cadmium intake, overall and among subgroups. Overall, median energy-adjusted daily cadmium intake was 6.04 μg/day (IQR: 5.24–6.83), with slightly higher intake in women than men, and in younger than older participants. A small increase going from normal weight, overweight and obese can be noted in overall participants, as well as with increasing years of educational attainment. On the converse, an inverse association was found with phototype, as phototypes III and IV showed lower intake than clearer ones. Increasing adherence to Greek-Mediterranean diet Index was positively associated with higher cadmium intake as well as for subjects with intake of fiber equal or more than 20 g/day. Similar distributions emerged by comparison of energy-adjusted residuals of daily cadmium intake with weight-adjusted residuals (Supplemental Table S1) or with weekly intake divided by body weight (Supplemental Table S2). Crude distributions of dietary cadmium intake (unadjusted for energy and weight) showed comparable results to the adjusted estimates, except for the higher intake found in men compared with women (Supplemental Table S3).

Table 3 provides ORs and 95% CIs for melanoma according to quintile of daily cadmium intake, after controlling for potential confounders. In the most adjusted model, we observed a positive association in the highest quintile of dietary exposure compared with the lowest one, and we estimated the OR for a 1-unit increase of dietary

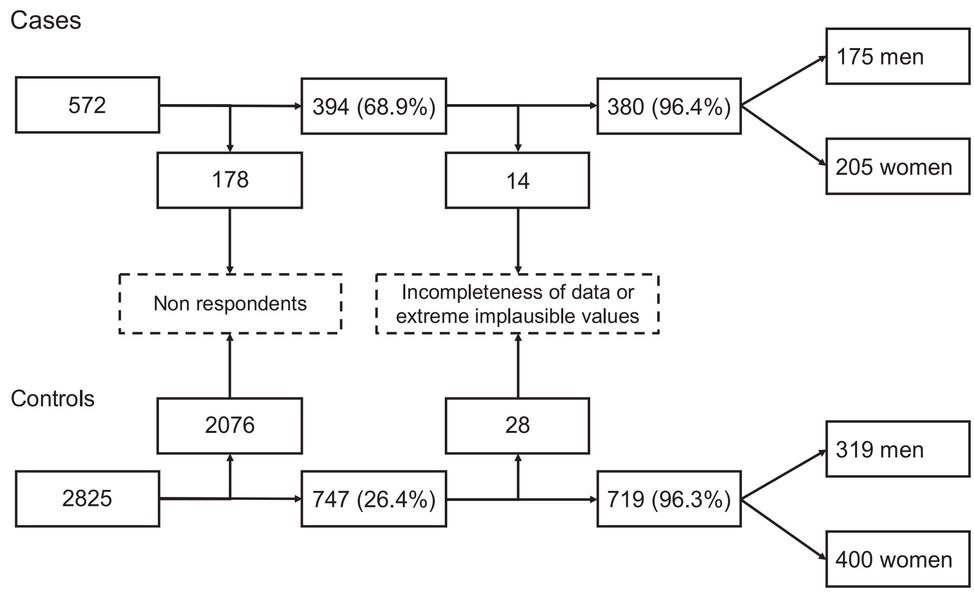

Fig. 1. Flow-chart of identification of final study population.

Table 1
Characterisics of final study population.

	All subjects N (%)	Cases N (%)	Controls N (%)	P value
Total	1099 (100)	380 (100)	719 (100)	
Sex				
Men	494 (45.0)	175 (46.1)	319 (44.4)	
Women	605 (55.0)	205 (53.9)	400 (55.6)	*0.593*
Age				
< 50 years	418 (38.0)	146 (38.4)	272 (37.8)	
≥50 years	681 (62.0)	234 (61.6)	447 (62.2)	*0.848*
BMI (kg/m^2)				
< 24.99	546 (49.7)	195 (51.3)	351 (48.8)	
25–29.99	420 (38.2)	133 (35.0)	287 (39.9)	
≥30	133 (12.1)	52 (13.7)	81 (11.3)	*0.214*
Education (years)				
≤5	261 (23.9)	91 (24.1)	170 (23.8)	
6–8	271 (24.8)	95 (25.1)	176 (24.6)	
9_13	402 (36.8)	136 (36.0)	266 (37.2)	
≥14	159 (14.5)	56 (14.8)	103 (14.4)	*0.983*
Phototype[a]				
I	214 (19.5)	105 (27.6)	109 (15.2)	
II	374 (43.0)	136 (35.8)	238 (33.1)	
III	434 (39.5)	122 (32.1)	312 (43.4)	
IV	77 (7.0)	17 (4.5)	60 (8.3)	*< 0.001*
Sunburn history				
Never	634 (57.7)	182 (47.9)	452 (62.9)	
Before 18 years	193 (17.6)	108 (28.4)	164 (22.8)	
After 18 years	272 (24.7)	90 (23.7)	103 (14.3)	*< 0.001*
GMI adherence score				
low (0–3)	351 (31.9)	133 (35.0)	218 (30.3)	
medium (4–6)	612 (55.7)	196 (51.6)	416 (57.9)	
high (7–9)	136 (12.4)	51 (13.4)	85 (11.8)	*0.137*
Fiber intake				
< 20 g/day	757 (68.9)	264 (69.5)	493 (68.6)	
≥20 g/day	342 (31.1)	116 (30.5)	226 (31.4)	*0.758*

Abbreviations: BMI: body mass index; GMI: Greek-Mediterranean diet Index.
[a] 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. P value from chi-squared test.

cadmium of 1.13 (95% IC 1.01–1.26). We found in general higher estimates in female population compared with men, and in subjects older than 50 years than younger subjects. Similar results were found in sensitivity analyses by using sex-specific quintile distributions (Supplemental Table S4). Additional adjustment for dietary glycemic load/dietary glycemic index, intake of vitamin C, vitamin D, or iron showed comparable results (data not shown).

regression analysis in overall population showed a substantial linear increase starting approximately from 5 μg/day of dietary cadmium intake, above which the risk seemed to plateau (Fig. 2). Sex- and age-stratified spline regression analyses showed comparable results (Fig. 3), though in men, but not women, a downward trend for disease risk at the highest level of cadmium intake. Finally, similar but slightly stronger ORs were found in subjects aged ≥50 years, compared with younger participants. Using five knots automatically identified instead of percentiles as cutpoints showed comparable results (Supplemental Figs. S1 and S2).

In sensitivity analysis using weight-adjusted residuals instead of energy-adjusted residuals to measure daily cadmium intake we found similar results, but estimates were less precise (Supplemental Table S5). Similarly, the use of weekly cadmium intake divided by body weight instead of daily cadmium intake using weight-adjusted residuals showed comparable results (Supplemental Table S6). However, in the spline regression analysis, we found stronger evidence of linearity in the association when we used weight-adjusted values (Supplemental Fig. S3). In this analysis, ORs increased more in women than in men, and in older than in younger participants (Supplemental Fig. S4). When we used five knots instead of percentiles as cutpoints, results were nearly identical (Supplemental Figs. S5 and S6). Spline regression analysis changing from daily intake from weight-adjusted residuals to weekly intake divided by body weight showed comparable results (Supplemental Figs. S7–S10).

4. Discussion

In this population-based case-control study in a Northern Italy population, we found a positive association between dietary cadmium intake and risk of developing cutaneous melanoma, particularly among women and older individuals. Additionally, we highlighted a generally linear increase in risk up to 6 μg/day of cadmium intake, while above this threshold, risk of cutaneous melanoma only slightly increased, reaching a plateau. Our findings disagree with the results of one previous studies of ours [14] that used toenail biomarker for exposure assessment, and the inconsistent results might be due to the different exposure assessment methods (FFQ and toenail levels) we used.

Table 2
Distribution of energy-adjusted residuals of cadmium daily intake in overall population, cases and controls and subgroups. Median and interquartile range (IQR) reported. Values in µg/day.

	All subjects		Cases		Controls		
	Median	(IQR)	Median	(IQR)	Median	(IQR)	P value
Total	6.04	(5.24–6.83)	6.11	(5.38–6.91)	5.97	(5.15–6.79)	
Sex							
Men	5.97	(5.15–6.74)	6.10	(5.24–6.77)	5.90	(5.09–6.69)	
Women	6.07	(5.35–6.93)	6.13	(5.47–7.02)	6.05	(5.26–6.87)	*0.236*
Age							
< 50 years	6.13	(5.39–6.91)	6.11	(5.47–7.04)	6.17	(5.38–6.90)	
≥50 years	5.98	(5.15–6.76)	6.11	(5.28–6.83)	5.91	(5.08–6.69)	*0.164*
BMI (kg/m^2)							
< 24.99	5.99	(5.30–6.80)	6.13	(5.47–7.02)	5.90	(5.20–6.69)	
25-29.99	6.07	(5.16–6.86)	6.05	(5.22–6.82)	6.08	(5.11–6.88)	
≥30	6.21	(5.33–6.92)	6.28	(5.42–6.63)	6.19	(5.05–7.03)	*0.408*
Education (years)							
≤5	5.98	(5.06–6.68)	6.10	(5.29–6.88)	5.90	(4.95–6.57)	
6-8	5.98	(5.16–6.81)	6.05	(5.28–6.76)	5.92	(5.12–6.87)	
9_13	6.02	(5.31–6.86)	6.00	(5.50–6.78)	6.02	(5.26–6.87)	
≥14	6.21	(5.46–6.97)	6.51	(5.48–7.20)	6.05	(5.37–6.79)	*0.340*
Phototype[a]							
I	6.09	(5.34–6.97)	6.04	(5.34–6.90)	6.09	(5.33–6.98)	
II	6.07	(5.19–6.93)	6.07	(5.20–6.97)	6.07	(5.19–6.91)	
III	5.99	(5.27–6.79)	6.15	(5.57–6.92)	5.90	(5.11–6.71)	
IV	5.86	(5.06–6.72)	6.34	(5.61–6.71)	5.72	(5.01–6.73)	*0.644*
Sunburn history							
Never	6.04	(5.22–6.83)	6.16	(5.47–6.92)	5.94	(5.11–6.76)	
Before 18 years	6.04	(5.34–6.68)	5.98	(5.34–6.58)	6.13	(5.24–6.82)	
After 18 years	6.04	(5.29–6.94)	6.13	(5.31–7.05)	6.00	(5.23–6.87)	*0.998*
GMI adherence score							
low (0–3)	5.63	(4.91–6.40)	5.65	(5.16–6.43)	5.60	(4.78–6.39)	
medium (4–6)	6.09	(5.32–6.87)	6.17	(5.46–6.95)	6.03	(5.24–6.82)	
high (7–9)	6.78	(5.99–7.65)	6.93	(6.15–8.04)	6.62	(5.97–7.46)	*< 0.001*
Fiber intake							
< 20 g/day	5.83	(5.13–6.56)	5.93	(5.28–6.68)	5.79	(5.07–6.50)	
≥20 g/day	6.54	(5.57–7.46)	6.51	(5.70–7.52)	6.55	(5.47–7.41)	*< 0.001*

Abbreviations: BMI: body mass index; GMI: Greek-Mediterranean diet Index.
[a] 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. P value from nonparametric equality-of-medians test.

There is some biological plausibility for a role of cadmium in melanoma etiology [16]. Among the several proposed etiopathogenetic mechanisms, particular attention is given to epigenetic effects leading to alterations of cellular component network, and modulation of level of expression of oxidative stress-related genes, such as changes in DNA methylation, histone modifications and non-coding RNA expression [42–47]. DNA methylation, in particular, reduced expression of key genes that regulate cell proliferation and apoptosis in melanoma cells [48,49]. Moreover, previous studies showed that cadmium-induced over-expression of metallothioneins was associated with progressive disease in malignant melanoma [50–52], and in a murine model exposed to cadmium, melanoma cell invasion was also enhanced through the induction of metallothioneins, suggesting their possible role in malignancy and metastasis [53].

The available evidence suggests that oxidative stress may play a central role in cadmium genotoxicity because of its involvement in aberrant gene expression, inhibition of DNA damage repair, and apoptosis [54]. This is the case also for other human diseases associated with cadmium exposure, including lung, prostate or breast cancer [55,56], as well as non-cancerous diseases such as diabetes and cardiovascular diseases [57,58]. In addition, in spite of its rather weak mutagenic potential, cadmium has been shown to act in synergy with other human carcinogens, like tobacco smoking and UV [59] to which subjects may be also co-exposed [60], as it is the case of cigarette smoking as relevant source of cadmium [2].

Of interest is the observation that, in our study, risk of melanoma started to increase below the threshold of tolerable dietary intake established by the European Food Safety Authority of 2.5 µg/kg bw/week corresponding to approximately 25 µg/day of cadmium [25]. However, our findings should be considered with caution since such a relation seem to be affected by other factors such as sex and age of participants, and the role of other possible confounding factors cannot be entirely ruled out. Finally, we did not consider in our analysis the possible influence of other sources of cadmium exposure, such smoking habits or environmental factors [61,62], although complex associations have been observed between smoking and melanoma risk, with even some suggestions of lower risk in smokers than never smokers [63].

Our study has some strengths and limitations. It is a large case-control study carried out over five North Italian provinces, including population control recruited. For exposure assessment, we used an FFQ validated by EPIC for the Northern Italy population, with a high accuracy of estimation of single food intake due to use several pictures for portion anchors and also inclusion of traditional seasoning and local dishes [29]. In addition as previously described, estimation of cadmium dietary intake was performed through the measurement of metal content in foods distributed and consumed in the same area of Emilia Romagna Region [22]. During the analysis, we took into account possible source of measurement errors [64]. Namely, we used the residual method to compute cadmium intake adjusting for total energy intake, and we also excluded subjects with extreme and potentially implausible values of energy intake [34,41].

Regarding study limitations, we did not collect information about type and number of dysplastic nevi, long-term exposure to UV light or family history of melanoma, and physical activity, due to the high risk of recall bias among cases [65], as well as information on occupational history, particularly related to solar radiation exposure, also

Table 3
Odds ratio (OR) and its 95% confidence interval (CI) of risk of cutanuous melanoma according to increasing quintile of energy-adjusted daily cadmium dietary intake.

	OR	Adjusted[a] (95% CI)	P for trend	OR	Adjusted[b] (95% CI)	P for trend	OR	Adjusted[c] (95% CI)	P for trend
All subjects									
Quintile I	1.00	–		1.00	–		1.00		
Quintile II	1.55	(0.99–2.43)		1.61	(1.03–2.54)		1.63	(1.04–2.57)	
Quintile III	1.51	(0.97–2.34)		1.60	(1.02–2.50)		1.62	(1.03–2.55)	
Quintile IV	1.72	(1.10–2.68)		1.85	(1.17–2.92)		1.89	(1.19–3.01)	
Quintile V	1.53	(0.98–2.38)		1.68	(1.06–2.68)		1.73	(1.08–2.78)	
Per 1-unit increase	1.09	(0.99–1.21)	*0.090*	1.12	(1.00–1.25)	*0.043*	1.13	(1.01–1.26)	*0.037*
Men									
Quintile I	1.00	–		1.00	–		1.00	–	
Quintile II	1.68	(0.87–3.26)		1.71	(0.88–3.31)		1.72	(0.88–3.35)	
Quintile III	1.53	(0.78–3.03)		1.56	(0.79–3.10)		1.51	(0.76–3.01)	
Quintile IV	1.84	(0.95–3.58)		1.91	(0.97–3.80)		1.80	(0.90–3.59)	
Quintile V	1.17	(0.59–2.34)		1.22	(0.60–2.48)		1.12	(0.54–3.32)	
Per 1-unit increase	1.08	(0.92–1.26)	*0.338*	1.09	(0.93–1.28)	*0.299*	1.06	(0.90–1.26)	*0.476*
Women									
Quintile I	1.00	–		1.00	–		1.00	–	
Quintile II	1.57	(0.84–2.93)		1.71	(0.91–3.24)		1.86	(0.97–3.55)	
Quintile III	1.61	(0.89–2.94)		1.83	(0.99–3.40)		1.99	(1.06–3.74)	
Quintile IV	1.75	(0.94–3.24)		1.96	(1.05–3.68)		2.18	(1.14–4.18)	
Quintile V	1.92	(1.05–3.50)		1.32	(1.22–4.38)		2.60	(1.34–5.01)	
Per 1-unit increase	1.13	(0.98–1.30)	*0.102*	1.17	(1.01–1.36)	*0.039*	1.21	(1.03–1.41)	*0.019*
Age < 50 years									
Quintile I	1.00	–		1.00	–		1.00	–	
Quintile II	1.33	(0.62–2.92)		1.46	(0.67–3.18)		1.55	(0.70–3.43)	
Quintile III	1.88	(0.91–3.86)		2.12	(1.03–4.39)		2.24	(1.07–4.67)	
Quintile IV	1.09	(0.50–2.38)		1.25	(0.57–2.74)		1.33	(0.60–2.95)	
Quintile V	1.63	(0.77–3.46)		2.07	(0.95–4.53)		2.35	(1.03–5.35)	
Per 1-unit increase	1.02	(0.86–1.20)	*0.852*	1.06	(0.89–1.26)	*0.504*	1.09	(0.90–1.31)	*0.371*
Age ≥50 years									
Quintile I	1.00	–		1.00	–				
Quintile II	1.63	(0.93–2.85)		1.63	(0.93–2.87)		1.63	(0.93–2.87)	
Quintile III	1.38	(0.78–2.44)		1.38	(0.77–2.48)		1.38	(0.77–2.49)	
Quintile IV	2.31	(1.33–4.03)		2.32	(1.31–4.12)		2.32	(1.29–4.17)	
Quintile V	1.48	(0.83–2.62)		1.48	(0.82–2.69)		1.48	(0.81–2.70)	
Per 1-unit increase	1.15	(1.01–1.32)	*0.040*	1.15	(1.00–1.33)	*0.052*	1.15	(0.99–1.33)	*0.063*

[a] Adjusted for matching variables, and further adjusted for education, phototype, history of sunburn, body mass index, non-alcoholic energy intake. Cutpoints for quintile subdivision are 4.99, 5.65, 6.26, and 7.01 μg/day. Median values from first to fifth quintile are 4.52, 5.36, 5.97, 6.59, and 7.67 μg/day.
[b] Additionally adjusted for adherence to Greek-Mediterranean diet Index.
[c] Additionally adjusted for fiber intake.

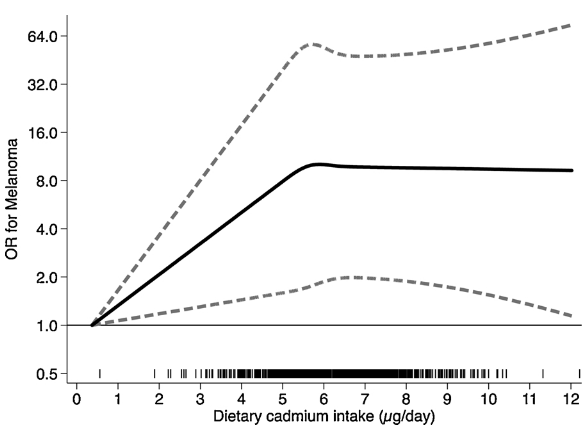

Fig. 2. Spline regression analysis of the odds of being a case according to daily energy-adjusted residual cadmium intake (μg/day) in all subjects. Model adjusted for matching variables, education, phototype, sunburn history, body mass index, non-alcohol energy intake, adherence to Greek-Mediterranean diet Index, and fiber intake. Number and placement of knots identified using 20th, 40th, 60th, and 80th percentiles as cutpoints. Dash lines, 95% confidence limits.

characterized by the lack of reliable and valid methods to estimate solar ration exposure in workers [66]. Nevertheless, these factors are unlikely to explain the sex- and age difference in the association we detected, also considering that men are more likely to be employed in outdoor working activity than women [67]. About assessment of dietary cadmium intake, in spite we used a validated FFQ we cannot entirely rule out a possible underestimation of its real intake, due to variation of contamination levels of foods actually consumed by participants. In addition, although we included some major confounders in the analysis, namely phototype and history of sunburn, we did not collect information about smoking habits, which is also a relevant source of cadmium exposure as well as of many other contaminants. In addition, presence of other factors not considered in the present study, and therefore unmeasured confounding, a potential inherent limitation of case-control studies, may explain the positive results. However, since we included in the multivariable model also a score of Greek-Mediterranean diet Index, to some extent we adjusted for dietary covariates, though we cannot entirely rule out confounding due to unmeasured dietary (or life-style) factors [13,68–70]. Finally, weight and height were self- reported by study participants, which may have introduced some non-differential misclassification of body mass index.

5. Conclusions

In conclusion, our results seem to indicate a positive association between cadmium intake and melanoma risk in an Italian population. This relation may be stronger in women and older individuals and possibly characterized by a non-linear increase. However, the use of dietary intake instead of biomarkers might have affected our assessment, including the inability to consider other important environmental sources of cadmium exposure. Finally, the possibility of unmeasured

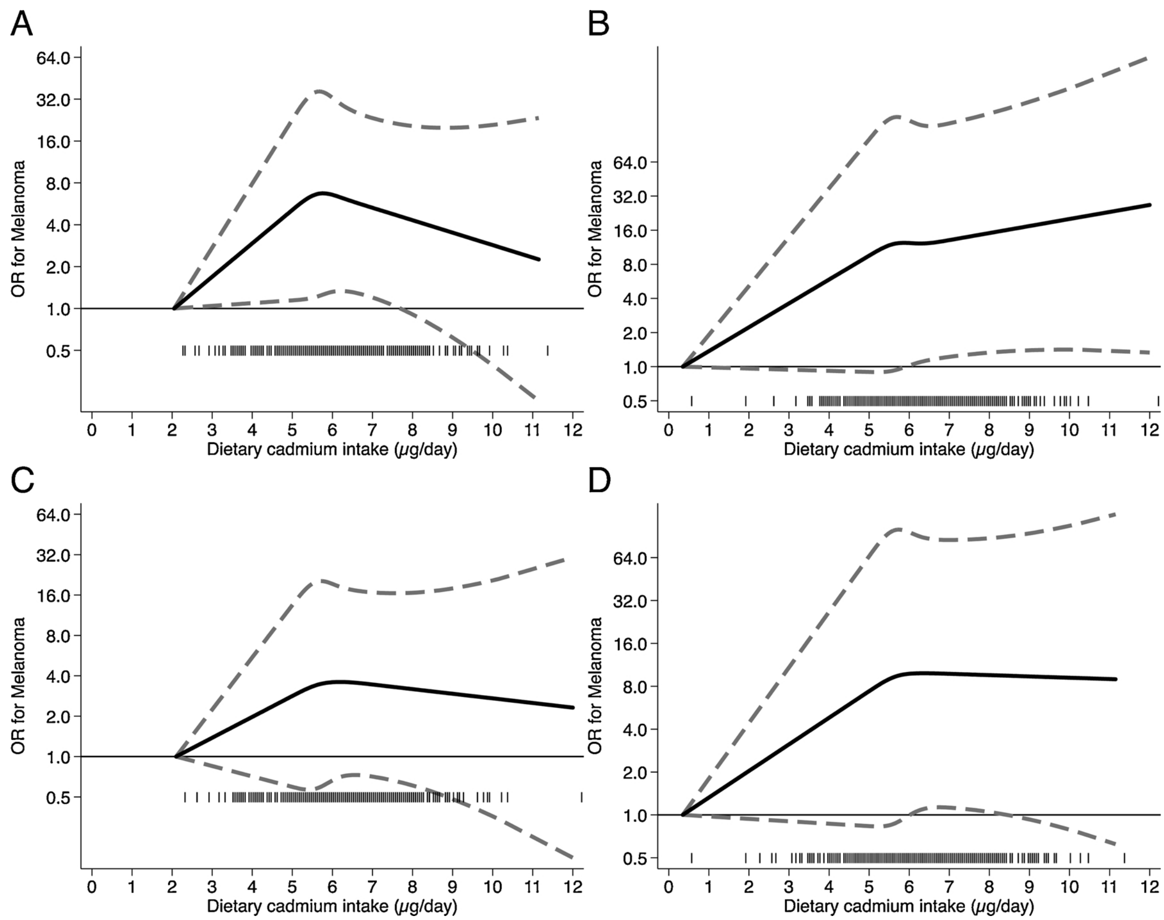

Fig. 3. Spline regression analysis of the odds of being a case according to daily energy-adjusted residual cadmium intake (μg/day) in men (A), women (B), subjects aged less than 50 years (C), and more equal or more than 50 years (D). Model adjusted for matching variables, education, phototype, sunburn history, body mass index, non-alcohol energy intake, adherence to Greek-Mediterranean diet Index, and fiber intake. Number and placement of knots identified using 20th, 40th, 60th, and 80th percentiles as cutpoints. Dash lines, 95% confidence limits.

confounding by smoking and other key variables cannot be entirely ruled out. Given the limited and conflicting evidence from epidemiological studies to date, further investigation of the association is needed to elucidate the existence and the shape of such a changeable relation.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jtemb.2019.08.002.

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