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#### Dietary cadmium exposure and risk of melanoma: an Italian population-based casecontrol study

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Background and aim. The heavy metal cadmium could be highly toxic to humans, and its environmental exposure has been linked to many adverse health effects, such as atherosclerosis, diabetes, and cancer, including melanoma. Although the underlying mechanisms need yet to be clearly identified, recent findings suggested that cadmium can specifically promote the malignant transformation of melanoma cells through the aberrant DNA methylation inducing dysregulation of specific gene expression. Since in the nonoccupationally exposed population, in addition to smoking, food intake is the major source of cadmium exposure, we aimed at assessing the risk of cutaneous melanoma in relation to dietary cadmium intake.

Methods. Using a population-based study design, we recruited 380 incident cases of newlydiagnosed melanoma and 719 sex- and age-matched controls in the Emilia-Romagna Region, Northern Italy. We evaluated their dietary habits through a semi-quantitative food frequency questionnaire and we computed the odds ratio (OR) and its 95% confidence interval (CI) for melanoma according to quintile distribution of cadmium intake, using a conditional logistic regression model, matching by sex, age and province of residence, and adjusting also for phototype, non-alcoholic energy intake, body mass index, and Italian Mediterranean Diet Index.

Results: Median intake of cadmium was 5.81  $\mu$ g/day (interquartile range 4.46-7.59) in cases, and 5.63  $\mu$ g/day (4.46-7.34) in controls. OR of melanoma associated with 1-unit increase in cadmium intake was 1.11 (95% CI 1.00-1.24). Melanoma risk 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) in the second to the highest quintile compared to the lowest quintile. Sex-stratified analysis showed substantially comparable results and a generally higher risk in female population, with continuous ORs of 1.10 (95% CI 0.93-1-29), and 1.15 (95% CI 0.99-1.33) in men and women, respectively.

Conclusions: Our results suggest a positive association between cadmium exposure through diet and risk of cutaneous melanoma in a Northern Italy population. Such association started to occur at a level of exposure lower than the tolerable intake established by the World Health Organization, and considered to be safe for humans.