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Plasma levels of polychlorinated biphenyls and risk of cutaneous malignant melanoma: A hospital-based case-control study☆

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ABSTRACT

Polychlorinated biphenyls (PCB) have been classified by the International Agency for Research on Cancer (IARC) in Group 1 as carcinogenic to human, based on sufficient evidence in humans of an increased risk of cutaneous malignant melanoma (CMM), however few studies have been done in the general population. This study examined the relationship between PCB plasma levels and risk of CMM adjusting for sun sensitivity and sun exposure in a province of Northern Italy (Brescia), where a chemical factory produced PCBs from 1938 to 1984 causing human contamination. A case–control study of 205 CMM patients and 205 control subjects was conducted. Cases and controls were assayed for plasma levels of 33 PCB congeners. No associations was found between risk of CMM and plasma levels of total PCB (OR = 0.81; 95% CI: 0.34–1.96 for highest vs lowest quartile) or specific congeners. The study confirmed the association with light skin colour (OR = 3.00; 95% CI: 1.91–4.73), cumulative lifetime UV exposure (OR = 2.56; 95% CI: 1.35–4.85) and high level of education (OR = 1.45; 95% CI: 1.03–2.05). This case-control study does not support the hypothesis of an association between current plasma levels of PCBs and CMM development in the general population.

1. Introduction

The global incidence rate of cutaneous malignant melanoma (CMM) in 2015 was estimated to be about five cases per 100,000 persons, with the greatest burden of incidence and mortality in the caucasic population of Australasia, North America and Europe (Karimkhani et al., 2017); in Italy is the third most frequent cancer in both sexes in the under 50 years old population (AIOM and AIRTUM, 2016).

The most important risk factors for CMM include exposure to environmental or artificial ultraviolet radiation (UVR) (International Agency for Research on Cancer (IARC), 1992), genetic predisposition, phenotypic features including fair phototype, number of acquired naevi, and aging (Fava et al., 2015; Caini et al., 2009).

However, the increasing incidence of melanoma in Italy and other European countries in the last decades cannot be fully explained by the hypothesis of an increase in cumulative lifetime UVR exposure and number of episodes of sunburns (AIOM and AIRTUM, 2016; Holterhues et al., 2013).

Most of current knowledge of melanoma aetiology derives from study of patients in populations of European descent, for whom the use of sun protection tools and screening procedures have appreciably decreased mortality. However, some melanoma subtypes that most commonly develop in other populations are not associated with exposure to ultraviolet (UV) light, suggesting a different disease aetiology. Further

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study of these subtypes is necessary to understand their risk factors and genomic architecture, and to tailor therapies and public health campaigns to benefit patients of all ethnic groups (Ossio et al., 2017).

At the same time, other risk factors for melanoma have been investigated, including non-UV related environmental and occupational carcinogens. In 2016, the International Agency for Research on Cancer (IARC) upgraded the classification of Polychlorinated Biphenyls (PCBs) to Group 1 "Carcinogenic to humans", based on sufficient evidence in humans of an increased risk of CMM. The decision was also supported by experimental data on animals and the evidence of aryl hydrocarbon receptor (AhR)-mediated mechanisms of carcinogenicity for dioxin-like PCB congeners (IARC, 2016).

Two more recent meta-analyses, however, found no, or limited, evidence of association between PCB exposure and risk of CMM and concluded that more epidemiological, clinical and laboratory studies are needed (Boffetta et al., 2016; Zani et al., 2017).

A chemical factory located in Brescia, an industrialized town in Northern Italy, produced PCBs and other organochlorines from the1930s to the 1980s, causing heavy PCB pollution of soil, water and local food (Donato et al., 2006; Turrio-Baldassarri et al., 2007; Turrio-Baldassarri et al., 2009). Some studies, performed in 2001–03 documented high levels of PCBs in the population living in the most polluted area of Brescia and in people who had eaten local products (Donato et al., 2006; Turrio-Baldassarri et al., 2007; Turrio-Baldassarri et al., 2009). Subsequently, various public health interventions have been established for reducing the environmental impact of PCB pollution. In fact, PCB serum levels decreased by more than half, on the average, in people living in the most polluted areas (approximately 25,000 residents), from 2003 to 2013 (Magoni et al., 2016)

The present study aimed to evaluate the association between current serum levels of total PCBs and specific PCB congeners and CMM in the population living in Brescia, taking into account the main risk factors for the disease. Secondary objectives were evaluation of the possible risk of CMM for PCB exposure according to CMM histology, gender, age, and the presence or absence of the main risk factors for CMM.

2. Materials and methods

The study protocol was approved by the local Ethics Committee (Protocol Number 1695, 12/04/2014).

The present hospital-based case-control study took place between July 2014 and November 2016 at the Spedali Civili Hospital of Brescia. CMM cases were recruited among patients attending a tertiary referral centre for CMM. We enrolled consecutively adult, Italian, Caucasian CMM patients who had first diagnosis of the disease based on histological lab results (incident cases); 19 of them reported history of a previous different melanoma that had been cured successfully, and therefore the present was considered as a new, incident, case. The CCM cases included also melanoma in situ.

Age and sex matched controls were recruited in the Surgical and Orthopaedic Departments of the same hospital among patients without history of cancer, hepatic, endocrine or autoimmune diseases. Enrolled people signed an informed consent, were face-to-face interviewed by a trained nurse using a structured questionnaire and gave a blood sample for laboratory analysis.

The interview lasted 30–45 min and collected information on the subject's demographic variables, residential and occupational history, smoking habit, and exposure to the main risk factors for melanoma.

According to study design, the enrolment of 200 cases and 200 controls would have provided 90% power of showing a statistically significant odds ratio of 2 or more for the highest compared to the lowest quartile of PCB distribution using a two-sided test with alpha = 0.05.

2.1. Laboratory analyses on serum samples

The PCB analyses were performed at the Institute of Occupational Health and Industrial Hygiene of the University of Brescia (Italy) using the same methodology described in previous studies carried out in the same population (Magoni et al., 2016; Raffetti et al., 2017).

A 20 ml blood sample was collected for each subject under fasting conditions for determination of PCB congeners and some biochemistry parameters after the diagnosis confirmation and before starting chemotherapy. The following 33 PCB congeners were determined: 28, 31, 52, 74, 77, 81, 99, 101, 105, 114, 118, 123, 126, 128, 138, 146, 153, 156, 157, 167, 169, 170, 172, 177, 180, 183, 187, 189, 194, 196, 201, 203, 206 and 209. We adopted, with minor adjustments, a previously published PCB analysis method (Turci et al., 2002), using an Agilent Technologies 6890N gas chromatograph coupled with an Agilent Technologies MSD 5973 (electron impact ionization, mass filter: quadrupole). A PONA column (Agilent Technologies; 50 m × 0.20 mm ID) was used for chromatographic separation with carrier gas Helium. A 2 ml injection at 250 °C was performed by a 7683 Series Injector (Agilent Technologies) in splitless mode with a salinized injection liner (Agilent Technologies; 4 mm, 78.5 × 6.5 OD).

The limit of quantification (10 times the signal-to-noise ratio peaks) varied among PCBs but was generally < 0.1 ng/ml for each congener.

PCB serum levels are reported as volumetric values (ng/ml). The total PCB value was computed by summing the serum values of each PCB congener. Lipid-adjusted PCB concentrations are also reported and expressed as ng/g lipid. Total serum lipid concentration was computed by serum cholesterol and triglyceride levels, using the formula proposed by Phillips et al. (1989): total serum lipid (g/l) = 2.27 ∗ serum cholesterol (g/l) + triglycerides (g/l) + 0.623. A twin version of Tables 4, 5,and 6 with PCB values expressed in ng/g lipid is provided as Supplementary tables.

2.2. Statistical analyses

Due to asymmetric, non-normal distribution of PCB values, the medians, range and 75th and 95th centile of the distribution are reported together with arithmetic means and standard deviations (SDs). Non-parametric statistical methods for distribution comparison and Spearman's correlation coefficient were used for continuous variables and chi square for linear trend tests were used for categorical variables.

The odds ratios (ORs) and their 95% confidence intervals (95% CIs) were estimated for assessing the associations between CMM and pigmentation variables, family and personal history of skin cancer, subject's sun sensitivity, sun exposure, education level and working history in agriculture and chemical factory, adjusted for gender and age by logistic regression analysis. A multivariable logistic regression model was fitted to assess the risk of CMM for PCBs serum levels, including age, gender and the investigated risk factors retained in the final model as possible confounders. The final model was chosen by a stepwise backward procedure with a p value of 0.1 for removing variables.

PCB serum concentration was considered both as a continuous, log transformed, variable and an ordinal variable using quartiles of PCB distribution in all subjects. These analyses were performed for total PCB and single PCB congeners detectable in at least 50% of the subjects. The lowest quartile was used as the reference category and subjects with PCB values below the detection limit were included in the lowest quartile.

A sub-group analysis was performed in people younger and older than the median age of the sample (56.67 years).

All the statistical tests were two sided and the corresponding p values are reported; 95% confidence intervals (CIs) of the ORs were computed using the commonly suggested methods. Statistical analyses were performed using the STATA software (Stata Statistical Software release 12.1, 2013; Stata Corporation, College Station, Texas).