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Original Research

Dietary polychlorinated biphenyls, long-chain n-3 polyunsaturated fatty acids and incidence of malignant melanoma



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Cutaneous malignant melanoma;
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Abstract Background: For malignant melanoma, other risk factors aside from sun exposure have been hardly explored. Polychlorinated biphenyls (PCBs)—mainly from fatty fish— may affect melanogenesis and promote melanoma progression, while long-chain n-3 polyunsaturated fatty acids seem to exert antineoplastic actions in melanoma cells.

Objectives: We aimed to assess the association of validated estimates of dietary PCB exposure as well as the intake of eicosapentaenoic acid and docosahexaenoic acid (EPA-DHA), accounting for sun habits and skin type, with the risk of malignant melanoma in middle-aged and elderly women.

Methods: We included 20,785 women at baseline in 2009 from the prospective population-based Swedish Mammography Cohort. Validated estimates of dietary PCB exposure and EPA-DHA intake were obtained via a food frequency questionnaire. Incident melanoma cases were ascertained through register-linkage.

Results: During 4.5 years of follow-up, we ascertained 67 incident cases of melanoma. After multivariable adjustments, exposure to dietary PCBs was associated with four-fold increased risk of malignant melanoma (hazard ratio [HR], 4.0 [95% confidence interval {CI}, 1.2–13; *P* for trend = 0.02]), while EPA-DHA intake was associated with 80% lower risk (HR, 0.2 [95% CI, 0.1–0.8; *P* for trend = 0.03]), comparing the highest exposure tertiles with the lowest.

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Conclusion: While we found a direct association between dietary PCB exposure and risk of melanoma, EPA-DHA intake showed to have a substantial protective association. Question of benefits and risk from fish consumption is very relevant and further prospective studies in the general population verifying these findings are warranted.

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1. Introduction

The incidence of malignant melanoma—the most lethal skin cancer due its high potential for metastasis—has increased abruptly over the past 50 years [1]. In Europe, incidence rates are particularly high in the Nordic countries and generally higher among women than among men [1], although with a female survival advantage [2]. Despite ultraviolet (UV) radiation is the major risk factor [3], other environmental factors such as chemical exposures may play a part in the aetiology of melanoma [4].

Polychlorinated biphenyls (PCBs) are extremely persistent synthetic organochlorine chemicals, with a well-known potential toxicity, that have been widely dispersed into the environment for decades, bio-accumulating and magnifying in the food chain. The general population is exposed to PCBs primarily via food, where fatty fish is a major contributor to dietary PCB exposure in populations with relatively high fish consumption [5,6]. PCBs are readily absorbed, distributed in the body and accumulated in adipose tissue, with half-life for the most persistent congeners ranging from a couple of years to decades [7].

The International Agency for Research on Cancer has recently upgraded PCBs to group 1, i.e. carcinogenic to humans [8]. The strongest evidence on PCB carcinogenicity in humans comes from epidemiological data on risk of malignant melanoma. Virtually all studies on occupational and accidental PCB exposure report excess risk [8]. To date, the only study conducted in a general population is a case–control study with 80 malignant melanoma cases and 310 controls [9]. A clear statistically significant higher odds was observed for the highest compared with the lowest quartile of total plasma PCB concentrations (odds ratio, 6.0; 95% confidence intervals [CI], 2.0–18.2), after adjusting for phenotypic factors, sun sensitivity and sun exposure.

Apart from being a major source of PCBs, fatty fish is also the main source of long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs), proposed to protect against several types of cancer [10] including melanoma [11]. Although *in vitro* and animal studies have provided convincing evidence to support these favourable effects of LC n-3 PUFAs (mainly eicosapentaenoic acid [EPA; 20:5 n-3] and docosahexaenoic acid [DHA, 22:6 n-

3]) against melanoma [12–15], the existing evidence from epidemiological studies exploring this relationship is very limited [11,16].

The aim of the present study was to assess the association between validated estimates of dietary PCB exposure and LC n-3 PUFA intake with the risk of malignant melanoma in a population-based prospective cohort study of middle-aged and elderly Swedish women.

2. Methods

2.1. Study population

The Swedish Mammography Cohort is a large population-based longitudinal cohort established in 1987–1990. All women born between 1914 and 1948, resident in two counties in Central Sweden ($n = 90,303$), were invited to complete a self-administrated questionnaire concerning diet (response rate 74%). In 1997, a more detailed questionnaire was sent to all participants still alive and living in the study area (response rate 70%). In 2009, an additional questionnaire that sought information on sun habits and skin type (information not available until then) was distributed to all remaining cohort members (response rate 84%). More details on the study design have been published elsewhere [17]. In the present study, the 1997 questionnaire was used for the exposure assessment, as there was sufficient documentation of the PCB content in different foods at that time [6]. In order to be able to control for sun habits and skin type (the major known risk factors for melanoma), we used the 2009 questionnaire as baseline in the present study ($n = 21,818$). For the final analyses, we excluded those women with implausible total energy intake (± 3 standard deviation from the log-transformed mean), those who had a diagnosis of cancer before 1997 and those with prevalent malignant melanoma at baseline (1 May 2009), resulting in 20,785 women available at the start of follow-up.

2.2. Dietary PCB exposure and other covariates

The 1997 questionnaire included a 96-item food frequency questionnaire (FFQ), constructed to reflect the women's average consumption of different foods and beverages during the last year. The FFQ has been

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