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# Dietary exposure to polychlorinated biphenyls and risk of breast, endometrial and ovarian cancer in a prospective cohort

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**Background:** Observational studies on polychlorinated biphenyl (PCB) exposure and hormone-related cancer risk are either inconsistent or lacking. We aimed to assess associations of dietary PCB exposure with breast, endometrial and ovarian cancer risk in middle-aged and elderly women.

**Methods:** We included 36 777 cancer-free women at baseline in 1997 from the prospective population-based Swedish Mammography Cohort. Validated estimates of dietary PCB exposure were obtained via a food frequency questionnaire. Incident cancer cases were ascertained through register linkage.

**Results:** During 14 years of follow-up, we ascertained 1593, 437 and 195 incident cases of breast, endometrial and ovarian cancer. We found no overall association between dietary PCB exposure and any of these cancer forms. The multivariable-adjusted relative risks comparing women in the highest and lowest tertile of PCB exposure were 0.96 (95% confidence interval (CI): 0.75, 1.24), 1.21 (95% CI: 0.73, 2.01) and 0.90 (95% CI: 0.45, 1.79) for breast, endometrial and ovarian cancer. In analyses stratified by factors influencing oestrogen exposure, possibly masking associations with PCBs, indications of higher risks were observed for endometrial cancer.

**Conclusions:** This study suggests that dietary exposure to PCBs play no critical role in the development of breast, endometrial or ovarian cancer during middle-age and old ages.

Polychlorinated biphenyls (PCBs), comprising 209 synthetic congeners, have been extensively used in industrial and commercial products from the 1930s until the use was banned in most countries in the 1980s. Because PCBs are highly persistent and lipophilic, they are still widespread in the environment, where they bioaccumulate and magnify along the food chain. Consequently, humans are mainly exposed through food, in particular foods of animal origin such as fatty fish from contaminated waters (Bergkvist *et al*, 2012; Malisch and Kotz, 2014). In the body, PCBs are readily absorbed, distributed and stored in adipose tissue with half-lives of up to 15 years. Thus, elevated concentrations of PCBs are still found in the majority of the general population worldwide (CDC, 2009).

In 2013, PCBs were classified as human carcinogens by the International Agency for Research on Cancer based on evidence of excessive risk of melanoma in both occupationally exposed and in the general population (Lauby-Secretan *et al*, 2013; IARC, 2015). Although an increased risk of breast cancer as a result of PCB exposure is considered biologically plausible, due to PCB endocrine disrupting properties, including oestrogen-like activity

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(Fang *et al*, 2000; Kester *et al*, 2000), the evidence is too limited to draw any conclusions. High levels of PCBs have been found in human breast tissue (Ellsworth *et al*, 2015) and experimental studies have suggested a role of PCBs in the aetiology of mammary tumour formation (Liu *et al*, 2010; Ptak *et al*, 2010). However, the observational data based on PCB biomarkers, either from case-control or nested-case-control studies, are partly inconsistent (Zhang *et al*, 2015; Leng *et al*, 2016). Some studies have observed a positive association, most often only with specific PCB congeners (Leng *et al*, 2016), certain groups of PCB congeners (Zhang *et al*, 2015), or in population sub-group analyses (Millikan *et al*, 2000), while others have observed no association.

Simultaneously, the capacity of PCBs to disrupt hormone-dependent pathways, including steroid hormone systems, raise concern about a potential link with other female hormone-sensitive cancers such as endometrial and ovarian cancer. Endometrial cancer has a relatively brief latency and is more sensitive towards exogenous and endogenous oestrogen than breast cancer (Adami *et al*, 1995; Akhmedkhanov *et al*, 2001). Still, only two case-control studies have explored the association of serum PCBs with endometrial cancer, without observing any significant association (Sturgeon *et al*, 1998; Weiderpass *et al*, 2000). To our knowledge, there is currently no published data on background exposure to PCBs and ovarian cancer. In electrical capacitor-manufacturing workers no clear increased mortality was observed for ovarian and uterine cancer (Ruder *et al*, 2014). Therefore, the aim of the present study was to prospectively assess the association between validated estimates of dietary PCB exposure and the risk of breast, endometrial and ovarian cancer in a large population-based cohort of middle-aged and elderly Swedish women.

## MATERIALS AND METHODS

**Study population.** The Swedish Mammography Cohort, a population-based prospective cohort of women, was established during a mammography-screening programme between 1987 and 1990 (Harris *et al*, 2013). The source population, consisting of 90 303 women born between 1914 and 1948, and residing in central Sweden (Uppsala and Västmanland counties), received a mailed self-administered questionnaire on diet and lifestyle (response rate 74%). In 1997, a second extended questionnaire was sent to all cohort members who were still alive and living in the study area (response rate 70%; $n = 39\,227$). The 1997 questionnaire was used as the baseline questionnaire in the present study, as there was sufficient documentation of the PCB content in different foods at this time (Bergkvist *et al*, 2012). Return of a complete questionnaire was considered as informed consent to participate in the study which has been approved by the Regional Ethical Review Board, Stockholm, Sweden (Harris *et al*, 2013).

For assessing the association of dietary PCB exposure and risk of breast, endometrial and ovarian cancer, we excluded women with an incorrect or missing personal identification number ($n = 243$), prevalent cancer at baseline ($n = 1717$) or implausible energy intake ($\pm 3$ s.d.'s of mean log-transformed energy intake, $n = 490$). Hence, the final study cohort consisted of 36 777 women at start of follow-up. For the assessment of endometrial and ovarian cancer we additionally excluded women with hysterectomy ($n = 504$) or bilateral oophorectomy ($n = 2637$), respectively, at baseline (Figure 1).

**Questionnaire on diet and lifestyle factors.** The baseline questionnaire included a 96-item food frequency questionnaire (FFQ), constructed to reflect the women's average consumption of

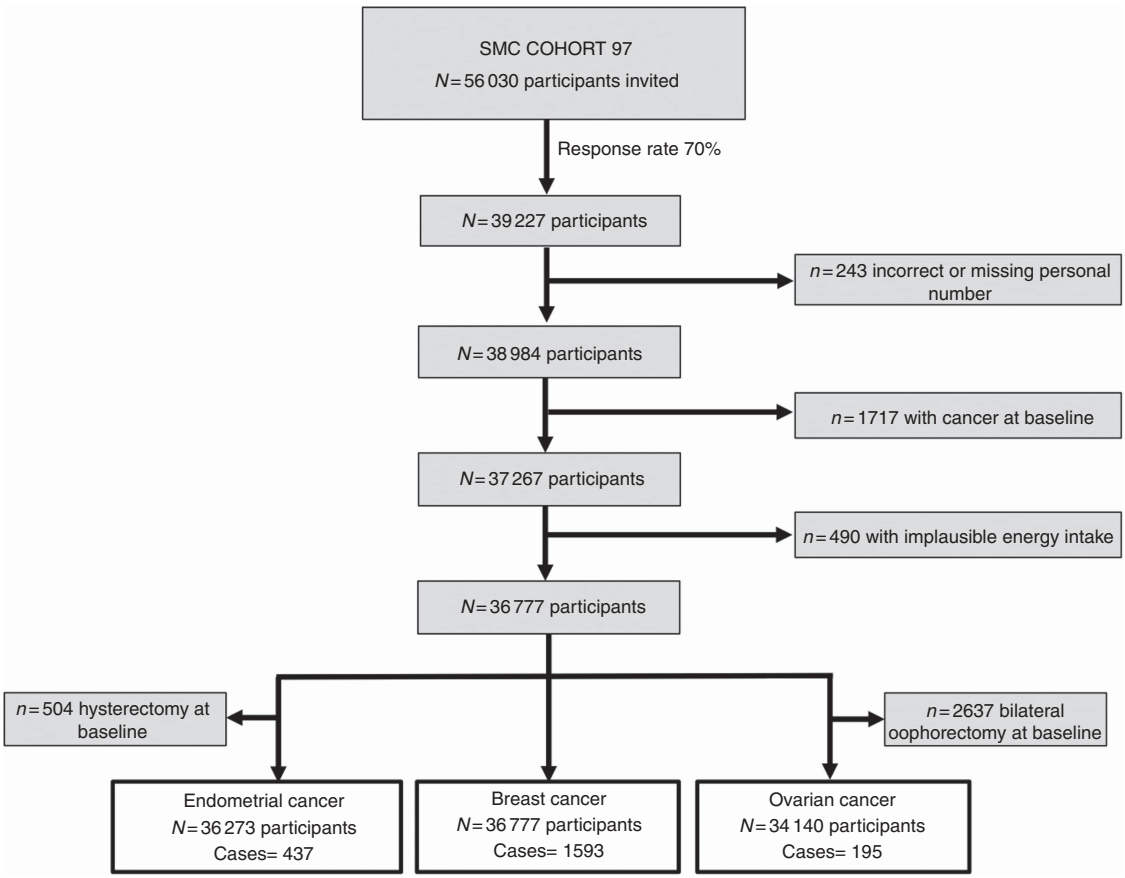


Figure 1. Flow chart of exclusion from the Swedish Mammography Cohort.

different foods and beverages during the last year. For frequently consumed foods, the FFQ contained open-ended questions with pre-specified serving sizes, whereas for other foods it had eight predefined frequency categories ranging from never to three times per day. Age-specific portion-sizes were estimated from 5922 weighted food records kept by 213 randomly selected women from the study area. The FFQ has been validated, obtaining Pearson correlation coefficients (r) between the average of four 1-week dietary records and the dietary questionnaire of 0.6 for fatty fish and 0.5–0.7 for dairy products (Wolk A, personal communication).

The questionnaire also included questions on history of certain diseases and medications (oral contraceptives and postmenopausal hormones), as well as on level of education, body weight, height, age at menarche, parity, age at menopause, smoking habits and physical activity. Body mass index (BMI) was calculated as the weight in kilograms (kg) divided by the square of the height in metres (m). The validity of BMI based on self-reported weight and height in the Swedish population has been shown to be high ($r = 0.85$; Kuskowska-Wolk *et al*, 1989). Women who did not report their menopausal status were classified as postmenopausal if they had gone through bilateral oophorectomy, used postmenopausal hormones, or were 55 years of age or older ($\sim$95% of the women reported to have entered menopause before 55 years of age). Physical activity was estimated using a validated questionnaire from which we obtained information about leisure-time activity (less or more than 2 hours of watching TV or sitting per day) and time spent walking or bicycling (less or more than 40 minutes per day; Orsini *et al*, 2008).

**Assessment of dietary PCB exposure and other dietary factors.** The dietary exposure to PCBs was estimated at the time of baseline through an extensive recipe-based database created for the FFQ, described in detail elsewhere (Bergkvist *et al*, 2012). The database was based on concentrations of the PCB-153 congener, which is the most abundant congener in food on the Swedish market and therefore a very good indicator of total PCBs, dioxin-like PCBs and the related polychlorinated dibenzodioxins and polychlorinated dibenzofurans in food and in human serum (Covaci *et al*, 2002; Bergkvist *et al*, 2012). The content of PCBs and long-chain omega-3 fish fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in foods was obtained from the Swedish Food Database provided by the Swedish National Food Agency.

Daily dietary exposure to PCBs (ng per day) and dietary intake of EPA-DHA (mg per day) was estimated by multiplying the average concentration in various foods with the respective consumption frequency and portion size, and then, adjusting for total energy intake (mean of 1700 kcal per day, for the cohort) using the residual-regression method (Willett and Stampfer, 1986). The FFQ-based dietary estimate of PCB exposure has been extensively validated against six serum PCB congeners (118, 138, 153, 156, 170 and 180) in a representative subsample of the cohort (Spearman correlation coefficients ranged from 0.30 to 0.58; Bergkvist *et al*, 2012). The FFQ-based dietary intake of EPA-DHA has been validated against adipose tissue concentrations; *r* of 0.32 and 0.48, respectively for concurrent, and 0.21 and 0.33, respectively for past exposure assessment (6 years before the adipose tissue sampling) in women (Wallin *et al*, 2014).

**Ascertainment of outcomes.** Incident cases of invasive breast cancer, endometrial adenocarcinoma and epithelial ovarian cancer were ascertained by computerised linkage via the personal identification number to the national and regional Swedish Cancer Registers, which is close to 100% complete (Mattsson and Wallgren, 1984). For breast cancer, information about oestrogen receptor (ER) status of the tumour was obtained from the Quality Register at the Regional Oncology Centre in Uppsala. Information about oophorectomies and hysterectomies was obtained from the National Patient Register. Ascertainment of deaths was also obtained through register linkage.

**Statistical analyses.** The women were followed from mid-September 1997 until the date of diagnosis of breast, endometrial or ovarian cancer, hysterectomy or bilateral oophorectomy (only for endometrial and ovarian cancer, respectively), death, or end of follow-up (31 December 2012), whichever occurred first. Women were categorised into tertiles of dietary PCB exposure at baseline. Hazard ratios (herein referred to as relative risks, RRs) and 95% confidence intervals (CI) were estimated using Cox proportional hazard regression models with attained age (1-year units) as the underlying timescale. The proportional hazard assumption was checked by evaluating Schoenfeld's residuals and no departure from this assumption was observed. The models were adjusted for: postsecondary education (no/yes), family history of breast cancer (no/yes), oophorectomy (only for breast and endometrial cancers), history of diabetes (no/yes), BMI ($<18.5$, 18.5–25, 25–30, $>30\,kg\,m^{-2}$), weight loss $>5$ kg within 1 year (no/yes), age at menarche ($<12$, 13, $\geqslant 14$ years), ever use of oral contraceptives (no/yes), parity (no child, 1–2, $\geqslant 3$ children), age at first birth (nulliparous, $<26$, 26–30, $\geqslant 30$ years), age at menopause (premenopausal, $<51$, $\geqslant 51$ years), ever use of postmenopausal hormones (no/yes), smoking habits (current, former, never), leisure-time inactivity (high/low) and daily walking/cycling (low/high), alcohol consumption (no use, 0.1–5, 5.1–15, $>15$ g per day) and total energy intake (continuous, kcal per day). We additionally adjusted for dietary EPA-DHA intake (tertiles, mg per day; Zheng *et al*, 2013). To test for linear trends across increasing categories of dietary PCB exposure we assigned the median exposure within each category and included it as a continuous variable.

We carried out a sensitivity analysis replicating the models after exclusion of premenopausal women at baseline ($<10$%). To explore whether any potential PCB-related oestrogenic effect on breast and endometrial cancer development was masked by factors affecting the exogenous or endogenous oestrogen exposure, we stratified by BMI ($\leqslant 25$, 25–30, $>30\,kg\,m^{-2}$ (for endometrial cancer only $\leqslant 25$ and $>25\,kg\,m^{-2}$); Akhmedkhanov *et al*, 2001), ever use of postmenopausal hormones (no/yes; Reeves *et al*, 2006) and smoking status (never/ever; Terry *et al*, 2002). Stratified analyses were not conducted for ovarian cancer due to the limited number of cases ($n = 195$). We tested for interactions on the multiplicative scale using the likelihood ratio test, comparing models with and without an interaction term. In addition, as endometrial cancer seems to be particularly sensitive to hormonal factors (Adami *et al*, 1995), in order to avoid as much as possible that the effect of PCBs was disguised by other factors affecting the oestrogen exposure, we conducted the analyses excluding women who were overweight and obese ($BMI > 25\,kg\,m^{-2}$), ever users of postmenopausal hormones and ever smokers.

Finally, based on recent experimental evidence showing that prenatal exposure to the polychlorinated organic pollutant dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin; same dietary sources as PCBs) doubled mammary tumour incidence only in mice fed an obesity-associated diet high in animal fat (La Merrill *et al*, 2010), we conducted stratified analysis among non-obese and obese women ($BMI \leqslant 30$ or $>30\,kg\,m^{-2}$) consuming a diet either low or high in saturated fat (median split). Missing values were generally below 5% for the covariates, with the exception of age at menopause (13%). We fitted the multivariable-adjusted models including the missing values in a separate category. The results did, however, not differ after replicating the main models using a multiple imputation chained equation technique with 20 imputations to handle missing data. All *P*-values presented were two-tailed, and *P*-values $<0.05$ were considered statistically

significant. Analyses were performed using STATA/SE version 13.0 (StataCorp LP, College Station, TX, USA).

## RESULTS

During 14 years of follow-up (505 623 person-years), we ascertained 1593, 437 and 195 incident cases of breast, endometrial and ovarian cancer. Information on ER status was available in 83% of the breast cancer cases out of which 1155 were ER+ and 162 were ER−. The mean age at diagnosis was 69, 71 and 69 years for breast, endometrial and ovarian cancer, respectively. The median dietary PCB exposure was 162 ng per day (5–95th percentile: 70–368 ng per day). No major differences in baseline age-standardised characteristics were observed across tertiles of dietary PCB exposure, with the exception of dietary intake of EPA-DHA, which was about three times higher among women in the highest tertile of dietary PCB exposure compared with those in the lowest tertile (Table 1).

We observed no significant association between dietary PCB exposure and breast cancer risk in either the age- or multivariable-adjusted model (Table 2). The RR of the fully adjusted model (additionally adjusted for dietary intake of EPA-DHA) was 0.96 (95% CI: 0.75, 1.24) when comparing women in the highest tertile of dietary PCB exposure with those in the lowest. Likewise, no associations were observed in relation to ER+ and ER− breast cancer. No association was observed between dietary PCB exposure and endometrial or ovarian cancer; comparing women in the highest with those in the lowest tertile of dietary PCB exposure, the fully multivariable-adjusted RR was 1.21 (95% CI: 0.73, 2.01) and 0.90 (95% CI: 0.45, 1.79), respectively (Table 2). In sensitivity analysis, the corresponding fully multivariable-adjusted RR for the three cancers after excluding premenopausal women at baseline was 1.00 (95% Cl: 0.77, 1.30; 1445 cases of breast cancer), 1.21 (95% Cl: 0.71, 2.05; 400 cases of endometrial cancer) and 1.06 (95% Cl: 0.51, 2.20; 174 cases of ovarian cancer).

To limit the potential impact of factors affecting the variation in endogenous and exogenous oestrogen exposure, which might obscure any relationship between dietary PCB exposure and cancer risk, we stratified by BMI, ever use of postmenopausal hormones, and smoking status. Comparing women in the highest and lowest tertile of dietary PCB exposure, the fully multivariable-adjusted RR for breast cancer differed slightly by BMI, but not by postmenopausal hormone use or smoking status ($P$ for interaction $>0.3$ for all; Table 3). Accordingly, the RR for lean women was 0.81 (95% Cl: 0.58, 1.14), for overweight women was 1.11 (95% Cl: 0.73, 1.71) and for obese women was 1.32 (95% Cl: 0.61, 2.85).

For endometrial cancer, the corresponding fully multivariable-adjusted RR for dietary PCBs was higher among lean women (RR 1.34; 95% CI: 0.60, 2.98) and even higher among never users of postmenopausal hormones (RR 1.57; 95% CI: 0.75, 3.32), but the association only reached statistical significance among never smokers (RR 2.02; 95% CI: 1.06, 3.86; Table 4) without evidence of any interactions ($P$ for interaction $>0.3$ for all). When we excluded women who were overweight and obese, ever used postmenopausal hormones and ever smoked, the multivariable-adjusted RR among the remaining women was 2.42 (95% Cl: 0.43, 13.73) when comparing women in the highest tertile of dietary PCB exposure with those in the lowest.

Finally, the RRs for breast cancer when we conducted a stratified analysis among non-obese and obese women (BMI$\leqslant$30 or $>30\,kg\,m^{-2}$) consuming a diet either low or high in saturated fat were 0.91 (95% Cl: 0.30, 2.73) for obese women with a low saturated fat intake and 2.19 (95% Cl: 0.73, 6.54) for obese women with a high saturated fat intake, comparing women in the highest and lowest tertile of dietary PCB exposure (Figure 2). No evidence of an interaction was observed between saturated fat intake and PCB exposure ($P$ for interaction $=0.96$).

## DISCUSSION

It is biologically plausible that hormonally active chemicals, including PCBs, contribute to the risk of cancers in hormone-sensitive tissues such as the breast, endometrium and ovary. In this large prospective cohort of Swedish women, we observed, however,

**Table 1. Age-standardised baseline characteristics of 36 777 women from the Swedish Mammography Cohort by tertiles of dietary PCB exposure**

| Tertiles of dietary PCB exposure range (median) ng per day[a] | <139 (110) | 139–193 (162) | >193 (256) |
|---|---|---|---|
| Age (years) | 62 ± 10 | 60 ± 9 | 63 ± 9 |
| Postsecondary education (%) | 25 | 27 | 26 |
| Family history of breast cancer (%) | 9 | 9 | 9 |
| History of diabetes (%) | 5 | 4 | 6 |
| BMI ($kg\,m^{-2}$) | 25 ± 4 | 25 ± 4 | 25 ± 4 |
| Weight loss >5 kg within 1 year (%) | 68 | 69 | 70 |
| Age at menarche ⩽12 years (%) | 28 | 27 | 29 |
| Ever use of oral contraceptives (%) | 55 | 58 | 58 |
| Nulliparous (%) | 10 | 9 | 9 |
| Age at first birth ⩾30 years (%) | 12 | 11 | 10 |
| Premenopausal (%) | 11 | 12 | 11 |
| Age at menopause ⩾51 years (%) | 42 | 43 | 43 |
| Ever use of postmenopausal hormones (%) | 50 | 52 | 51 |
| Current smoker (%) | 24 | 22 | 24 |
| Leisure-time daily physical activity (%) | | | |
| ⩽2 h sitting/watching TV | 56 | 55 | 56 |
| >40 min walking/bicycling | 36 | 35 | 36 |
| Alcohol consumption (%) | | | |
| No use | 22 | 14 | 16 |
| >15 g per day | 7 | 9 | 9 |
| Total energy intake (kcal per day) | 1780 ± 5 | 1710 ± 4 | 1710 ± 5 |
| EPA-DHA intake (mg per day) | 164 ± 68 | 289 ± 54 | 555 ± 326 |

Abbreviations: BMI = body mass index; EPA-DHA = eicosapentaenoic acid-docosahexaenoic acid; PCB = polychlorinated biphenyl.
[a]Adjusted for total energy intake.
Note: All variables are expressed as mean ± s.d. or percentage (%).

**Table 2. RR (95% CIs) of breast, endometrial and ovarian cancer by tertiles of dietary PCB exposure**

| Tertiles of dietary PCB exposure range (median) ng per day[a] | <139 | 139–195 | >195 | *P* trend |
|---|---|---|---|---|
| **Breast cancer** | | | | |
| All invasive tumours | | | | |
| Cases/person-years | 530/167 793 | 561/171 616 | 502/166 214 | |
| Age-adjusted RR | 1 (ref.) | 1.03 (0.92, 1.16) | 0.95 (0.84, 1.07) | 0.31 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 1.00 (0.89, 1.13) | 0.93 (0.82, 1.05) | 0.18 |
| Multivariable-adjusted RR[c] | 1 (ref.) | 0.98 (0.83, 1.17) | 0.96 (0.75, 1.24) | 0.77 |
| ER+ tumours[d] | | | | |
| Cases/person-years | 379/166 712 | 407/170 555 | 369/165 282 | |
| Age-adjusted RR | 1 (ref.) | 1.04 (0.91, 1.20) | 0.99 (0.85, 1.14) | 0.76 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 1.01 (0.88, 1.16) | 0.95 (0.83, 1.10) | 0.48 |
| Multivariable-adjusted RR[c] | 1 (ref.) | 1.01 (0.82, 1.23) | 0.98 (0.73, 1.32) | 0.90 |
| ER− tumours[d] | | | | |
| Cases/person-years | 54/166 712 | 53/170 555 | 53/165 282 | |
| Age-adjusted RR | 1 (ref.) | 0.96 (0.66, 1.40) | 0.98 (0.67, 1.43) | 0.93 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 0.96 (0.66, 1.41) | 0.99 (0.67, 1.45) | 0.97 |
| Multivariable-adjusted RR[c] | 1 (ref.) | 0.98 (0.57, 1.70) | 1.25 (0.54, 2.75) | 0.54 |
| **Endometrial cancer** | | | | |
| Cases/person-years | 146/165 017 | 133/169 615 | 158/163 827 | |
| Age-adjusted RR | 1 (ref.) | 0.90 (0.71, 1.14) | 1.03 (0.82, 1.29) | 0.65 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 0.99 (0.78, 1.26) | 1.05 (0.84, 1.32) | 0.64 |
| Multivariable-adjusted RR[c] | 1 (ref.) | 1.26 (0.90, 1.77) | 1.21 (0.73, 2.01) | 0.54 |
| **Ovarian cancer** | | | | |
| Cases/person-years | 66/155 626 | 63/159 995 | 66/154 671 | |
| Age-adjusted RR | 1 (ref.) | 0.92 (0.67, 1.33) | 0.95 (0.65, 1.31) | 0.93 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 0.88 (0.62, 1.24) | 0.97 (0.69, 1.37) | 0.98 |
| Multivariable-adjusted RR[c] | 1 (ref.) | 0.71 (0.43, 1.16) | 0.90 (0.45, 1.79) | 0.95 |

Abbreviations: BMI = body mass index; CI = confidence interval; EPA-DHA = eicosapentaenoic acid-docosahexaenoic acid; ER = oestrogen receptor; PCB = polychlorinated biphenyl; RR = relative risk.

[a]Adjusted for total energy intake.

[b]Adjusted for attained age, postsecondary education, family history of breast cancer, oophorectomy (only for breast and endometrial cancer), history of diabetes, BMI, weight loss > 5 kg within 1 year, age at menarche ⩽12 years, use of oral contraceptives, parity, age at first birth ⩾30 years, age at menopause ⩾51 years, ever use of postmenopausal hormones, smoking habits, leisure-time inactivity, time spent walking or bicycling, alcohol consumption and total energy intake.

[c]Additionally adjusted for dietary EPA-DHA intake.

[d]Excluding 278 cases with no information on ER status of the tumour.

no indication of an overall association between validated estimates of dietary PCB exposure and incident breast, endometrial or ovarian cancer. To account for variations in exogenous and endogenous oestrogen exposures potentially obscuring any associations, we stratified by adiposity, postmenopausal hormone use and smoking status. Focusing on breast cancer, we observed no association among women expected to be less influenced by oestrogen exposures (lean, never users of postmenopausal hormones and never smokers). For the more oestrogen sensitive endometrial cancer, indications of higher risks were suggested in these three groups of women, but statistical significance was only reached among never smokers.

Our null results on breast cancer risk are in accordance with the majority of the previous case-control (Zheng *et al*, 2000; Gammon *et al*, 2002; Lopez-Carrillo *et al*, 2002; Rubin *et al*, 2006; Gatto *et al*, 2007) and nested-case-control studies (Wolff *et al*, 1993; Krieger *et al*, 1994; Helzlsouer *et al*, 1999; Ward *et al*, 2000; Wolff *et al*, 2000; Laden *et al*, 2001; Raaschou-Nielsen *et al*, 2005), observing no association between either total PCB exposure—measured in adipose tissue or blood—or between specific congeners (including PCB-153) and risk of breast cancer. In addition, two meta-analyses found no significant association with total PCB exposure when comparing the highest and lowest catesgories (odds ratio = 1.15, 95% CI: 0.92, 1.43; $I^2 = 70.6\%$ (Zani *et al*, 2013) and odds ratio = 1.09, 95% CI: 0.97, 1.22; $I^2 = 55.4\%$ (Zhang *et al*, 2015)).

Although several studies have reported significant associations between specific PCB congeners and breast cancer, the pooled OR from congener-specific meta-analysis were only statistically significant for PCB-99, PCB-183 and PCB-187 (Leng *et al*, 2016). Nevertheless, the results are difficult to interpret due to multiple comparisons, as well as the high correlation between different congeners, resulting in collinearity. Moreover, when congeners are assessed individually, the potential additive or synergistic effects are not taken into account. By grouping PCBs according to their structural, biological and pharmacokinetics properties, Zhang *et al* (2015), observed significant pooled ORs for PCB group II (potentially anti-oestrogenic and immunotoxic, dioxin-like) and group III (phenobarbital, CYP1A and CYP2B inducers, biologically persitent), but not for group I (potentially oestrogenic) (Zhang *et al*, 2015).

Interestingly, in an experimental study on early-life exposure, the polychlorinated organic pollutant dioxin induced mammary tumour incidence in obese mice depending on whether the animals were fed a diet high in saturated fat or not (La Merrill *et al*, 2010). In line with this, we observed a statistically non-significant increased breast cancer risk with increasing long-term dietary PCB exposure among obese women with a high intake of saturated fat, while no association was observed among obese women with a low intake of saturated fat or among the non-obese women. Any potential mechanism behind this finding remains to be elucidated.

Although our study is the first one to explore an association between background exposure to PCBs and ovarian cancer risk, our null findings for endometrial cancer are in accordance with two other previous population-based case-control studies (Sturgeon *et al*, 1998; Weiderpass *et al*, 2000). In the study by Weiderpass and coworkers, which included 154 cases and 205 controls residing in Sweden, no association was observed between quartiles of total PCBs (10 congeners) in serum and endometrial cancer (OR 1.2; 95% CI: 0.6, 2.2; Weiderpass *et al*, 2000). They also

**Table 3. RR (95% CIs) of breast cancer according to tertiles of dietary PCB exposure stratified by BMI, use of postmenopausal hormones and smoking status**

| Tertiles of dietary PCB exposure range (median) ng per day[a] | <139 | 139–195 | >195 | *P* trend |
|---|---|---|---|---|
| **BMI** | | | | |
| <25 kg m$^{-2}$ (median 22.6 kg m$^{-2}$) | | | | |
| Cases/person-years | 289/94 148 | 308/97 495 | 243/86 243 | |
| Age-adjusted RR | 1 (ref.) | 1.02 (0.87, 1.20) | 0.93 (0.78, 1.10) | 0.32 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 0.89 (0.70, 1.12) | 0.81 (0.58, 1.14) | 0.25 |
| 25–30 kg m$^{-2}$ (median 26.8 kg m$^{-2}$) | | | | |
| Cases/person-years | 163/53 568 | 190/56 051 | 185/57 457 | |
| Age-adjusted RR | 1 (ref.) | 1.12 (0.91, 1.38) | 1.03 (0.84, 1.28) | 0.92 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 1.14 (0.84, 1.54) | 1.11 (0.73, 1.71) | 0.72 |
| >30 kg m$^{-2}$ (median 32.0 kg m$^{-2}$) | | | | |
| Cases/person-years | 71/16 880 | 56/15 925 | 67/19 639 | |
| Age-adjusted RR | 1 (ref.) | 0.83 (0.59, 1.18) | 0.80 (0.57, 1.12) | 0.23 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 0.90 (0.54, 1.49) | 1.32 (0.61, 2.85) | 0.49 |
| **Use of postmenopausal hormones** | | | | |
| Never users | | | | |
| Cases/person-years | 218/82 800 | 236/81 821 | 198/79 013 | |
| Age-adjusted RR | 1 (ref.) | 1.10 (0.92, 1.33) | 0.93 (0.77, 1.13) | 0.36 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 0.93 (0.72, 1.21) | 0.91 (0.62, 1.34) | 0.66 |
| Ever users | | | | |
| Cases/person-years | 306/82 922 | 319/87 974 | 300/85 568 | |
| Age-adjusted RR | 1 (ref.) | 0.98 (0.84, 1.14) | 0.95 (0.81, 1.12) | 0.55 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 1.03 (0.82, 1.29) | 1.00 (0.72, 1.40) | 0.98 |
| **Smoking habits** | | | | |
| Never smokers | | | | |
| Cases/person-years | 263/87 916 | 281/88 626 | 258/89 646 | |
| Age-adjusted RR | 1 (ref.) | 1.06 (0.90, 1.26) | 0.95 (0.80, 1.13) | 0.44 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 1.03 (0.81, 1.32) | 1.08 (0.76, 1.55) | 0.67 |
| Current and former smokers | | | | |
| Cases/person-years | 260/76 777 | 275/80 254 | 234/73 464 | |
| Age-adjusted RR | 1 (ref.) | 1.01 (0.85, 1.20) | 0.93 (0.78, 1.11) | 0.40 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 0.91 (0.72, 1.16) | 0.81 (0.57, 1.15) | 0.24 |

Abbreviations: BMI = body mass index; CI = confidence interval; EPA-DHA = eicosapentaenoic acid-docosahexaenoic acid; PCB = polychlorinated biphenyl; RR = relative risk.
[a]Adjusted for total energy intake.
[b]Adjusted for attained age, postsecondary education, family history of breast cancer, oophorectomy (only for breast and endometrial cancer), history of diabetes, BMI, weight loss > 5 kg within 1 year, age at menarche ⩽12 years, use of oral contraceptives, parity, age at first birth ⩾30 years, menopausal status, age at menopause ⩾51 years, ever use of postmenopausal hormones, smoking habits, leisure-time inactivity, time spent walking or bicycling, alcohol consumption and intake of total energy and EPA-DHA.

observed no significant associations for individual congeners (e.g., for PCB-153 the OR was 0.9 (95% CI: 0.5, 1.7)) or congeners grouped by different hormonal activity. Similarly, the other study (Sturgeon *et al*, 1998), based on 90 cases and 90 controls from a multicenter study in five geographic regions in the US, obtained an OR of 0.9 (95% CI: 0.4, 2.5) when comparing the highest quartile of total serum PCBs (in total 27 congeners assessed jointly) with the lowest quartile.

Our overall null-findings observed in this large population-based prospective cohort could be explained by that PCBs, at the levels present in the general population, do not increase the risk of cancer in the breast, endometrium or ovary. Specific PCB congeners have been shown to exert opposite hormonal effects (e.g., oestrogenic, anti-oestrogenic or/and anti-androgenic (Fang *et al*, 2000; Fang *et al*, 2003; Zhang *et al*, 2015)), suggesting that the balance between these opposite responses to individual congeners may be the reason for the overall null findings. We did, however, observe a statistically significant positive dose-response association between dietary PCBs and endometrial cancer risk among never smokers, whereas no association was observed in smokers. Although we cannot exclude that this represents a chance finding, it can be speculated that tobacco smoking – which exerts anti-oestrogen effect via increased metabolic clearance of circulating oestrogen concentrations, a reduction in relative body weight, and an earlier age at menopause (Terry *et al*, 2002) – obscured the association between PCBs and endometrial cancer. Likewise, it can be speculated that the suggested higher endometrial cancer risk observed among lean women and never users of hormone replacement therapy, reflects masking of the associations by adiposity and postmenopausal hormone use.

The major strengths of our study include (i) its prospective population-based design, which avoids reverse causation bias and allows us to take into account long-term exposure to dietary PCBs, (ii) the large sample size with an ample number of cases, (iii) the almost 100% complete cancer ascertainment in the Swedish Cancer Registry (Mattsson and Wallgren, 1984), minimising differential loss to follow-up, (iv) the availability of detailed and validated data on PCBs and other dietary exposures and data on other potential risk factors for these female cancers, and (vi) that we took into account both the time-trend of decreasing PCB concentrations in food and the effect of the processing on the PCB concentrations in cooked food in the dietary PCB exposure estimation (Bergkvist *et al*, 2012). Potential limitations include the measurement error and subsequent misclassification of PCB exposure and the limited number of cases in some stratified analyses, which could influence the lack of observed associations. Although the diet is the major route of exposure to PCBs (>95%) in the general population (Malisch and Kotz, 2014) and various dietary patterns have been associated with serum PCB levels (Ax *et al*, 2015), additional exposures from other non-dietary sources, such as indoor air PCBs, cannot be excluded. Exposure via inhalation in contaminated buildings constructed in 1950–70, may mainly contribute to the less chlorinated PCB congeners (Bräuner *et al*, 2016). Also, because it is not possible to discriminate between different contaminants present in the same foods as PCBs, we

**Table 4. RR (95% CIs) of endometrial cancer according to tertiles of dietary PCB exposure stratified by BMI, use of postmenopausal hormones and smoking status**

| Tertiles of dietary PCB exposure range (median) ng per day[a] | <139 | 139–195 | >195 | *P* trend |
|---|---|---|---|---|
| **BMI** | | | | |
| ⩽25 kg m$^{-2}$ (median 22.6 kg m$^{-2}$) | | | | |
| Cases/person-years | 57/93 380 | 59/96 806 | 57/85 950 | |
| Age-adjusted RR | 1 (ref.) | 1.01 (0.70, 1.46) | 1.02 (0.71, 1.47) | 0.92 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 1.34 (0.80, 2.22) | 1.34 (0.60, 2.98) | 0.49 |
| >25 kg m$^{-2}$ (median 27.5 kg m$^{-2}$) | | | | |
| Cases/person-years | 86/68 512 | 74/70 666 | 97 034 | |
| Age-adjusted RR | 1 (ref.) | 0.85 (0.62, 1.16) | 0.99 (0.74, 1.32) | 0.93 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 1.17 (0.74, 1.85) | 1.11 (0.58, 2.13) | 0.85 |
| **Use of postmenopausal hormones** | | | | |
| Never users | | | | |
| Cases/person-years | 76/81 741 | 60/81 096 | 76/78 135 | |
| Age-adjusted RR | 1 (ref.) | 0.81 (0.58, 1.14) | 1.00 (0.72, 1.37) | 0.85 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 1.08 (0.66, 1.77) | 1.57 (0.75, 3.32) | 0.22 |
| Ever users | | | | |
| Cases/person-years | 68/81 237 | 70/86 801 | 81/84 092 | |
| Age-adjusted RR | 1 (ref.) | 0.97 (0.70, 1.36) | 1.08 (0.78, 1.49) | 0.58 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 1.50 (0.82, 2.25) | 1.04 (0.43, 1.86) | 0.79 |
| **Smoking habits** | | | | |
| Never smokers | | | | |
| Cases/person-years | 90/86 340 | 82/87 769 | 107/88 702 | |
| Age-adjusted RR | 1 (ref.) | 0.91 (0.67, 1.22) | 1.10 (0.83, 1.46) | 0.38 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 1.61 (1.06, 2.44) | 2.02 (1.06, 3.86) | 0.04 |
| Current and former smokers | | | | |
| Cases/person-years | 53/75 568 | 51/79 135 | 48/72043 | |
| Age-adjusted RR | 1 (ref.) | 0.94 (0.64, 1.38) | 0.91 (0.62, 1.35) | 0.67 |
| Multivariable-adjusted RR[b] | 1 (ref.) | 0.90 (0.51, 1.61) | 0.54 (0.24, 1.22) | 0.11 |

Abbreviations: BMI = body mass index; CI = confidence interval; EPA-DHA = eicosapentaenoic acid-docosahexaenoic acid; PCB = polychlorinated biphenyl; RR = relative risk.
[a]Adjusted for total energy intake.
[b]Adjusted for attained age, postsecondary education, family history of breast cancer, oophorectomy (only for breast and endometrial cancer), history of diabetes, BMI, weight loss > 5 kg within 1 year, age at menarche ⩽12 years, use of oral contraceptives, parity, age at first birth ⩾30 years, menopausal status, age at menopause ⩾51 years, ever use of postmenopausal hormones, smoking habits, leisure-time inactivity, time spent walking or bicycling, alcohol consumption and intake of total energy and EPA-DHA.

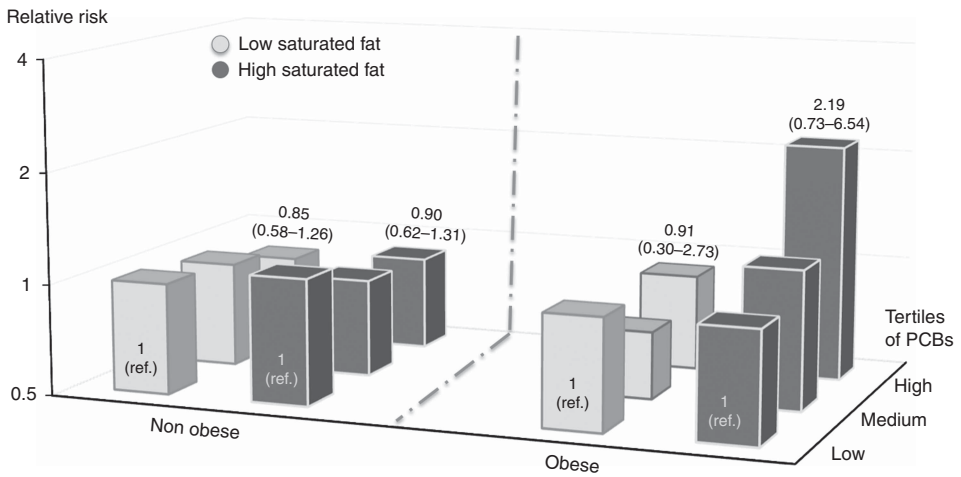


Figure 2. Relative risk (95% confidence intervals) of breast cancer by tertiles of dietary PCB exposure among non-obese and obese women, stratified by low and high intake of saturated fat.

cannot dismiss the possibility that the co-exposure to other chemicals has confounded the associations observed.

In conclusion, the present study suggests that dietary PCB exposure in middle-aged and older women does not play a major role in the development of cancers of the breast, endometrium or ovary. Further research exploring other susceptible exposure windows and subgroups, as well as taking into account other potential non-dietary sources of PCB exposure, is nevertheless justified.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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