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Polychlorinated biphenyls and breast cancer: A congener-specific meta-analysis

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ABSTRACT

The incidence of breast cancer is related to various risk factors, especially that the environmental and lifestyle factors account for major contribution at the rate of 70% to 95% over all. However, there still remains some controversy over the epidemiological evidence regarding the effects of environmental carcinogens on the risk of breast cancer. We conducted a quantitative meta-analysis aiming at full evaluation of the effects of polychlorinated biphenyls (PCBs) on breast cancer in a congener-specific fashion. Four online literature databases were systematically searched before 1st January 2015, for studies stating correlation between PCB congeners and breast cancer. The Newcastle–Ottawa Scale was used to evaluate the quality of the studies that were included in our analysis. Sixteen studies were included in our final meta-analysis after screening based on the priori inclusion criteria. Nine PCB congeners were reported by more than two studies and they were presented in detail. The pooled Odds Ratios (ORs) showed a significant increase in the risk of breast cancer in individuals with higher plasma/fat levels of PCB 99 (OR: 1.36; 95% CI: 1.02 to 1.80), PCB 183 (OR: 1.56; 95% CI: 1.25 to 1.95) and PCB 187 (OR: 1.18; 95% CI: 1.01 to 1.39). Besides, the outcomes did not support a relationship between dioxin-like PCB congeners and the risk of breast cancer. The results of our meta-analysis imply that PCB 99, PCB 183 and PCB 187 would increase the risk of breast cancer. The mechanism of this increased risk may be by the induction of the CYP2B family in cytochrome P450 enzymes.

1. Introduction

Breast cancer is one of the most frequently occurred cancers affecting women health; there are approximately 1.7 million cases estimated with 521,900 deaths worldwide in 2012 (Torre et al., 2015). The incidence of breast cancer is related to various risk factors. The factors related to environment and lifestyles are considered to contribute about 70% to 95% in overall risk factors (Macon and Fenton, 2013). A number of environmental carcinogens have been defined by the International Agency for Research on Cancer (IARC), on the basis of sufficient evidences of carcinogenicity in humans and in experimental animals, such as 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) (IARC, 1997) and polychlorinated biphenyls (PCBs) (Lauby-Secretan et al., 2013). However, there still remains considerable controversy over the effects of environmental carcinogens exposure on breast cancer.

PCBs are a class of synthetic organic chemicals containing 209 congeners. Due to their properties of high thermal stability and chlorination, PCBs were wide used in capacitors, transformers and building materials, until 1980s when the PCB manufacture was prohibited in most of countries. Although PCBs have been banned for more than three decades, their characteristics such as high persistence and biological accumulation has aroused ongoing ecological issues (Yun et al., 2015) and human health concerns (Jensen et al., 2014; Neugebauer et al., 2015). Recently, PCBs were classified as carcinogenic to humans (group 1) by the IARC according to their excessive potential of the increase in the risk of melanoma (Lauby-Secretan et al., 2013). The IARC also considered the risk of breast cancer, yet there remains inconsistent with associations in epidemiological studies.

PCB congeners are abundant in both human serum and breast tissue (Cohn et al., 2012; Ellsworth et al., 2015; Huetos et al., 2014; Raaschou-Nielsen et al., 2005). PCB 180 and PCB 153 are present at

Abbreviations: PCBs, polychlorinated biphenyls; IARC, International Agency for Research on Cancer; TCDD, 2,3,7,8-tetrachlorodibenzopara-dioxin; MFOs, mixed function oxidases; CYP, cytochrome P450 enzymes; RR, risk ratio; OR, odds ratio; SE, standard errors; CI, confidence interval; NOS, Newcastle–Ottawa Scale; CS, case–control study; CO, cohort study; CS, nested case–control study; HRT, hormone replacement therapy; ER, estrogen receptor; PR, progesterone receptor.

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the highest levels and they could be detected in more than 99% of participants in several populations (Cohn et al., 2012; Huetos et al., 2014). The natures of biochemical and toxic effects of PCB congeners are largely determined by their structure, as well as different PCB congeners sometimes exert conflicting actions (Warner et al., 2012). For instance, some PCB congeners act as the estrogen agonists both in vitro and in experimental animal systems, while some others have been shown to be antiestrogenic (Lasserre et al., 2009; Lind et al., 1999; Qian et al., 2015; Zhang et al., 2014). In addition, the toxicity of some PCB congeners has correlation with the induction of mixed function oxidases (MFOs) such as cytochrome P450 (CYP) enzymes in a 3-methylcholanthrene/TCDD or phenobarbital correlated manner. Thus, various classifications have been proposed to assess the adverse effects of PCBs. For instance, Wolff and Toniolo assigned PCB congeners to three groups: estrogenic/neurotoxic, antiestrogenic (dioxin-like), and enzyme-inducing (phenobarbital (PB)-type cytochrome P450) (Wolff and Toniolo, 1995).

In recent decades, there have been a great number of epidemiological studies conducted to investigate the relationship of total PCBs in the risk of breast cancer. Although some studies have reported the increased risk for breast cancer (Cohn et al., 2012; Recio-Vega et al., 2011), majority of results were equivocal (Gatto et al., 2007; Holmes et al., 2014; Itoh et al., 2009). However, the relationship between total PCBs and breast cancer might not reflect the actual relationship between individual PCB congeners and breast cancer (Wolff and Toniolo, 1995). Therefore, it is required to provide a comprehensive list of PCB congeners when assessing the association of PCBs with adverse outcomes (Hansen, 1998). However, so far, no meta-analysis has attempted to fully evaluate the adverse effects of PCBs to breast cancer in a congener-specific fashion.

This study presented a quantitative meta-analysis with aim at full evaluation on the epidemiological evidence, in terms of individual PCB congeners and breast cancer, further to determine if certain PCB congeners are associated with breast cancer. We also examined the agreement across studies and identified characteristics of the studies that might act as sources of heterogeneity.

2. Methods

2.1. Search strategy

The Preferred reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were used in the preparation of this meta-analysis. The publications from inception till 1st January 2015, presenting population studies regarding PCBs or breast cancer were identified from PubMed, Science Direct, Proquest and Web of Science with searching terms of “polychlorinated biphenyls”, “biphenyls”, “breast cancer”, “cancer”, “breast neoplasms” and “neoplasms” on each and in combination (see Supplemental material, Search strategy). The reference lists of related reviews (Ahlborg et al., 1995; Allam and Lucena, 2001; Bosetti et al., 2003; Moysich et al., 2002; Negri et al., 2003; Shakeel et al., 2010; Zani et al., 2013) and the articles potentially relevant were also taken into account as the source of pertinent articles.

2.2. Study selection

The original studies were included if published in English as well as fulfilling following criteria: (1) the study which covers a female population with unequivocal evidence of exposure to any one or more of 209 PCB congeners. (2) The study which indicates a clear diagnosis of breast cancer, such as in situ or invasive breast cancer confirmed by biopsies, histological analysis or pathology reports, or by linkage to a Cancer Registry. (3) The study which reports RR/OR along with 95% confidence interval (CI), or which provides sufficient data to determine these statistics. When there were multiple publications available from the same study area, the more recent publication was selected. Besides, it was out of our consideration if studies focused on genetic polymorphisms or mutations.

2.3. Data extraction

The data extraction and quality assessment were performed independently by two authors, and any disagreement was resolved by a third reviewer. Most relevant information on the eligible studies were recorded, including the study population, study design, sample size (cases), biological samples, PCB concentration, adjusted effect size and 95% CI, as well as covariates adjusted in multivariable models. In addition, the timing of biological sample collection was extracted to clearly capture whether PCB exposure occurred prior to or subsequent to breast cancer diagnosis for cases. When ORs/RRs for more than two exposure levels were presented, we extracted the main OR/RR from the highest group compared to the lowest exposure group (e.g., fourth quartile vs. first quartile).

2.4. Quality assessment

To evaluate the quality of eligible studies, the Newcastle–Ottawa Scale (NOS) was used in our meta-analysis (Wells et al., 2009). The NOS was a widely used scale to assess the quality of nonrandomized studies in meta-analyses (Hernandez et al., 2015; Quansah et al., 2015; Wang et al., 2014). PubMed search for “Newcastle Ottawa Scale” revealed 557 citations, nearly all of which were used as an instrument for quality assessment in meta-analysis. Over all, sixteen studies were assessed, including five nested case–control studies and eleven case–control studies. All of these studies were analyzed in accordance with the Coding Manual for Case–control Studies, which assigns eight as a maximum score. When evaluating the comparability of cases and controls, if the OR (or RR) for the exposure of interest was adjusted for family history of breast cancer and menopausal status, or if the family history of breast cancer and menopausal status were matched between cases and controls in the design, then the groups were considered to be comparable and rated two stars for this portion of the evaluation. Upon this, age was not scored, as all of the statistics that were incorporated in the meta-analysis were already adjusted for age.

Recently, some publications have shown that the reliability for the overall score was low when it was used for quality assessment (Hartling et al., 2013; Lo et al., 2014; Oremus et al., 2012). In our meta-analysis, the raters were well trained before the quality assessment to raise the reliability. In particular, the quality assessment was performed twice for the studies included; because in the first pilot rating phase, there appeared some disagreement between the two raters. After profound deliberation, guidelines were standardized to assess the studies for the second time.

2.5. Statistical analysis

The ORs and RRs are not equivalent statistics; however, the difference of two values could be ignored when there is low incidence of the disease, such as in the case of our meta-analysis. The diagnosis of breast cancer is relatively frequent than other cancers, nevertheless the worldwide incidence of breast cancer is lower than 0.001 (Torre et al., 2015). According to the formula supported by the Cochrane collaboration (Higgins and Green, 2011), we recalculated the results by using RR as effect estimates. As a result, we found that the pooled RRs of PCB 99, PCB 183 and PCB 187 were identical to the originals. Therefore, ORs and RRs were pooled together in our meta-analysis.

As previously reported (Camargo et al., 2011), the standard errors (SEs) for the ln(RR) or the ln(OR) were calculated on the basis of the reported CIs. When significant heterogeneity was detected, the overall pooled RRs or ORs and their corresponding 95% CIs were obtained using random-effect methods. Otherwise, fixed-effect models were