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Polycyclic Aromatic Hydrocarbons and Breast Cancer: A Review of the Literature

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Summary
Polycyclic aromatic hydrocarbons (PAHs) exist and persist in the atmosphere due to the incomplete combustion of fossil fuels, and are established human carcinogens. The influence of PAHs on the development of breast cancer, the most commonly diagnosed cancer in women worldwide, remains unclear. As established risk factors only account for approximately 41% of the breast cancer cases in the USA, researchers have sought to uncover environmental factors involved in breast cancer development. The breasts are particularly susceptible to aromatic carcinogenesis, and the implementation of biomarkers has provided promising insights regarding PAH-DNA adducts in breast cancer. The use of biomarkers measuring PAH-DNA adducts assesses exposure to eliminate the bias inherent in self-reporting measures in case-control studies investigating the link between PAHs and cancer. Adduct levels reflect exposure dose as well as how the body responds to this exposure, which is partially attributable to genetic variability. Evidence suggests that exposure to PAHs has a causational effect on breast cancer in humans, yet this interaction is not clearly understood. In vitro and animal-based studies have consistently revealed that exposure to PAHs deleteriously affects breast tissue, but there is no definitive link between these compounds and breast cancer.

Introduction

Polycyclic aromatic hydrocarbons (PAHs) exist and persist in the atmosphere due to the incomplete combustion of fossil fuels, and are established human carcinogens in the lungs. Additionally, oral uptake of PAHs may also occur via consumption of smoked and grilled meat and fish, and dermal exposure to PAHs may result from the use of consumer products that contain black rubber. However, the influence of PAHs on the development of breast cancer, the most commonly diagnosed cancer in women worldwide, remains unclear [1]. Given that established risk factors only account for approximately 41% of the breast cancer cases in the USA, researchers have sought to uncover environmental factors involved in breast cancer development [2, 3].

PAHs are a group of over 100 chemicals, usually occurring as mixtures. According to the Agency for Toxic Substances and Disease Registry, PAHs have been identified in 600 of the 1,430 National Priorities List sites identified by the United States Environmental Protection Agency (USEPA) [4]. PAHs are produced due to the incomplete combustion of hydrocarbons, fossil fuels (coal and gas), and biomass for energy production. PAHs produced from these processes include: benz(a)pyrene (BaP), dibenz(ah)anthracene (DB(ah)A), 1-nitropyrene (1-NP), and 7,12-dimethylbenz(a)anthracene (DMBA), as well as the monocyclic hydrocarbon benzene, all of which are established experimental breast carcinogens [3]. Currently, benzene, BaP, and DB(ah)A are listed as priority pollutants by the USEPA; priority pollutants are chemical pollutants the USEPA regulates and for which it has established analytical test methods [5]. The concentration of benzene in the atmosphere is mainly attributed to automobile use; as such, the highest concentrations exist around highways and high-traffic urban areas. The benzene content in gasoline ranges from < 1% to 15%, depending on the country [6]. Benzene also serves as a chemical intermediate for various products, including ethylbenzene (used to make styrene), many of which ultimately aid in the production of plastics and pesticides [6]. Benzene and other PAHs are also produced from the

burning of wood and organic material, and it is found in tobacco smoke. Moreover, humans can also be exposed to PAHs through the consumption of smoked and grilled foods. As a hydrophobic compound, PAHs can be absorbed through the dermis [7]. It has been established that benzene, through inhalation or ingestion, is a multipotential carcinogen. The PAHs BaP, DB(ah)A, and 1-NP have all been proven to induce breast tumors in animals [3].

Results and Discussion

The breasts are particularly susceptible to aromatic carcinogenesis. Fat cells can store and concentrate aromatic carcinogens [2], and breasts are largely composed of fat. PAHs can be harbored in mammary and other fat tissues [3]. Several in vitro studies have shown that, in breast epithelial tissue, PAHs are metabolized to their most potent and deleterious state [8–10], ultimately affecting cellular morphology as well as cellular division, growth, and repair. Furthermore, the cells in these studies displayed anchorage independence, a potential reflection of tumorigenicity [10]. Multiple experiments have shown that PAH induces mammary neoplasms in animals [11, 12]. p53 mutations have been implicated in breast cancer and, in fact, approximately half of all human cancers have a p53 mutation [13–15]. Mordukhovich et al. [16] concluded that PAHs may alter the effect, type, and number of p53 mutations.

The use of biomarkers in measuring PAH-DNA adducts has been implemented to assess exposure to eliminate the bias that is inherent with self-reporting measures in case-control studies that have investigated the link between PAHs and cancer. Adducts appear to be instrumental in the development of mutation and cancer, although the precise relationship is not understood [17]. Adduct levels reflect exposure dose as well as how the body responds to this exposure, which is partially attributable to genetic variability [18, 19]. In essence, exposure and repair or detoxification are at odds with one another; thus, when either exposure exceeds detoxification or detoxification alone is insufficient, PAH-DNA adducts form [7], predisposing one to abnormal cellular growth and division. A study conducted by Rundle et al. [17] that controlled for known breast cancer risk factors indicated that inter-individual variation in metabolic and/or DNA repair pathways may play a significant role in breast cancer. Rundle and colleagues also investigated the relationship between PAHs and polymorphisms in the glutathione S-transferase M1 (*GSTM1*) gene, which is known to be highly polymorphic and involved in the detoxification of carcinogenic compounds [20]. Rundle et al. [8] concluded that *GSTM1* polymorphisms play a role in predicting adduct levels for cases but not controls. Evidence suggests that the *XPD* gene (also called *ERCC2*), which has numerous single-nucleotide polymorphisms and is involved in nucleotide excision repair, may influence an individual's ability to repair DNA from bulky DNA adducts [21]. Polymorphisms in the *XPD* gene, such as the Asn/Asn or Gln/Gln genotypes, may be associated with greater PAH-DNA adduct levels in tumor tissue [22]. Shen et al. [23] investigated the relationship of polymorphisms in X-ray repair cross-complimenting group 1 (*XRCC1*), an important DNA base excision repair gene, and breast cancer risk. Two polymorphisms, Arg194Trp and Arg399Gln, do not appear to directly influence breast cancer risk. Among never-smokers, a suggestive additive interaction was observed between the *XRCC1* 399Gln allele and PAH-DNA adducts. Yet, *XRCC1* 194Trp carriers, through high fruit and vegetable consumption, may have a decreased breast cancer risk.

In 1996, Li et al. [2] assessed aromatic adducts in human tissue from breast cancer patients undergoing mastectomy versus breast tissue from non-cancer patients undergoing reduction mammoplasty. Aromatic DNA adducts, although detected in all samples, were significantly higher in the breast cancer patients versus the healthy controls ($p < 0.01$); therefore, these results indicate that PAHs may play a role in the development of breast cancer. The Long Island Breast Cancer Study Project (LIBCSP), conducted from 1992 to 1996 in response to concerns about environmental effects on breast cancer risk in Long Island, NY, showed that the average level of PAH-DNA adducts measured per 10^8 nucleotides was only minimally greater in breast cancer patients than in the controls (5.48 vs. 5.37). Additionally, the data suggested that the effect of PAH adduct levels may be enhanced in premenopausal women (overall response (OR) 1.56) [24]. Rundle et al. [8] conducted a case-control study including women with benign breast disease (BBD) as controls. This study showed that PAH-DNA adduct levels were significantly greater in tumor tissue from breast cancer patients versus benign tissue from women with BBD (OR 2.40). However, there was no significance between adduct levels in non-tumor tissue from breast cancer patients versus the BBD controls (OR 1.97).

The LIBCSP analyzed peripheral mononuclear cells and not breast tissue to assess the PAH-DNA adducts; Gammon et al. [24] and Perera and Rundle [25] indicate that this method may not be as accurate, yielding lower measurements than from breast tissue. Rundle et al. [8] have also opted to include women diagnosed with BBD as controls, in contrast to tissue from women undergoing reduction mammoplasty. However, they acknowledge that selection bias may inadvertently result from selecting women with BBD as controls. Rundle et al. [8] note that tissue adducts assessed by immunohistochemical assays, as in their study, are scored by individuals and there is no standard method for scoring; thus, there may be variability between reviewers and studies. Regardless of the tissue from which PAHs are assessed, it is not a strong measure of long-term exposure [24]. A possible confounder associated with the LIBCSP was attenuation. The results of studies with larger sample sizes can become nullified, versus smaller studies in which variations are more evident [24, 26, 27].

In examining the potential relationship between PAHs and breast cancer, it is also crucial to consider the geographic location and socioeconomic status of the patients. Studies conducted in Western New York in 2005 and 2007 have noted the necessity of investigating exposure to PAHs in relation to the location where patients resided during various critical periods in their lives, such as at the times of menarche and first birth [28, 29]. Furthermore, in response to reports of high breast cancer mortality rates in the North-

eastern USA, a 1997 study of the region was conducted; this study found statistically significant clusters of breast cancer deaths in the New York City-Philadelphia metropolitan area, particularly in affluent suburban communities with ample access to health care [30]. The researchers noted that they were unaware of any studies indicating greater exposure to PAHs in these communities, but it is nonetheless worth considering environmental conditions as a contributing factor to breast cancer mortality rates, as such factors can vary widely with location. Subsequent research conducted among breast cancer patients in one such significant suburban cluster – Long Island, NY – reported that PAH-DNA adduct levels were higher, albeit not significantly, among this area's breast cancer patients than in the control population [31]. The researchers in this study also observed a 50% increase in breast cancer risk for patients in the highest quintile of PAH-DNA adduct levels, even after accounting for potential confounding factors. Such results indicate that further research is required to understand the risks of exposure to PAHs as they relate to geographic and socioeconomic factors.

Conclusions

PAHs, released by use of fossil fuels and biomass for energy production, are established carcinogens to other parts of the body [3, 19]. Evidence suggests that exposure to PAHs has a causational effect on breast cancer in humans, yet this interaction is not clearly understood. In vitro and animal-based studies have consistently revealed that exposure to PAHs deleteriously affects breast tissue, while the implementation of biomarkers has provided promising insights regarding PAH-DNA adducts in breast cancer. Environmental exposure to PAHs produced by fuel combustion, especially as mediated by geographic region and socioeconomic status, must be taken into account as researchers strive to understand the effects of PAHs on breast cancer risk.

Disclosure Statement

None of the authors have anything to disclose or have any conflicts of interest.

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