

Review article:

Polycyclic Aromatic Hydrocarbons and their Association with Breast Cancer

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Abstract:

Background and Rationale: Polycyclic aromatic hydrocarbons are a lipophilic group of pollutants that persist in the atmosphere for long periods, constituting a permanent source of exposure for humans. They have been associated, for a long time, with the risk in developing breast cancer, but there are still unresolved questions. **Conclusion:** Integrated strategies are required that should consider molecular and population-level studies, to understand and elaborate approaches to prevent the risks in developing breast cancer.

Keywords: Polycyclic aromatic hydrocarbons, pollutants, breast cancer

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Introduction

Polycyclic aromatic hydrocarbons (PAHs), structurally conformed by the fusion of 2 or more benzene rings, are a group of more than 100 chemicals that persist in the atmosphere for long periods. They usually occur as complex mixtures, as products of the incomplete incineration of charcoal, petroleum, gas, and waste. Among the most common PAHs generated from these processes are benz[a]pyrene, the most potent, and dibenz[a,h]anthracene. In addition, some PAHs have been classified as possible human carcinogens¹⁻⁴ (Table).

PAHs are found in the environment attached to dust or other particles in the air coming from tobacco smoke, vehicle exhausts, residential wood burning, industrial waste incineration, volcanoes, and forest fires. PAHs can also be found in soil and asphalt roads, dyes, plastics, grilled and smoked food, pesticides, medicines, and are also used for drinking water purification⁵⁻⁷. Thus, humans are daily exposed to PAHs, and epidemiological studies do not identify a specific type of PAH, since the exposures correspond to a mixture of them.

PAH are lipophilic, and in that way, they are able to diffuse through the plasma membrane. They can be stored in fat's animal tissues, liver and kidneys, and in lower amounts in spleen, adrenal glands and ovaries. PAH are absorbed from lung, skin and gut, where they can be metabolized; but liver is where PAHs are primarily metabolized and activated. They are mostly oxidized by cytochrome P450 monooxygenases (CYP) to epoxides, phenols and dihydrodiols. Afterwards, they can be conjugated with glucuronide, sulphate or glutathione to be transformed into water-soluble metabolites, so that they can be excreted in feces and urine, with higher urinary levels in females^{1,6}.

PAH biotransformation has been implicated in the development of different types of cancers, such as lung, skin and breast cancer^{1,8-11}. Considering that everybody is exposed to PAH, but since breast cancer is the most prevalent cancer among women and the second cause of cancer-related death in the world^{12,13,14}, we will focus in the effects of PAHs and breast cancer.

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PAHs and breast cancer

Table. Some PAHs priority pollutants* with carcinogenic potentiality to humans

PAH	N° of rings	Carcinogenicity group (IARC**)	Genotoxicity	Sources
Benzo[a]anthracene	4	2B	Positive	Product of the incomplete burning of organic matter. Present in gasoline/diesel exhaust, soot smoke, coal tar, asphalt, mineral oils, tobacco smoke, charcoal-broiled foods
Benzo[a]pyrene	5	1	Positive	Product of the incomplete burning of organic matter. Present in gasoline/diesel exhaust, soot smoke, coal tar, asphalt, petroleum, tobacco smoke, charcoal-broiled foods, oil
Benzo[b]fluoranthene	5	2B	Positive	Product of the incomplete burning of organic matter. Present in gasoline exhaust, soot smoke, coal tar, tobacco smoke
Benzo[k]fluoranthene	5	2B	Positive	Product of the incomplete burning of organic matter. Present in gasoline exhaust, coal tar, lubricating oils, tobacco smoke
Dibenz[a,h]anthracene	5	2A	Positive	Product of the incomplete burning of organic matter. Present in gasoline/diesel exhaust, soot smoke, coal tar, tobacco smoke, smoked and barbecued foods
Indeno[1,2,3-cd] pyrene	6	2B	Positive	Product of the incomplete burning of organic matter. Present in gasoline/diesel exhaust, soot smoke, coal tar, asphalt, tobacco smoke

*: US Environmental Protection Agency (EPA)³

** : Group 1: carcinogenic to humans; group 2A: probably carcinogenic to humans; group 2B: possibly carcinogenic to humans⁴

As a result of the metabolism of PAH, reactive diol epoxide enantiomers are generated, which can bind and alter DNA by forming DNA adducts. The clinical study performed by Gammon et al., 2002, found that women with high levels of blood PAH-DNA adducts have 50% more probability in developing breast cancer. High adduct levels could be due to high levels of PAH exposure or an increased sensitivity to PAH¹⁶. Population- and family-based cohort studies indicated that there is an association between PAH-DNA adducts and postmenopausal breast cancer in women that were overweight or obese, and a stronger association between higher PAH-DNA adducts and breast cancer in women with higher risk due to cancer family history and specific DNA polymorphisms^{17,18}. Another cohort study performed by Agudo et al. (2017) also showed an association between higher levels of DNA adducts and the risk in developing breast cancer in pre- and postmenopausal women, and in smoking women with normal weight. On the other side, according to Rundle et al. (2000), dietary PAH and active or passive smoking are not significantly associated with PAH-DNA adducts and breast cancer. Additionally, two cohort studies did not report an association between PAHs exposure and breast cancer^{21,22}. The discrepancies between all these studies could be related with the way the experiments were performed and the type of PAHs that were measured in urine. Even though there

are controversy between studies, DNA adducts are considered good biomarkers, since they are a sign of exposure dose and body's behaviour, which is attributable to genetic variability¹⁰.

Other studies have evaluated the relationship between environment and gene interactions, suggesting that the effect of specific DNA polymorphisms in certain genes increased the incidence of breast cancer. A case control study performed by Mordukhovich et al. (2010), and other reports^{24,25}, suggested an association between PAHs exposure and particular mutations in p53 gene and DNA repair genes, that lead to breast cancer. It has also been demonstrated that grilled/smoked food and well-done meat consumption can increase up to 50% the frequency of breast cancer^{15,26}. Additionally, occupational exposure to PAHs is related with an increase, up to 10-fold, in the risk of breast cancer. Also, men with mutations in the tumor suppressor genes BRCA1 and BRCA2, and pre-menopausal women, both occupationally exposed to elevated levels of PAHs, presented an increased frequency in the risk of developing breast cancer^{27,28}. In addition, it has been shown that PAHs can decrease BRCA1 mRNA levels in estrogen receptor-positive MCF-7 breast cancer cells, by increasing the production of reactive oxygen species (ROS)²⁹. Additionally, other PAH exposures, such as tobacco smoking and dietary intake, also contribute to an increase in the risk of developing breast cancer^{30,31}.

An elevated association between post-menopausal breast cancer and high and prolonged exposure to traffic emissions has been found. In fact, women exposed to elevated levels of traffic emissions during their first menstruation or by giving birth, presented higher probabilities in developing breast cancer^{9,32}. But other studies showed that girls exposed to PAHs before developing adult sexual characteristics and nulliparous women, are more susceptible to develop breast cancer¹¹. The study performed by Hung et al. (2012), in Taiwan, showed an association between higher levels of air suspended fine particulate, and an incremented probability of dying from breast cancer. However, the report by Mordukhovich et al. (2016) showed that only women highly exposed to traffic-generated PAHs, who ate low levels of vegetables and fruits, presented an increased incidence in breast cancer.

After PAH exposure, these compounds can induce the expression of metabolizing enzymes, such as human CYP1A1, 1A2 and 1B1, that constitute the most common activation mechanism, through either aryl hydrocarbon receptor (AhR) or pregnane X receptor (PXR) stimulation. Accordingly, genetic variations in the CYP genes have shown to affect PAHs metabolism^{1,35-37}. And some types of CYP1A1 polymorphisms are linked to adduct formation and mutagenesis^{38,39}.

It is known that the methylation pattern of cancer susceptibility genes has a relevant role in breast cancer development^{40,41}. The study performed by Callahan et al. (2018) suggested an association between environmental pollution exposure and changes in the methylation pattern of several tumor suppressor genes in breast tumor tissues. It has also been shown that benzo[a]pyrene alters the transcription of the BRCA-1 gene through modifications in its methylation pattern, only in ER(+) breast cancer cells⁴³. Moreover, a population-based study showed an association between PAH-DNA adducts, the methylation pattern of the retinoic acid receptor β (RAR β) gene's promoter and breast cancer in ER(+)/PR(+) tumours⁴⁴. This could be related to the fact that some PAHs behave as xenoestrogens, with estrogenic or anti-estrogenic activities, due to their structural similarities, and by binding to estrogen receptor alfa (ER α) and beta (ER β), affecting

their signaling pathways and increasing the risk of developing breast cancer^{37,45-47}.

On the other side, PAHs mostly bind, as previously mentioned, to AhR or PXR. AhR is a transcription factor that regulates xenobiotic metabolism enzymes, growth arrest, alterations in chromatine structure, and apoptosis, and is activated, at least, by 400 different ligands. In this way, by binding to AhR, PHAs affect several signaling pathways, some of them, involved in the development of breast cancer^{35,43}. The PXR nuclear receptor has a broad specificity, exerting important roles in the pharmacokinetics of several endogenous and xenobiotic compounds⁴⁸. It has been suggested that PXR could be involved in breast cancer, by increasing breast cancer cells proliferation and resistance to chemotherapeutic drugs; but others studies suggested that binding to PXR induces apoptosis⁴⁹⁻⁵¹.

Discussion

Humans are regularly exposed to a mixture of PAHs, but unfortunately, epidemiological studies do not identify the specific type of PAH that correlates with disease association. In addition, the linking between environmental exposures to PAH and epidemiologic evidences are limited, and the results are not consistent. In future studies, it would be relevant to specify, when the exposure took place (in womb, newborn, puberty or post-menopausal), since the risk of developing breast cancer during adulthood varies according to the time of the exposure⁵².

Considering the relationship described between PAH exposure and breast cancer, such as PAH-DNA adducts, changes in the epigenome, and the presence of specific gene polymorphisms, together with the consumption of grilled/smoked food and well-done meat, smoking, and traffic emissions, it is worth to consider the possible genotoxic effects induced by PAHs. Thus, it is important to evaluate the type of exposure that people daily face, since countries are moving forward to industrialization, and consequently, to more toxic environmental exposures. This is relevant, since breast cancer incidence has increased with industrialization^{8,53,54}, and, in this context, geographic area and lifestyle due to socioeconomic conditions should be considered. In addition, considering that breast cancer is a

multifactorial neoplastic disorder, studies should consider the genome haplotype of participants, to determine if particular polymorphisms predispose or decrease susceptibility to PAHs, in order to identify, which group of women could be at higher risk.

In conclusion, even though PAH research studies have been performed for long time, there are still many unresolved questions about the effects of the exposure in human health. Integrated strategies are required that should consider molecular and population-level studies, in order to understand and elaborate approaches to prevent the risks in developing breast cancer, and in this way, minimize the effects of PAHs in the health of exposed and vulnerable populations.

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Authors's contribution

Data gathering and idea owner of this study: S. Pilar Zamora-León

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