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Review

Aromatics from fossil fuels and breast cancer

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SUMMARY

Polycyclic aromatic hydrocarbons (PAHs) from fossil fuels initiate breast cancer in animal models, and in humans a link between PAH exposure and breast cancer risk has been established. In women, it takes approximately two decades for PAH-exposed breast cells to progress to diagnosable breast cancer, and the exposure needs to happen during a time window when breast is vulnerable to PAHs. Further, not everyone exposed to high levels of PAHs develops breast cancer. PAHs are most likely to lead to breast cancer initiation among individuals who were exposed *in utero* through pregnant mothers to environmental pollutants or maternal obesity or both. These early life exposures are shown to increase daughter's later susceptibility to breast cancer by causing in the daughter (1) an increase in the number of structures in the breast in which breast cancer initiation takes place, (2) a suppression, perhaps epigenetically, in the ability of cells to repair DNA damage caused by PAHs by inhibiting expression of tumor suppressor genes, or (3) a persistent gut dysbiosis, which then impacts immune cells in the tumor microenvironment. Among the early life environmental pollutants that increase breast cancer susceptibility may be volatile aromatic BTEX compounds. Thus, aromatics from fossil fuels are likely to be involved in causing breast cancer, and efforts should be directed toward reducing human exposure to these compounds to prevent breast cancer.

Causes of breast cancer

Breast cancer, which strikes one of every eight women during their lifetime in the US, is referred as a disease caused by a single initiating gene mutation, followed by a second or more hits[1]; together these hits then drive malignant transformation. This dogma has recently been questioned.[2] In some cases an epigenetic change[3] or a single mutation[4] is sufficient to drive malignant transformation. Further, immune,[5] vascular,[6] and neuronal cells[7,8] and stromal fibroblasts[9,10] in the tumor microenvironment (TME) influence progression of transformed cells toward tumor. For example, immune cells can kill and thus eliminate pre-malignant cells.[11] However, some immune cells, such as tumor-associated macrophages, T regulatory cells, and myeloid-derived suppressor cells can help tumors to grow.[12,13] Immune cell infiltration and activation in the TME are impacted by the gut microbiome.[14–16] The knowledge of the role of gut microbiota in affecting immune cells in cancer cell death, growth, metastasis, and responsiveness to immunotherapies is rapidly emerging.[17,18] Thus, cancer is not simply a result of gene mutations/epimutations, but the risk of developing cancer is affected by many factors.

Several factors that increase breast cancer risk have been identified and they are divided into those that can be modified and those that cannot.[19–21] The first category includes reproductive and lifestyle factors, such as taking postmenopausal hormones, especially progestin, post-menopausal obesity; physical inactivity; working in a nightshift; inadequate dietary intake of fruits, vegetables, and fiber; lack of breast feeding; and gut dysbiosis. However, although these risk factors are considered modifiable, several factors can hinder women's ability to modify them, such as socioeconomic factors influencing access to fresh food and safe places to be physically active.[22] Non-modifiable risk factors include gender, age, race, family history, having early menarche, late menopause, dense breasts, or benign breast disease and being tall. Importantly, two-thirds of newly diagnosed patients did not have any of these traditional breast cancer risk factors.[23] More recently identified risk factors include having high birthweight (>4,000 g)[24,25] and having been exposed *in utero* to diethylstilbestrol (DES)[26,27] or dichlorodiphenyltrichloroethane (DDT).[28] Exactly how these factors elevate breast cancer risk is unclear.

Breast cancer incidence continues to increase annually. Between 2000 and 2019, the rate of increase in the US was 0.79%.[29] During the first six years of this time period, the increase in incidence was modest (0.24%), whereas from 2016 onward the annual increase was dramatic (3.76%).[29] When trying to understand what might have caused the more recent increase, it is important to consider the fact that most cancers are initiated several decades before they are diagnosed. Calculations based on cancer driver mutations indicate that such mutations can proceed with the diagnosis by decades.[30] If the estimation is based on the presence of atypical hyperplasia, a

precursor for this disease, invasive breast cancer diagnosis typically occurs 20–28 years after hyperplasia first forms.[31] Interestingly, the proportion of familial breast cancers of all newly diagnosed breast cancers is also increasing.[32] Family history of breast cancer (mother and/or sister diagnosed with breast cancer), which include women with germline mutations, such as in BRCA1/2 gene, currently accounts approximately 15% of all breast cancers.[33] However, at least half of women with strong family history have no known breast cancer mutations.[34,35] In some families, cancer may be inherited through epigenetic alterations.[36,37]

We propose that two factors are required for sporadic breast cancer to develop: (1) events that lead to increased susceptibility for cancer initiation and progression and (2) mutagen exposure. Neither factor alone is sufficient for breast cancer to develop. Penetrance of familial breast cancer might also require two factors: (1) inherited germline mutation (or epimutation) and (2) events that lead to increased breast cancer penetrance.

Breast cancer carcinogens: Polycyclic aromatic hydrocarbons

The mutagens that cause malignant transformation in the breast in women at increased susceptibility to cancer are radiation and carcinogens. The role of radiation as a breast mutagen has been addressed in several articles.[38,39] Breast cancer risk is elevated by radiation most among those exposed to the highest radiation levels and those exposed at a young age.[40,41] Women who were under 20 years of age when exposed to radiation from atomic bomb represented 75% of all breast cancer cases diagnosed between 1958 and 2009 in a cohort of over 60,000 Japanese females.[42] Other risk factors may influence the impact of radiation. For example, radiation exposure at an early age increased breast cancer risk significantly more in women who also had early puberty onset, compared with women having late puberty onset; radiation exposure itself did not modify puberty onset.[42] One factor linked to early puberty onset is maternal obesity during pregnancy,[43] suggesting that women most affected by radiation are those exposed already *in utero* to factors that increase breast cancer susceptibility.

In this short review, we will focus on carcinogens as the initiating and susceptibility initiating factors for breast cancer, specifically polycyclic aromatic hydrocarbons (PAHs) and associated volatile BTEX (benzene, toluene, ethylbenzene, and xylene) compounds. PAHs and BTEX compounds are products derived from transportation systems, such as cars and airplanes, heat and power generation, refuse burning, industrial processes, and oil contamination (effluent disposal or spills).[44–46] An important exposure pathway to gasoline for an average person is through infiltration to homes from the attached garage where cars and other gasoline sources are stored.[47]

Pre-clinical models

Rudel et al. (2014)[48] identified 13 PAHs that specifically caused mammary gland tumors in animal models. Of the five PAHs shown to cause mammary gland tumors in rodents, two—3-methylcholanthrene and 7,12-dimethylbenz[a]anthracene (DMBA)—are products generated in research laboratories, and three—benzo[a]pyrene (BaP), dibenz[a,h]anthracene, and dibenzo[def,p]chrysene—are products of combustion.

The most used carcinogen to initiate mammary tumors in rodents is DMBA, the carcinogenic mechanism of which has been characterized in detail by Drs. Russo and Russo.[49] DMBA is a PAH and its mechanisms of action are similar to other PAHs, i.e., it needs to be activated and the resulting metabolites form DNA adducts, which then can cause mutations. The major carcinogenic DNA adducts of DMBA and traffic pollutant PAH BaP are diol-epoxides.[50,51] These metabolites are formed in the liver through activation of P450 genes, such as CYP1A1 and CYP1B1. BaP upregulates CYP1A1 gene.[52] Aryl hydrocarbon receptor (AhR) is a transcriptional regulator of CYP1A1, and in its absence in AhR−/− knockout mice, BaPs is not carcinogenic.[53] Carcinogenicity of DMBA also is dependent on the activation of P450 genes.[52,54]

When DMBA is given to 50-day-old Sprague-Dawley rats as a single dose of 10 mg via oral gavage, at least 2/3 of exposed rats develop estrogen-receptor-positive (ER+) mammary tumors that mimic invasive ER+ breast cancers in women.[55,56] DMBA also induces mammary tumors in mice, but mice have to be primed to DMBA by a pre-treatment with progestin and then mice are given four 1 mg doses of DMBA, administered once a week between weeks 7 and 10.[57] DMBA-initiated mammary tumors in mice are either ER+ luminal or ER-negative basal types.[58] The reason why DMBA is provided after puberty onset, which occurs at end of 1st month of life in mice and rats and before rodents are over 2 months of age, is that at that time window rodent mammary glands contain the structures in which mammary tumors can be initiated.[49] These structures are terminal end buds (TEBs), and they contain cells that are suggested to be stem/progenitor cells[59,60] and that can be transformed to malignancy.[49] Mutations in DMBA-induced mammary tumors include high frequency of Pi3kca and/or Pten mutations (64% of tumors).[58] Ras mutations also are present, although they are not found in all studies,[61,62] as well as several other mutations.[58,62] All these mutations occur in human ER+ breast cancers. For example, 30%–40% of human ER+/HER2− breast cancer contain PI3KCA mutations.[63,64]

Another PAH that initiates mammary tumors in rats is 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP).[65,66] In contrast to DMBA, this PAH is naturally present in the human environment, mostly in grilled and broiled meat.[67] The weakness of PhIP as a preclinical model of breast cancer is that to induce mammary tumors, rats require multiple exposures and still develop relatively low number of mammary tumors. For example, exposing 43-day-old female Sprague Dawley to 10 doses of PhIP over a 2-week period resulted 31% of rats to develop mammary tumors after 25 weeks of the last exposure.[68] As indicated above, only one DMBA dose is needed for at least two- of three-quarters of Sprague-Dawley rats to form mammary tumors within 20 weeks of exposure.[55,56]

A third PAH that induces mammary tumors in preclinical models is benzo[a]pyrene. BaP is a byproduct of incomplete combustion of burning of carbon-containing organic products present, for example in gasoline, wood, and cigarettes.[69] The major BaP exposures originate from vehicle emissions and industrial sources. Other BaP exposure sources are consumption of grilled or well-done meats.[70,71] Dr. Hecht's group compared BaP and PhIP as carcinogens to initiate mammary tumors in

rats.[65] They exposed rats to 50 mmol of one of the two carcinogens once per week for eight weeks, starting when rats were 5 weeks of age, and followed them for 41 weeks. Mammary tumor incidence was similar in BaP- (∼90%) and PhIP (>70%)-treated rats. These results show that in rodents PAHs effectively initiate mammary cancer, and although DMBA needs to be given only as a single dose and tumors develop twice as fast as when rats are given BaP or PhiP, all three PAHs initiate mammary tumorigenesis in animal models. Further, most mammary tumors in rats initiated by PAHs resemble invasive, ER+ luminal breast cancers,[55] whereas in mice some are luminal and some basal-like.[58,72]

Human studies

Many studies have investigated a link between air pollution and breast cancer, using measures assessing exposures to PAHs, particulate matter, or nitric oxidase. The two latter measures are directly linked to PAH exposure.[73,74] In fact, particulate matter is formed via secondary pathways from the combustion of aromatic hydrocarbons contained in gasoline, aviation fuels as well as fossil fuels used for electric power generation.[75] Results from an ecological study conducted in Atlanta showed that breast cancer incidence rates and PAH exposure levels were higher in the metro than rural areas.[76] Although the incidence of breast cancer and PAH exposures in the Atlanta study may not be causally linked, a finding in another study indicating that women with high circulating levels of PAH-DNA adducts were 50% more likely to develop breast cancer than women with lowest quantile of PAH-DNA adducts[77] is more convincing in suggesting that PAH exposure increases breast cancer risk. Several other studies have reported an association between PAH, or specifically BaP exposure, and increased breast cancer risk. These include reports that exposures to PAHs originating from consumption of grilled or barbecued meat, synthetic log burning,[78] and vehicle emissions[79] significantly increased breast cancer risk, in some of these studies by 30%–50%. BaP exposure via diet was reported to be linked to increased breast cancer risk in a case-control study involving 460 cases and 638 controls in Uruguay.[80] A recent nested case-control study in French E3N cohort[81] that included over 5,000 incident breast cancers and similar number of matched controls found that each interquartile range increase in BaP exposure levels (1.42 ng/m^3) increased breast cancer risk by 15% compared to lowest BaP levels.

Studies also indicate that it may be critical to define when the exposure occurred during a woman's life for it to have impacted breast cancer risk.[82] A case-control study conducted in Erie and Niagara counties in New York state reported that women exposed to high levels of traffic emissions around the time of menarche exhibited increased premenopausal breast cancer risk and at the time of woman's first birth exhibited increased postmenopausal breast cancer risk.[82] Another example of timing of exposure being a critical factor is smoking and breast cancer risk. Most studies suggest that smoking does not increase breast cancer risk.[83] However, if smoking starts in the early teenage years and before first pregnancy, it increases breast cancer risk.[84–87]

The reason why PAH exposure increases sporadic breast cancer risk if the exposure occurred between puberty onset and first birth probably involves changes in breast epithelial morphology during reproductive years. TEB-like structures in human breast epithelial tree are terminal lobular ductal unit (TLDU), and human breast cancers typically are diagnosed, i.e., they are initiated in TDLUs.[88–90] Two studies have investigated a link between TDLU/acini number and size and breast cancer risk. These studies reported that the higher the TLDU number and size, and acini count within TLDU, the higher the breast cancer risk.[91,92] Pregnancy has a dual effect on breast cancer risk. While pregnancy before age 20 years reduces life-time breast cancer risk, women who have their first child after age 30 years are at an increased risk.[93] The increase in risk may be caused by the high pregnancy hormonal environment increasing the growth of pre-existing malignant cells in TDLUs; malignant cells are less likely to be present in the breasts of young than older women.[94] Consistent with this interpretation, pregnancy also causes a short-term increase in breast cancer risk, and the risk is higher in older than younger mothers.[95] Pregnancy affects TDLU involution,[96–98] possibly explaining why PAH exposures after having given birth may not increase mother's breast cancer risk.

Air pollution also seems to increase breast cancer risk, especially in women with a high familial risk.[99] In a study investigating a link between PAH exposure and breast cancer risk, women with the highest familial breast cancer risk score and highest PAH exposure levels had 4 times higher risk of developing breast cancer than non-PAH-exposed women.[100] Since germline genetic or epigenetic mutations in women at high familial breast cancer risk often involve silencing of genes that protect cells from cancer-initiating DNA damage, such as BRCA1, it makes sense that these women are particularly vulnerable to PAH-induced DNA damage. BaP has also been shown to reduce expression and protein levels of BRCA1 in breast cancer cell lines[101] and in the offspring of BaP-exposed pregnant mouse dams.[102] Taken together, the studies in animal models and humans provide strong evidence that traffic pollution, especially PAHs, are carcinogenic and can initiate breast cancer.

BTEX compounds and breast cancer

Volatile organic compounds (VOCs), such as BTEX compounds, are present both in the outdoor and indoor areas, and represent a serious human health risk.[103] Main sources of BTEX compound exposures are from petrochemical processes, petroleum refineries, and industries using coal.[45,46] In the urban areas, outdoor BTEX compounds originate mainly from transportation fuels and thus automobile and aviation exhaust. Switching to electric cars does not eliminate BTEX compounds, if electricity is produced at fossil fuel (coal) power plants.[104] Standard petrochemical procedures and the solvents and chemicals used by these industries result in the BTEX release into the air, soil, and water, with air being the main exposure source for humans. Accidents involving petrochemical processes at petroleum refineries further contribute to the BTEX release.[105] BTEX compounds also are present at high concentrations inside homes and public indoor environments[106–108] as they evaporate to air from various sources, such as indoor combustion processes (cooking and heating), house-building materials and furniture (paints, varnishes), and human activities (smoking).[109] Besides BTEX, vehicle exhaust contains other VOCs, such as 1,3-butadiene

and ethylene oxide: these two are shown to be genotoxic and increase mammary tumorigenesis in rodent models,[110] similar to benzene.

The regulatory reference concentrations for BTEX compounds are set by the United States Environmental Protection Agency (US EPA).[108] In our unpublished study (Northrup et al.), a standard car engine in a laboratory environment under 0 to 20 mph acceleration generated 11 times less BTEX compounds when the engine was operating with 15% ethanol gasoline blend (E15), compared with 0% ethanol gasoline (E0). Toluene concentrations were the highest of the four BTEX species produced by E0 but dropped below detection limit when E15 was used. Further, benzene levels dropped below detection limit under driving 30 mph condition and acceleration condition with E15. Our results are consistent with findings by other investigators showing that BTEX exposure levels can be significantly reduced by adding ethanol to gasoline.[111–113]

BTEX compounds are proposed to be among the most hazardous components of gasoline.[114,115] They have been linked to damage in the liver, nervous system, heart, lung, and kidneys.[108,116,117] Of the BTEX compounds, benzene is categorized as a carcinogen,[118,119] ethylbenzene as a carcinogen in animal but not human studies,[120] but neither toluene nor xylene is carcinogenic.[121] However, whether exposure to these four compounds together affects cancer risk has received little attention.

Preclinical studies

A study that investigated the effect of prenatal exposure to a 23-chemical mixture, which is used for unconventional oil gas operations and included benzene, toluene, and ethylbenzene, found that these chemicals increased mammary ductal epithelial density in adulthood in C57BL/6 mice.[122] Since high mammographic density is a strong risk factor for breast cancer,[123–125] BTEX compounds might increase susceptibility to breast cancer rather than initiate it. However, since mammographic density in women is a measure of fibro-glandular tissue, and the association between high density and elevated breast cancer risk might reflect tissue stiffness and collagen crosslinking rather than dense epithelium,[126] no direct prediction to humans can be drawn from the mouse study. We are currently studying whether BTEX compounds alter the expression of oncogenes and tumor suppressor genes in human breast cancer cell lines and zebrafish. Our preliminary data indicate that the administration of a mixture of BTEX compounds from average to high environmental exposure relevant doses[127] dose-dependently reduced the expression of BRCA1 in MCF-7 human breast cancer cells. Interestingly, earlier studies have found that BaP suppresses BRCA1 *in vitro* and *in vivo*.[101,102]

Human studies

Few studies have explored a possible connection between BTEX levels and breast cancer. In a study by Wei et al.,[128] a highly significant correlation between breast cancer incidence in 1973–2007 and an exposure to volatile organic compounds 20 years earlier in 1953–1987, which included BTEX compounds, was discovered. In a recent study in Tehran, Iran, involving 1,148 breast cancer patients, an exposure to BTEX compounds singly, or in combination, was associated with increased incidence of developing more aggressive breast cancer.[129] Strongest evidence that BTEX compounds will increase breast cancer risk comes from prospective Multiethnic Cohort (MEC) study composed of residents in Hawaii and California recruited between 1993 and 1996[130]; 48,665 female participants did not have breast cancer when recruited to the study but were followed for possible diagnosis through the Hawaii and California Cancer Registries. Their exposures to 15 suspected or established carcinogens via air were assessed in an exposure window between 1998 and 2003. Both ER+ and ER-negative breast cancer incidence was significantly elevated in women exposed to benzene, ethylbenzene, or toluene at least 5 years after exposure levels were estimated,[130] providing convincing evidence of a link between BTEX exposures and increased breast cancer risk.

Among 140 pregnant African American women in Detroit, those who were exposed to the highest levels of BTEX compounds, based on the measurements done of outdoor air pollution levels in the areas they reside, exhibited increased circulating levels of inflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNF-α) mid-pregnancy, compared with African-American women living in areas where BTEX exposure was significantly lower.[131] Inflammation is a risk factor for all cancers,[132,133] including breast cancer,[134] and earlier studies indicate that maternal exposures that cause chronic low-grade inflammation both in mothers and their offspring, i.e., maternal obesity during pregnancy,[135,136] also increases offspring's mammary tumorigenesis.[137,138] In summary, results from these few human studies suggest that maternal BTEX exposure during pregnancy or an exposure prior to breast cancer diagnosis may increase susceptibility for later breast cancer development.

Neither mutagen exposures nor inherited mutations alone can cause breast cancer

Even when a person is exposed daily to a strong mutagen and the exposure continues for decades, the carcinogen does not automatically cause cancer. Cigarette smoking is an excellent example. Tobacco smoke contains multiple compounds that the International Agency for Research on Cancer (IARC) categorizes carcinogenic agents into in humans: PAH, 2-naphthylamine, 4-aminobiphenyl (aromatic amines), formaldehyde (aldehyde), benzene (volatile hydrocarbon), vinyl chloride (organic compound), and the following metals and inorganic compounds: arsenic, beryllium, nickel, chromium, and cadmium.[139] According to US Department of Health and Human services, smoking is linked to an increased risk of many cancers, but most strongly to lung cancer. Nevertheless, although cigarette smoking is one of the major risk factors to develop lung cancer, only 10%–20% of smokers develop lung cancer.[140] Thus, exposure to smoking alone, despite cigarettes containing many strong carcinogens, is not sufficient to initiate lung cancer in most smokers. For this reason, it is unlikely that PAH exposure alone initiates breast cancer, even if there is strong evidence that PAHs are carcinogenic for the breast.

The question is what determines which women of those exposed to high levels of PAHs will develop breast cancer? Are there other factors that increase a woman's susceptibility to mutagens? It was mentioned above that women with a high number of TDLUs and acini in the breast are at increased risk for developing breast cancer.[91,92] We have shown that the higher the number of human TDLU equivalent TEBs in rat or mouse

mammary gland, the more the PAH-induced mammary tumors these rodents develop.[141,142] We also have found that epigenetic silencing of tumor suppressor genes[141,143] or gut dysbiosis[144] increases the risk of developing PAH-initiated mammary tumors.

Identifying factors that increase the number of TDLUs/TEBs in the mammary gland or cause epigenetic silencing of tumor suppressor genes or persistent gut dysbiosis is likely to lead to development of strategies to prevent breast cancer. In our studies, *in utero* exposures to estradiol,[145] ethinyl estradiol,[141] maternal estrogen levels increasing high n-6 polyunsaturated fatty acid diet,[142] or obesity-inducing diet through pregnant dam[137,138] increases the number of TEBs in offspring's mammary gland. Our studies and findings by others also show these and other maternal exposures, such as an exposure to chemicals DES or DDT, cause epigenetic changes in the mammary gland[141–143,146–148] and induce gut dysbiosis.[144,149–152]

Germline BRCA1 mutation carriers

Germline mutations in breast cancer initiating genes are not sufficient alone to cause this disease. Humans inherit only one mutated BRCA1 allele. If a fetus inherits mutations in both BRCA1 alleles, i.e., one from mother and another from father, fetus does not survive.[153] For breast cancer to develop in BRCA1 mutation carriers, they either must have the other allele silenced in adult life or earlier,[154] acquire another mutation, such as a mutation in p53 or PTEN gene,[155] or have a specific breast cancer risk increasing genetic variant.[156] In preclinical models, heterozygous Brca1$^{+/-}$ mice need to be crossed with other genetically modified breast cancer mouse models[157] or administered DMBA carcinogen[158] for them to develop mammary tumors. Exposure to ionizing radiation will also increase mammary tumorigenesis in Brca1$^{+/-}$ rats.[159] In humans, men who are BRCA1/2 mutation carriers and are exposed to high levels of traffic pollution as truck drivers have higher breast cancer penetrance than other male BRCA1/2 carriers.[160] The Sister study discovered a significant correlation between an exposure to air pollution containing PAHs and BTEX compounds and increased breast cancer risk among women with strong family history of this disease.[99] Similar findings were obtained in women residing in New York: the highest breast cancer risk was seen in women with strong family history of breast cancer and the highest PAH exposure levels.[100]

Taken together, these findings suggest that adult exposure to mutagens is more likely to cause breast cancer in women who are exposed already in the womb to compounds or diets that increase later number of TLDU, induce epigenetic silencing of tumor suppressor genes, and/or cause gut dysbiosis. The compounds exposed *in utero* through a pregnant mother could include BTEX compounds or low enough doses of PAHs that do not cause miscarriage, both from vehicle emissions. Furthermore, the association between high PAH levels and breast cancer in women with strong family history suggests that one of the factors promoting penetrance of familial breast cancer is exposure to traffic pollutants.

Additional mechanisms of traffic pollutants on breast cancer risk

Besides forming DNA adducts, PAHs might affect mammary tumorigenesis by other means that do not directly cause malignant transformation but increase susceptibility to breast cancer or its metastasis. Guo et al.[161] reported that BaP exposure promoted the growth and metastatic potential of both human and mouse breast cancer cells by up-regulating ROS-induced ERK signaling, which then led to activation of metastasis-promoting MMP9. In another study, exposure of human breast cancer cells (MCF-7 and MDA-MB-231) to BaP promoted inflammatory pathways, including TNF-α, nuclear factor κB (NF-κB), and IL-6.[162]

Some of these changes may involve the epigenome.[163] Studies addressing changes in the whole epigenome or promoter regions of individual genes found that BaP exposure epigenetically modified genes.[164] Interestingly, BaP can cause both hypomethylation of pro-oncogenes, leading to oncogenic activation, as well as hypermethylation of tumor suppressor genes to silence them.[163]

PAHs also have estrogenic properties.[165,166] Gozgit et al.[167] studied estrogenicity of 14 different PAHs in ER+ MCF-7 human breast cancer cells and five of them, including BaP, induced ER-reporter activity. It was found that the reporter activity was dependent on the metabolism of PAHs in MCF-7 cells through the AhR pathway. These results that are confirmed by other investigators indicate that PAHs can induce estrogenic effects *in vivo*, and the effects may explain why PAHs are suggested to increase the risk of developing ER+ more than ER-negative breast cancer.[81] Over 70% of newly diagnosed breast cancers are ER+.

The key PAH used to generate mammary tumors in mice and rats—DMBA—also alter the expression of multiple oncogenic genes as well as suppress those that are involved in mammary gland differentiation,[168] induces inflammation,[169] and has estrogenic properties.[170,171] The role of PAHs' effects on these endpoints in increasing susceptibility to breast cancer, in addition to causing malignant transformation by inducing mutations, remains to be determined.

The gut microbiome

The gut microbiome has emerged as a critical factor in affecting human health and diseases, including breast cancer,[172,173] and as outlined below, PAHs affect the gut microbial composition. The gut microbiota is composed of about equal number of microbes, mainly bacteria, as there are human cells,[174] although this might be an underestimate.[175] Each human cell consists of about 20,000–25,000 different genes, whereas there are 100–500 times more genes in the microbes, i.e., 2–10 million.[176,177] Bacterial nucleic acids (DNA and RNA) can bind to receptors in human cells and play an important role in inflammatory responses.[178,179] However, the main reason why humans (and animals with gut) have gut microbiota is that human cells are unable to perform many critical functions that are required to maintain health. The key functions of the gut microbiota are digestion and detoxification reactions to provide nutrients to human cells, protection against inflammation, promotion of immune system development, and contribution to cognition and mood.[14,180–183] These functions are carried out by bacterial metabolites, such as neurotransmitters and their precursors. The bacterial metabolites currently receiving most interest are short-chain fatty acids (SCFAs).

Humans in fact have two genomes: one inherited from parents and the other acquired early in life as the microbiome. The key difference between the two is that the inherited genome remains relatively stable during a lifetime, whereas the microbiome can be influenced by lifestyle and several other factors, including diet. Many factors can modify the gut microbiota, such as changes in diet, exercise, alcohol intake, smoking, exposure to hazardous environment, stress, and diseases.[184,185] However, if these factors are removed, composition of the gut microbiota returns to its original form.[186] Further, in contrast to the human genome, which is about 1% different between any two individuals, the gut microbiome is unique for each individual.[187,188]

Factors affecting the gut microbiome

Humans can modify their gut microbial composition in different ways, including through their diet, physical activity, exposure to environmental factors, and stress. The human body can also control the microbiota several ways through immunity, barrier function, transit, and physiology.[189] For example, when a pathogenic bacterium enters the gastrointestinal track, diarrhea can clear it. Oxygen control represents another example as to how host physiology can regulate microbes. In mammals, the small intestine can reduce oxygen levels by the intestinal villi scavenging oxygen[190] and in the large intestine epithelial cells consume oxygen rapidly and create conditions that promote microbial fermentation.[191] Vaccines are also under development to target specific gut microbial bacteria.[192]

It is still a matter of debate when humans acquire gut microbiota (*in utero* or starting at birth), but the gut microbiota composition is established by age 2.5 years and remains relatively stable throughout the rest of life.[193,194] Based on findings in homozygotic twins, the human genome is suggested to affect the gut microbial composition.[195,196] However, other investigators have concluded that shared household is the critical factor in determining gut microbiota composition rather than shared genetic similarity.[197] Others have confirmed that individuals who started cohabiting as adults exhibit more gut bacterial strain sharing (13%) than twins living apart (10%).[198] Further, several diseases are linked to specific changes in the gut microbiome, and at least in some cases these changes are causative for the development of a disease. One of these diseases is Alzheimer disease, and it has been discovered that co-habiting caretakers of Alzheimer patients acquire gut microbial changes similar to the patients.[199] As the spouses of Alzheimer disease patients are at a significantly increased risk of dementia,[200] the risk of developing specific diseases might be mediated through the shared environment and gut microbiome.

SCFAs

When the bidirectional beneficial communication between the gut microbiome and human host is disrupted, gut dysbiosis ensues. Since the gut microbiome is unique to each individual, there is no straightforward way to characterize bacterial changes to define gut dysbiosis. Dysbiotic gut produces low levels of SCFAs,[201,202] which are metabolized by multiple different bacteria, such as bacterial species belonging to the families *Ruminococcaceae* and *Lachnospiraceae*[203,204] of *Firmicutes* phylum. *Akkermansia muciniphila* is the main producer of propionate[205] but also leads to an increase in the abundance of bacteria that generate butyrate[206] and acetate.[204,205]

SCFAs generate gastrointestinal mucus that works as a barrier to prevent the release of inflammatory microbes and their products, such as lipopolysaccharides, into the circulation.[183] SCFAs also prevent and reduce inflammation and activate anti-tumor immune responses,[207–209] provide energy for the host cells and improve mitochondrial metabolism,[210,211] and impact the epigenome by acting as histone deacetylase inhibitors.[212–214] A dysbiotic gut produces reduced levels of SCFAs.[201] Further, gut dysbiosis and low SCFAs are linked to increased breast cancer.[215] Thus, in an individual who acquires gut dysbiosis before age 2.5 years, such as offspring born to obese mothers,[151,216] the interventions that change the gut microbiome to a state that supports the host health need to continue through life.

PAHs alter the gut microbiome

Several studies have been carried out to investigate the impact of PAHs on the gut microbiome. BaP administration to Nile tilapia via a single injection led to increased abundance of *Fusobacteria* and *Bacteroidetes* phyla and a decrease in *Proteobacteria* and *Spirochaete* phyla.[217] Changes were also observed in the gut microbiome of fathead minnow exposed to BaP.[218] Exposure of zebrafish embryos with BaP caused changes mainly in microbial diversity, but only a few alterations in specific microbes, including *Actinobacteria* phylum.[219] In mice, BaP caused alterations in 31 gut microbes at the genera level in the intestine and colon.[220] Among the changes were reduced abundance of *Akkermansia* genus of *Verrucomicrobia* phylum and increased *Corynebacterium* genus of Actinobacteria phylum. Another study[221] exposed wild-type or germ-free mice to either BaP or 1-nitropyrene, which also is a PAH from traffic exhaust but structurally different from BaP. Further, nitropyrenes induce mammary tumors when given to newborn rats[222] and benign and malignant mammary tumors when administered to pubertal rats.[65,223] Endpoint examined was P450 activity in the liver to determine whether the gut microbiome affects bioactivation of PAHs into carcinogenic electrophilic epoxides. Findings indicated that the microbiome alters PAH metabolism in the liver.[221]

In humans, The CALINE4 line dispersion model was used to estimate prior year residential concentrations of nitrogen oxides (NOx) as a marker of traffic emission.[224] Results of the study indicated that exposure to freeway-traffic-related air pollution correlated with decreased fecal abundance of *Bacteroidaceae* family of *Bacteroidetes* phylum and increased *Coriobacteriaceae* family of *Actinobacteria* phylum.

Several studies have investigated changes in the gut microbiome of smokers who are exposed to many different PAHs. A large study involving male smokers[225] discovered that the abundance of the phylum *Bacteroidetes* was increased, whereas *Firmicutes* and *Proteobacteria* phyla were reduced in current smokers. These differences were no longer present in individuals who had quit smoking. A systemic review,[226] however, found that gut bacterial changes were present both in current and former smokers. As expected, results as to which phylum or genus was altered in smokers and former smokers varied from study to study. However, two relatively consistent changes were noted: the abundance of *Prevotella* spp. of *Bacteroidetes* phylum was reduced in smokers and former smokers, whereas *Proteobacteria* phylum increased with the number of pack-years of cigarette in current smokers, compared to individuals who never smoked. The

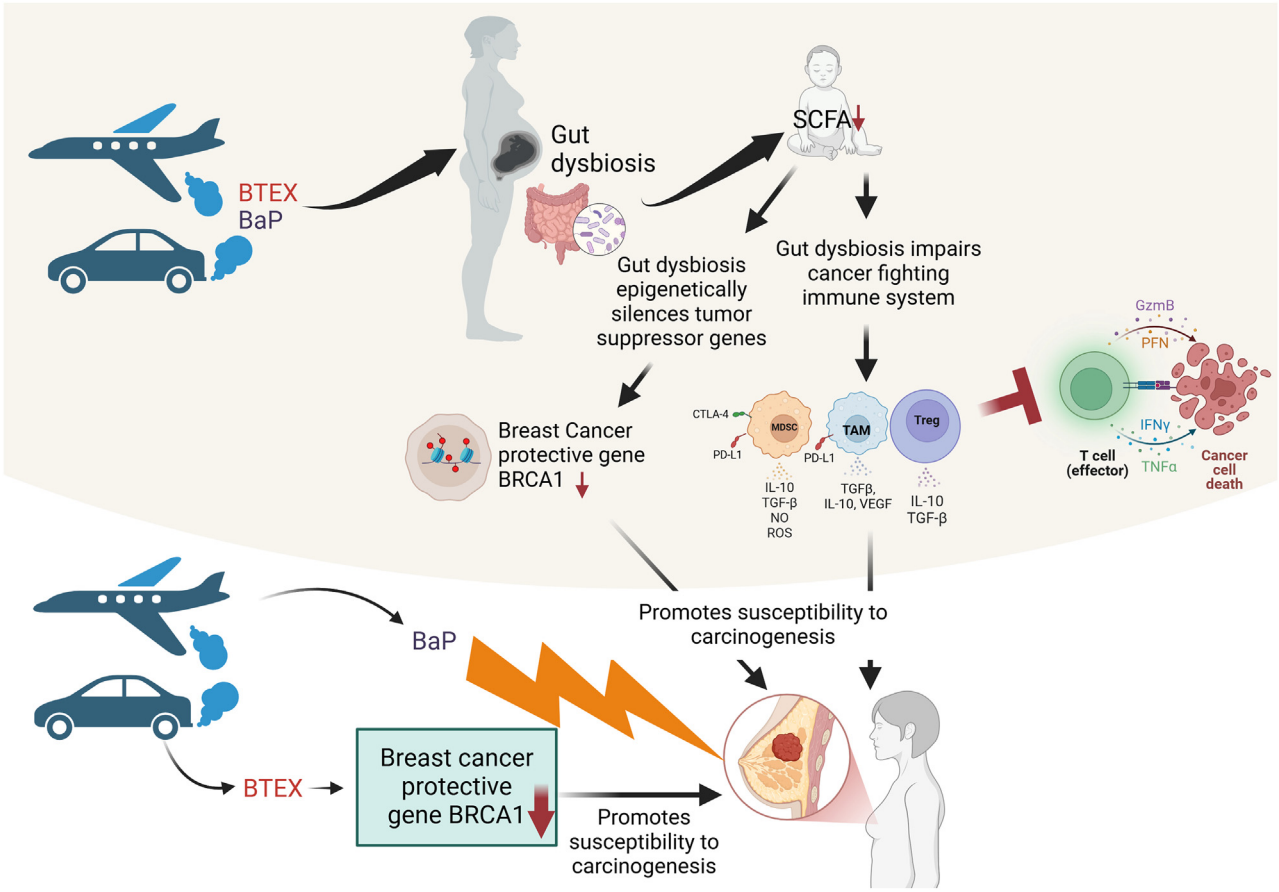

Figure 1. Vehicle emissions and increased breast cancer risk

Maternal exposure to volatile aromatics benzene, toluene, ethylbenzene, xylene (BTEX), or low levels of benz[*a*]pyrene (BaP) from vehicle emission during pregnancy is expected to cause gut dysbiosis in the mother and her offspring. Gut dysbiosis, characterized by a reduced production of short-chain fatty acids (SCFAs) will then cause epigenetic changes, possibly involving suppression of BRCA1 tumor suppressor gene and impair anti-cancer immune system among offspring, by inducing immune suppressive cells. Consequently, female offspring will be at high risk of malignant transformation in the breast, induced by an exposure to BaP. Continued exposure to BTEX compounds during adult life will further suppress tumor suppressor genes, potentiating the risk of developing breast cancer upon BaP exposure. BRCA1: MDSC, myeloid-derived suppressor cells; TAM, tumor-associated macrophage; Treg, T regulatory cells; GzmB, Granzyme B; INFγ, interferon gamma; PFN, perforin; TNFα, tumor necrosis factor alpha; IL-10, interleukin 10; TGFβ, transforming growth factor β; NO, nitric oxide; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor. Created using BioRender.

findings regarding *Proteobacteria* are opposing in Lee et al.[225] and Antinozzi et al.[226] studies, highlighting the difficulty of identifying specific "smoking" or BaP exposure signatures. These findings, however, do not negate the possibility that PAHs may modify cancer susceptibility partly by modifying the gut microbiome and consequently by impairing immune responses, targeting epigenetic regulation of tumor suppressor genes and other mechanisms involved in promoting malignant transformation.

Although the impact of BTEX exposure on the gut microbiota has not been studied, there are some reports of the effects of toluene. Toluene caused gastrointestinal symptoms and accelerated the development of irritable bowel syndrome in humans.[227] In earthworm[228] and lizard,[229] toluene adversely affected gut microbes. We are planning studies to investigate whether inhalation of BTEX compounds affects the gut microbiome, particularly among offspring when the exposure occurs during pregnancy. Figure 1 illustrates how maternal exposure to BTEX compounds and non-carcinogenic doses of BaP during pregnancy by inducing gut dysbiosis among offspring might lead to increased breast cancer risk and promote vulnerability to breast cancer initiation by an exposure to DNA adducts from BaP. Gut dysbiosis, marked by reduced production of SCFAs, will impair the ability of effector T cells to eliminate cancer. Reduced SCFA production might also epigenetically suppress tumor suppressor genes, as they function as histone deacetylase inhibitors. Whether gut dysbiosis might also regulate mammary gland development is not known.

CONCLUSIONS

No single risk factor alone causes breast cancer. Even women with a strong family history need an additional event to take place, besides for example inheriting a germline mutation in BRCA1/2 gene for cancer to develop.[154–156] The penetrance

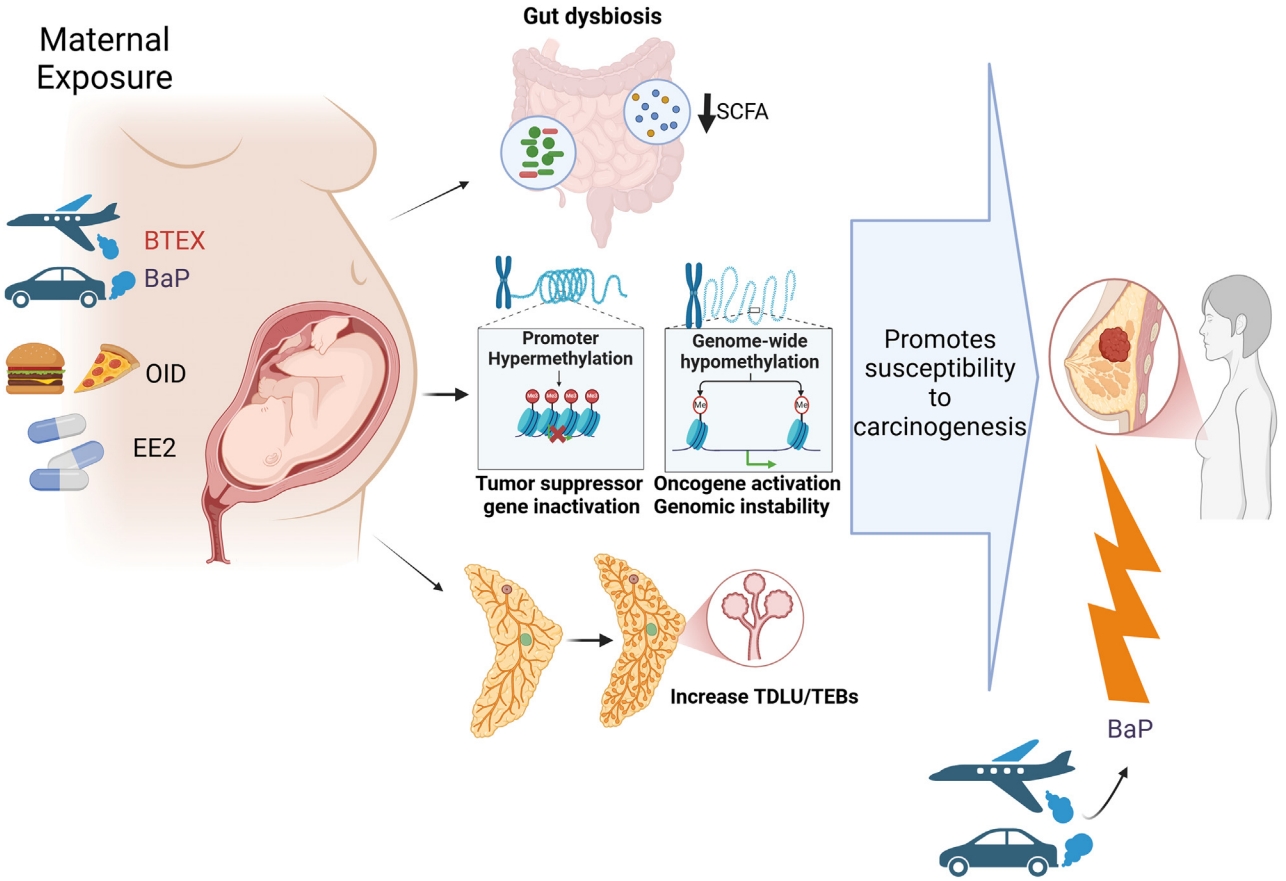

Figure 2. Factors increasing susceptibility to polycyclic aromatic hydrocarbon (PAH)-initiated breast cancer

Maternal exposures to obesity-inducing diet (OID), hormones, including ethinyl estradiol (EE2) from drinking water, or aromatics from fossil fuels, such as benz[*a*]pyrene (BaP) and BTEX (benzene, toluene, ethylbenzene and xylene) compounds, can increase breast cancer susceptibility among adult daughters by increasing the number of structures in the mammary gland which give rise to cancer (terminal ductal lobular unit - TDLU - in women and terminal end bud -TEB – in mice), epigenetically silencing tumor suppressor genes or upregulating oncogenes, and/or causing gut dysbiosis, defined as reduced bacterial production of short chain fatty acids (SCFAs). Women who were exposed *in utero* to these breast cancer susceptibility increasing factors are most likely to develop breast cancer later on when they encounter an exposure to high levels of PAHs. Created using BioRender.

of breast cancer in BRCA1 and BRCA2 mutation carriers by age 70 years has increased from 57% and 49%, respectively, in a meta-analysis published in 2007[230] to 65% and 61% in an updated meta-analysis published by the same authors in 2020,[231] suggesting the impact of additional factors relative to inherited factors has increased. Previous studies indicate that BaP inhibits the expression of BRCA1 in human breast cancer cells and in mice,[101,102] and our preliminary data show that BTEX compounds also suppress the expression of BRCA1 in human breast cancer cell lines. As a loss of the wild-type BRCA1 allele contributes to breast cancer penetrance in women with heterozygous germline BRCA1 mutations,[154] an exposure to vehicle emissions could play a role in developing breast cancer among BRCA1 mutation carriers. In support of this suggestion, several studies have established a link between PAH exposure and increased breast cancer risk in women at high familial risk.[76,82,99]

We proposed earlier[232,233] and again highlight here that both mutagen exposure and exposures to factors that increase susceptibility for mutagens are needed for sporadic breast cancer to be initiated or for it to progress from an initial premalignant state to cancer (Figure 2). Based on the literature reviewed here, the main mutagens for breast cancer are PAHs. One of the key sources of PAHs are vehicle emissions.[44] PAHs may also contribute to increasing susceptibility and promotion of breast cancer through their estrogenic properties, altering the epigenome and causing gut dysbiosis. Other compounds from vehicle emissions, especially BTEX compounds, might also contribute to increasing susceptibility to breast cancer.[128,129] Benzene in BTEX mixture can also have direct mutagenic effects.[234,235] Importantly, the timing of both DNA damage causing PAHs and other biological changes induced by them and BTEX compounds may be critical. These compounds likely increase vulnerability to breast cancer most when exposed *in utero* through a pregnant mother or before age of 2.5–3 years when they can permanently modify the gut microbiome and epigenome. As a consequence of these changes, female offspring could exhibit epigenetic silencing of tumor suppressor

genes,[141,143] increased number of TEBs,[138,142] and gut dysbiosis.[144] Mutagenic PAH exposure needs to happen when TDLUs are most susceptible for malignant transformation, and this is suggested to be between puberty onset and birth of first child.[236]

Future research to identify causes of breast cancer and tools to prevent it needs to focus on both exposures that increase breast cancer susceptibility and those that initiate malignant transformation. These exposures could include compounds from vehicle emissions, such as BaP as a mutagen and BTEX as breast cancer susceptibility increasing compounds. Further, efforts should be directed toward regulating BTEX exposures, and these efforts could include adding ethanol to gasoline.

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AUTHOR CONTRIBUTIONS

L.H.C. conceptualized the contents of the review; L.H.C., T.J., and S.M. performed investigation of the literature; J.L.S. performed preliminary studies cited in the review; L.H.C. wrote original draft; L.H.C., T.J., J.L.S., F.O.A., and S.M. participated in reviewing and editing the manuscript; F.O.A. prepared all figures; and S.M. and G.D. acquired financial support for the project.

DECLARATION OF INTERESTS

None of the authors have any interests related to the manuscript to declare.

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