

## 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<sup>1</sup>; together these hits then drive malignant transformation. This dogma has recently been questioned.<sup>2</sup> In some cases an epigenetic change<sup>3</sup> or a single mutation<sup>4</sup> is sufficient to drive malignant transformation. Further, immune,<sup>5</sup> vascular,<sup>6</sup> and neuronal cells<sup>7,8</sup> and stromal fibroblasts<sup>9,10</sup> in the tumor microenvironment (TME) influence progression of transformed cells toward tumor. For example, immune cells can kill and thus eliminate pre-malignant cells.<sup>11</sup> However, some immune cells, such as tumor-associated macrophages, T regulatory cells, and myeloid-derived suppressor cells can help tumors to grow.<sup>12,13</sup> Immune cell infiltration and activation in the TME are impacted by the gut microbiome.<sup>14–16</sup> 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.<sup>17,18</sup> 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.<sup>19–21</sup> 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.<sup>22</sup> 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.<sup>23</sup> More recently identified risk factors include having high birthweight (>4,000 g)<sup>24,25</sup> and having been exposed *in utero* to diethylstilbestrol (DES)<sup>26,27</sup> or dichlorodiphenyltrichloroethane (DDT).<sup>28</sup> 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%.<sup>29</sup> 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%).<sup>29</sup> 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.<sup>30</sup> 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.<sup>31</sup> Interestingly, the proportion of familial breast cancers of all newly diagnosed breast cancers is also increasing.<sup>32</sup> 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.<sup>33</sup> However, at least half of women with strong family history have no known breast cancer mutations.<sup>34,35</sup> In some families, cancer may be inherited through epigenetic alterations.<sup>36,37</sup>

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.<sup>38,39</sup> Breast cancer risk is elevated by radiation most among those exposed to the highest radiation levels and those exposed at a young age.<sup>40,41</sup> 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.<sup>42</sup> 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.<sup>42</sup> One factor linked to early puberty onset is maternal obesity during pregnancy,<sup>43</sup> 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).<sup>44–46</sup> 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.<sup>47</sup>

### Pre-clinical models

Rudel et al. (2014)<sup>48</sup> 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.<sup>49</sup> 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.<sup>50,51</sup> These metabolites are formed in the liver through activation of P450 genes, such as CYP1A1 and CYP1B1. BaP upregulates CYP1A1 gene.<sup>52</sup> Aryl hydrocarbon receptor (AhR) is a transcriptional regulator of CYP1A1, and in its absence in AhR–/– knockout mice, BaPs is not carcinogenic.<sup>53</sup> Carcinogenicity of DMBA also is dependent on the activation of P450 genes.<sup>52,54</sup>

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.<sup>55,56</sup> 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.<sup>57</sup> DMBA-initiated mammary tumors in mice are either ER+ luminal or ER-negative basal types.<sup>58</sup> The reason why DMBA is provided after puberty onset, which occurs at end of 1<sup>st</sup> 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.<sup>49</sup> These structures are terminal end buds (TEBs), and they contain cells that are suggested to be stem/progenitor cells<sup>59,60</sup> and that can be transformed to malignancy.<sup>49</sup> Mutations in DMBA-induced mammary tumors include high frequency of *Pi3kca* and/or *Pten* mutations (64% of tumors).<sup>58</sup> *Ras* mutations also are present, although they are not found in all studies,<sup>61,62</sup> as well as several other mutations.<sup>58,62</sup> All these mutations occur in human ER+ breast cancers. For example, 30%–40% of human ER+/HER2– breast cancer contain *PI3KCA* mutations.<sup>63,64</sup>

Another PAH that initiates mammary tumors in rats is 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP).<sup>65,66</sup> In contrast to DMBA, this PAH is naturally present in the human environment, mostly in grilled and broiled meat.<sup>67</sup> 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.<sup>68</sup> 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.<sup>55,56</sup>

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.<sup>69</sup> The major BaP exposures originate from vehicle emissions and industrial sources. Other BaP exposure sources are consumption of grilled or well-done meats.<sup>70,71</sup> Dr. Hecht's group compared BaP and PhIP as carcinogens to initiate mammary tumors in

rats.<sup>65</sup> 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,<sup>55</sup> whereas in mice some are luminal and some basal-like.<sup>58,72</sup>

### Human studies

Many studies have investigated a link between air pollution and breast cancer, using measures assessing exposures to PAHs, particulate matter, or nitric oxide. The two latter measures are directly linked to PAH exposure.<sup>73,74</sup> 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.<sup>75</sup> 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.<sup>76</sup> 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<sup>77</sup> 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,<sup>78</sup> and vehicle emissions<sup>79</sup> 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.<sup>80</sup> A recent nested case-control study in French E3N cohort<sup>81</sup> 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<sup>3</sup>) 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.<sup>82</sup> 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.<sup>82</sup> 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.<sup>83</sup> However, if smoking starts in the early teenage years and before first pregnancy, it increases breast cancer risk.<sup>84–87</sup>

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.<sup>88–90</sup> Two studies have investigated a link between TDLU/acini number and size and breast cancer risk. These studies reported that the higher the TDLU number and size, and acini count within TLDU, the higher the breast cancer risk.<sup>91,92</sup> 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.<sup>93</sup> 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.<sup>94</sup> 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.<sup>95</sup> Pregnancy affects TDLU involution,<sup>96–98</sup> 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.<sup>99</sup> 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.<sup>100</sup> 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<sup>101</sup> and in the offspring of BaP-exposed pregnant mouse dams.<sup>102</sup> 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.<sup>103</sup> Main sources of BTEX compound exposures are from petrochemical processes, petroleum refineries, and industries using coal.<sup>45,46</sup> 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.<sup>104</sup> 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.<sup>105</sup> BTEX compounds also are present at high concentrations inside homes and public indoor environments<sup>106–108</sup> 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).<sup>109</sup> 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,<sup>110</sup> similar to benzene.

The regulatory reference concentrations for BTEX compounds are set by the United States Environmental Protection Agency (US EPA).<sup>108</sup> 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.<sup>111–113</sup>

BTEX compounds are proposed to be among the most hazardous components of gasoline.<sup>114,115</sup> They have been linked to damage in the liver, nervous system, heart, lung, and kidneys.<sup>108,116,117</sup> Of the BTEX compounds, benzene is categorized as a carcinogen,<sup>118,119</sup> ethylbenzene as a carcinogen in animal but not human studies,<sup>120</sup> but neither toluene nor xylene is carcinogenic.<sup>121</sup> 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.<sup>122</sup> Since high mammographic density is a strong risk factor for breast cancer,<sup>123–125</sup> 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,<sup>126</sup> 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<sup>127</sup> 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*.<sup>101,102</sup>

#### **Human studies**

Few studies have explored a possible connection between BTEX levels and breast cancer. In a study by Wei et al.,<sup>128</sup> 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.<sup>129</sup> 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<sup>130</sup>; 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,<sup>130</sup> 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-1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor alpha (TNF- $\alpha$ ) mid-pregnancy, compared with African-American women living in areas where BTEX exposure was significantly lower.<sup>131</sup> Inflammation is a risk factor for all cancers,<sup>132,133</sup> including breast cancer,<sup>134</sup> 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,<sup>135,136</sup> also increases offspring's mammary tumorigenesis.<sup>137,138</sup> 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.<sup>139</sup> 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.<sup>140</sup> 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.<sup>91,92</sup> 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.<sup>141,142</sup> We also have found that epigenetic silencing of tumor suppressor genes<sup>141,143</sup> or gut dysbiosis<sup>144</sup> 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,<sup>145</sup> ethinyl estradiol,<sup>141</sup> maternal estrogen levels increasing high n-6 polyunsaturated fatty acid diet,<sup>142</sup> or obesity-inducing diet through pregnant dam<sup>137,138</sup> 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<sup>141–143,146–148</sup> and induce gut dysbiosis.<sup>144,149–152</sup>

### 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.<sup>153</sup> For breast cancer to develop in BRCA1 mutation carriers, they either must have the other allele silenced in adult life or earlier,<sup>154</sup> acquire another mutation, such as a mutation in p53 or PTEN gene,<sup>155</sup> or have a specific breast cancer risk increasing genetic variant.<sup>156</sup> In preclinical models, heterozygous *Brca1*<sup>+/-</sup> mice need to be crossed with other genetically modified breast cancer mouse models<sup>157</sup> or administered DMBA carcinogen<sup>158</sup> for them to develop mammary tumors. Exposure to ionizing radiation will also increase mammary tumorigenesis in *Brca1*<sup>+/-</sup> rats.<sup>159</sup> 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.<sup>160</sup> 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.<sup>99</sup> 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.<sup>100</sup>

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.<sup>161</sup> 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- $\alpha$ , nuclear factor  $\kappa$ B (NF- $\kappa$ B), and IL-6.<sup>162</sup>

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

PAHs also have estrogenic properties.<sup>165,166</sup> Gozgit et al.<sup>167</sup> 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.<sup>81</sup> 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,<sup>168</sup> induces inflammation,<sup>169</sup> and has estrogenic properties.<sup>170,171</sup> 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,<sup>172,173</sup> 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,<sup>174</sup> although this might be an underestimate.<sup>175</sup> 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.<sup>176,177</sup> Bacterial nucleic acids (DNA and RNA) can bind to receptors in human cells and play an important role in inflammatory responses.<sup>178,179</sup> 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.<sup>14,180–183</sup> 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.<sup>184,185</sup> However, if these factors are removed, composition of the gut microbiota returns to its original form.<sup>186</sup> Further, in contrast to the human genome, which is about 1% different between any two individuals, the gut microbiome is unique for each individual.<sup>187,188</sup>

### **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.<sup>189</sup> 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<sup>190</sup> and in the large intestine epithelial cells consume oxygen rapidly and create conditions that promote microbial fermentation.<sup>191</sup> Vaccines are also under development to target specific gut microbial bacteria.<sup>192</sup>

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.<sup>193,194</sup> Based on findings in homozygotic twins, the human genome is suggested to affect the gut microbial composition.<sup>195,196</sup> However, other investigators have concluded that shared household is the critical factor in determining gut microbiota composition rather than shared genetic similarity.<sup>197</sup> Others have confirmed that individuals who started cohabiting as adults exhibit more gut bacterial strain sharing (13%) than twins living apart (10%).<sup>198</sup> 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.<sup>199</sup> As the spouses of Alzheimer disease patients are at a significantly increased risk of dementia,<sup>200</sup> 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,<sup>201,202</sup> which are metabolized by multiple different bacteria, such as bacterial species belonging to the families *Ruminococcaceae* and *Lachnospiraceae*<sup>203,204</sup> of *Firmicutes* phylum. *Akkermansia muciniphila* is the main producer of propionate<sup>205</sup> but also leads to an increase in the abundance of bacteria that generate butyrate<sup>206</sup> and acetate.<sup>204,205</sup>

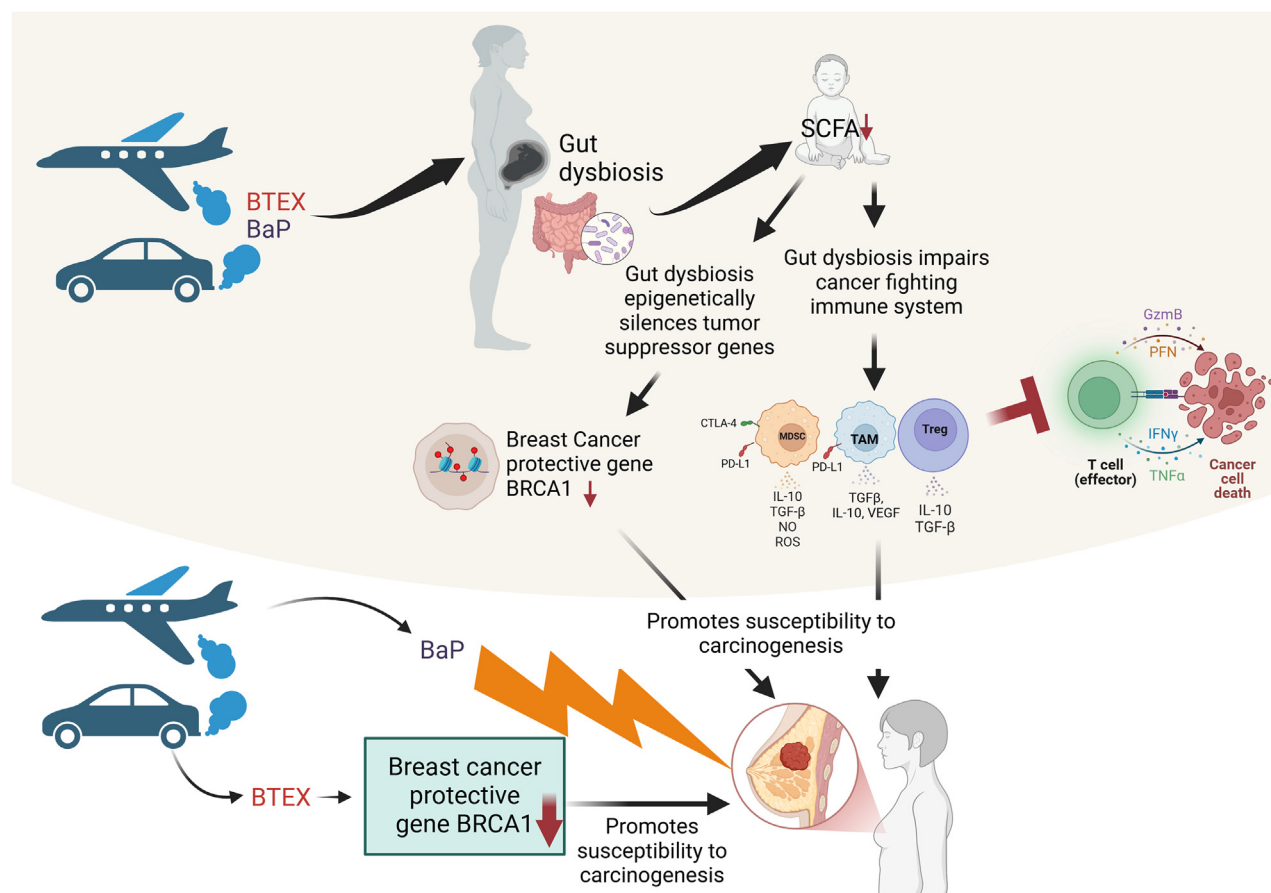
SCFAs generate gastrointestinal mucus that works as a barrier to prevent the release of inflammatory microbes and their products, such as lipopolysaccharides, into the circulation.<sup>183</sup> SCFAs also prevent and reduce inflammation and activate anti-tumor immune responses,<sup>207–209</sup> provide energy for the host cells and improve mitochondrial metabolism,<sup>210,211</sup> and impact the epigenome by acting as histone deacetylase inhibitors.<sup>212–214</sup> A dysbiotic gut produces reduced levels of SCFAs.<sup>201</sup> Further, gut dysbiosis and low SCFAs are linked to increased breast cancer.<sup>215</sup> Thus, in an individual who acquires gut dysbiosis before age 2.5 years, such as offspring born to obese mothers,<sup>151,216</sup> 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.<sup>217</sup> Changes were also observed in the gut microbiome of fathead minnow exposed to BaP.<sup>218</sup> Exposure of zebrafish embryos with BaP caused changes mainly in microbial diversity, but only a few alterations in specific microbes, including *Actinobacteria* phylum.<sup>219</sup> In mice, BaP caused alterations in 31 gut microbes at the genera level in the intestine and colon.<sup>220</sup> Among the changes were reduced abundance of *Akkermansia* genus of *Verrucomicrobia* phylum and increased *Corynebacterium* genus of *Actinobacteria* phylum. Another study<sup>221</sup> 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<sup>222</sup> and benign and malignant mammary tumors when administered to pubertal rats.<sup>65,223</sup> 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.<sup>221</sup>

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.<sup>224</sup> 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<sup>225</sup> 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,<sup>226</sup> 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; IFN $\gamma$ , interferon gamma; PFN, perforin; TNF $\alpha$ , tumor necrosis factor alpha; IL-10, interleukin 10; TGF $\beta$ , transforming growth factor  $\beta$ ; NO, nitric oxide; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor. Created using BioRender.

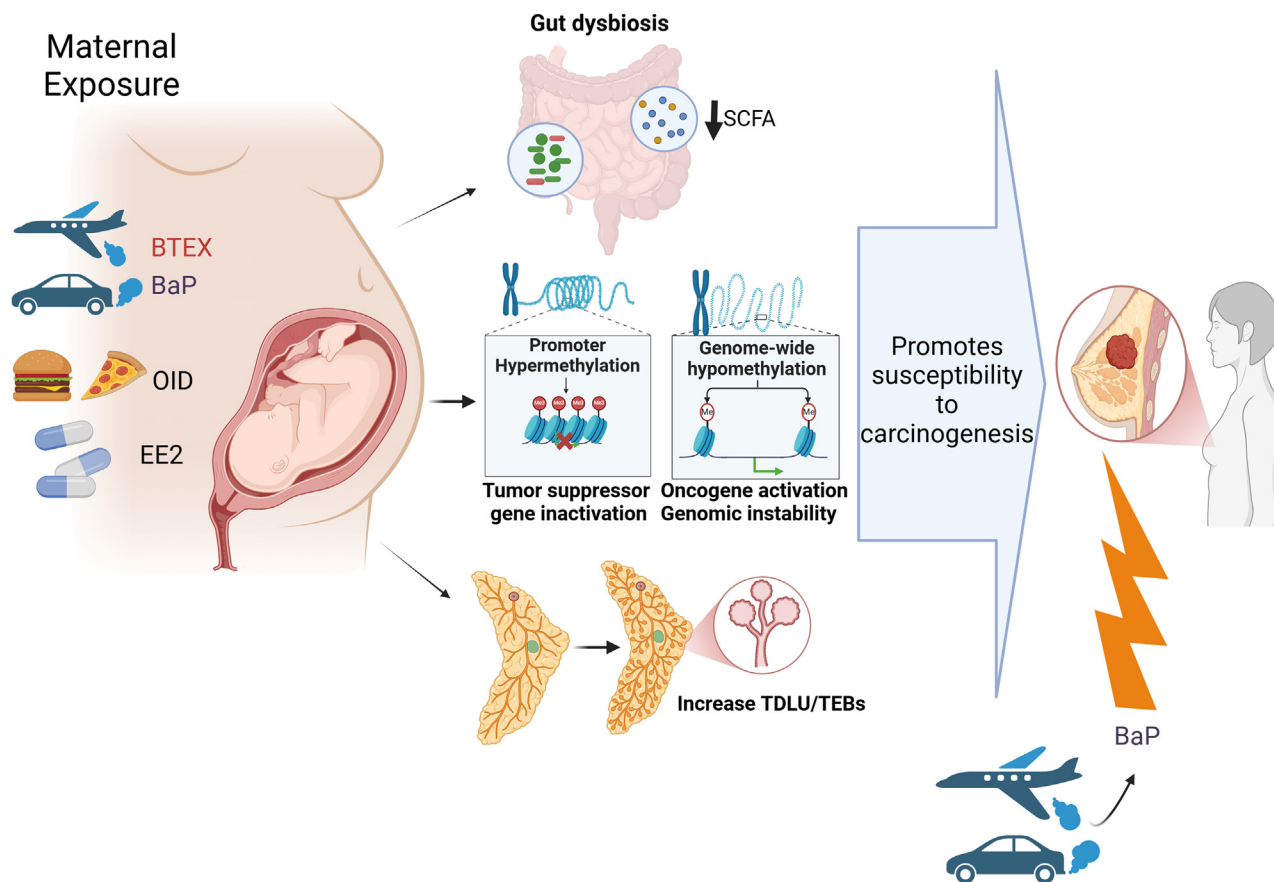
findings regarding *Proteobacteria* are opposing in Lee et al.<sup>225</sup> and Antinozzi et al.<sup>226</sup> studies, highlighting the difficulty of identifying specific “smoking” or BaP exposure signatures. These findings, however, do not negate the possibility that PAHs may modify cancer susceptibility 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.<sup>227</sup> In earthworm<sup>228</sup> and lizard,<sup>229</sup> 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.<sup>154–156</sup> 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<sup>230</sup> to 65% and 61% in an updated meta-analysis published by the same authors in 2020,<sup>231</sup> 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,<sup>101,102</sup> 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,<sup>154</sup> 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.<sup>76,82,99</sup>

We proposed earlier<sup>232,233</sup> and again highlight here that both mutagen exposure and exposures to factors that increase sus-

ceptibility 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.<sup>44</sup> 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.<sup>128,129</sup> Benzene in BTEX mixture can also have direct mutagenic effects.<sup>234,235</sup> 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,<sup>141,143</sup> increased number of TEBs,<sup>138,142</sup> and gut dysbiosis.<sup>144</sup> 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.<sup>236</sup>

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.

## REFERENCES

- Vogelstein, B., Papadopoulos, N., Velculescu, V.E., Zhou, S., Diaz, L.A., Jr., and Kinzler, K.W. (2013). Cancer genome landscapes. *Science* 339, 1546–1558.
- Gargiulo, G., Serresi, M., and Marine, J.C. (2024). Cell States in Cancer: Drivers, Passengers, and Trailers. *Cancer Discov.* 14, 610–614.
- Parreno, V., Loubiere, V., Schuettengruber, B., Fritsch, L., Rawal, C.C., Erokhin, M., Györfy, B., Normanno, D., Di Stefano, M., Moreaux, J., et al. (2024). Transient loss of Polycomb components induces an epigenetic cancer fate. *Nature* 629, 688–696.
- Yuan, S., Almagro, J., and Fuchs, E. (2024). Beyond genetics: driving cancer with the tumour microenvironment behind the wheel. *Nat. Rev. Cancer* 24, 274–286.
- Togashi, Y., Shitara, K., and Nishikawa, H. (2019). Regulatory T cells in cancer immunosuppression - implications for anticancer therapy. *Nat. Rev. Clin. Oncol.* 16, 356–371.
- Folkman, J. (2006). Angiogenesis. *Annu. Rev. Med.* 57, 1–18.
- Liu, V., Dietrich, A., Kasperek, M.S., Benhaqi, P., Schneider, M.R., Schemann, M., Seeliger, H., and Kreis, M.E. (2015). Extrinsic intestinal denervation modulates tumor development in the small intestine of Apc(Min/+) mice. *J. Exp. Clin. Cancer Res.* 34, 39.
- Balood, M., Ahmadi, M., Eichwald, T., Ahmadi, A., Majdoubi, A., Roversi, K., Roversi, K., Lucido, C.T., Restaino, A.C., Huang, S., et al. (2022). Nociceptor neurons affect cancer immunosurveillance. *Nature* 611, 405–412.
- Olumi, A.F., Grossfeld, G.D., Hayward, S.W., Carroll, P.R., Tlsty, T.D., and Cunha, G.R. (1999). Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. *Cancer Res.* 59, 5002–5011.
- Costa, A., Kieffer, Y., Scholer-Dahirel, A., Pelon, F., Bourachot, B., Cardon, M., Sirven, P., Magagna, I., Fuhrmann, L., Bernard, C., et al. (2018). Fibroblast Heterogeneity and Immunosuppressive Environment in Human Breast Cancer. *Cancer. Cell.* 33, 463–479.
- Whiteside, T.L. (2006). Immune suppression in cancer: effects on immune cells, mechanisms and future therapeutic intervention. *Semin. Cancer Biol.* 16, 3–15.
- Ohue, Y., and Nishikawa, H. (2019). Regulatory T (Treg) cells in cancer: Can Treg cells be a new therapeutic target? *Cancer Sci.* 110, 2080–2089.
- Saha, T., Dash, C., Jayabalan, R., Khiste, S., Kulkarni, A., Kurmi, K., Mondal, J., Majumder, P.K., Bardia, A., Jang, H.L., and Sengupta, S. (2022). Intercellular nanotubes mediate mitochondrial trafficking between cancer and immune cells. *Nat. Nanotechnol.* 17, 98–106.
- Schirmer, M., Smeekens, S.P., Vlamakis, H., Jaeger, M., Oosting, M., Franzosa, E.A., Horst, R.T., Jansen, T., Jacobs, L., Bonder, M.J., et al. (2016). Linking the Human Gut Microbiome to Inflammatory Cytokine Production Capacity. *Cellule* 167, 1125–1136.e8.
- Zitvogel, L., Ayyoub, M., Routy, B., and Kroemer, G. (2016). Microbiome and Anticancer Immunosurveillance. *Cell* 165, 276–287.
- Gopalakrishnan, V., Spencer, C.N., Nezi, L., Reuben, A., Andrews, M.C., Karpnits, T.V., Prieto, P.A., Vicente, D., Hoffman, K., Wei, S.C., et al. (2018). Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* 359, 97–103.
- Helmink, B.A., Khan, M.A.W., Hermann, A., Gopalakrishnan, V., and Wargo, J.A. (2019). The microbiome, cancer, and cancer therapy. *Nat. Med.* 25, 377–388.
- Yonekura, S., Terrisse, S., Alves Costa Silva, C., Lafarge, A., Iebba, V., Ferrere, G., Goubet, A.G., Fahrner, J.E., Lahmar, I., Ueda, K., et al. (2022). Cancer Induces a Stress Ileopathy Depending on  $\beta$ -Adrenergic Receptors and Promoting Dysbiosis that Contributes to Carcinogenesis. *Cancer Discov.* 12, 1128–1151.
- Petracci, E., Decarli, A., Schairer, C., Pfeiffer, R.M., Pee, D., Masala, G., Palli, D., and Gail, M.H. (2011). Risk factor modification and projections of absolute breast cancer risk. *J. Natl. Cancer Inst.* 103, 1037–1048.
- Mertens, E., Barrenechea-Pulache, A., Sagastume, D., Vasquez, M.S., Vandevijvere, S., and Peñalvo, J.L. (2023). Understanding the contribution of lifestyle in breast cancer risk prediction: a systematic review of models applicable to Europe. *BMC. Cancer.* 23, 687.
- Rea, D., Coppola, G., Palma, G., Barbieri, A., Luciano, A., Del Prete, P., Rossetti, S., Berretta, M., Facchini, G., Perdonà, S., et al. (2018). Microbiota effects on cancer: from risks to therapies. *Oncotarget* 9, 17915–17927.
- Singh, G.K., DiBari, J.N., and Lee, H. (2021). Prevalence and Social and Built Environmental Determinants of Maternal Prepregnancy Obesity in 68 Major Metropolitan Cities of the United States, 2013–2016. *J. Environ. Public Health* 2021, 6650956.
- American Cancer Society (2019). Breast Cancer Facts & Figures 2019–2020 (Atlanta: American Cancer Society, Inc.).
- Michels, K.B., Trichopoulos, D., Robins, J.M., Rosner, B.A., Manson, J.E., Hunter, D.J., Colditz, G.A., Hankinson, S.E., Speizer, F.E., and Willett, W.C. (1996). Birthweight as a risk factor for breast cancer. *Lancet* 348, 1542–1546.
- Silva, I.d.S., De Stavola, B., and McCormack, V.; Collaborative Group on Pre-Natal Risk Factors and Subsequent Risk of Breast Cancer (2008). Birth size and breast cancer risk: re-analysis of individual participant data from 32 studies. *PLoS Med.* 5, e193.
- Palmer, J.R., Hatch, E.E., Rosenberg, C.L., Hartge, P., Kaufman, R.H., Titus-Ernstoff, L., Noller, K.L., Herbst, A.L., Rao, R.S., Troisi, R., et al. (2002). Risk of breast cancer in women exposed to diethylstilbestrol in utero: preliminary results (United States). *Cancer Causes Control* 13, 753–758.
- Troisi, R., Hatch, E.E., Titus, L., Strohsnitter, W., Gail, M.H., Huo, D., Adam, E., Robboy, S.J., Hyer, M., Hoover, R.N., and Palmer, J.R. (2017). Prenatal diethylstilbestrol exposure and cancer risk in women. *Environ. Mol. Mutagen.* 60, 395–403.

28. Cohn, B.A., Cirillo, P.M., and Terry, M.B. (2019). DDT and Breast Cancer: Prospective Study of Induction Time and Susceptibility Windows. *J. Natl. Cancer. Inst.* 111, 803–810.
29. Xu, S., Murtagh, S., Han, Y., Wan, F., and Toriola, A.T. (2024). Breast Cancer Incidence Among US Women Aged 20 to 49 Years by Race, Stage, and Hormone Receptor Status. *JAMA Netw. Open* 7, e2353331.
30. Gerstung, M., Jolly, C., Leshchiner, I., Dentre, S.C., Gonzalez, S., Rosebrock, D., Mitchell, T.J., Rubanova, Y., Anur, P., Yu, K., et al. (2020). The evolutionary history of 2,658 cancers. *Nature* 578, 122–128.
31. Umar, A., Dunn, B.K., and Greenwald, P. (2012). Future directions in cancer prevention. *Nat. Rev. Cancer* 12, 835–848.
32. Shiyanbola, O.O., Arao, R.F., Miglioretti, D.L., Sprague, B.L., Hampton, J.M., Stout, N.K., Kerlikowske, K., Braithwaite, D., Buist, D.S.M., Egan, K.M., et al. (2017). Emerging Trends in Family History of Breast Cancer and Associated Risk. *Cancer Epidemiol. Biomarkers Prev.* 26, 1753–1760.
33. Brewer, H.R., Jones, M.E., Schoemaker, M.J., Ashworth, A., and Swerdlow, A.J. (2017). Family history and risk of breast cancer: an analysis accounting for family structure. *Breast Cancer Res. Treat.* 165, 193–200.
34. Oldenburg, R.A., Meijers-Heijboer, H., Cornelisse, C.J., and Devilee, P. (2007). Genetic susceptibility for breast cancer: how many more genes to be found? *Crit. Rev. Oncol. Hematol.* 63, 125–149.
35. Keeney, M.G., Couch, F.J., Visscher, D.W., and Lindor, N.M. (2017). Non-BRCA familial breast cancer: review of reported pathology and molecular findings. *Pathology* 49, 363–370.
36. Nikolaienko, O., Eikesdal, H.P., Ognedal, E., Gilje, B., Lundgren, S., Blix, E.S., Espelid, H., Geisler, J., Geisler, S., Janssen, E.A.M., et al. (2023). Prenatal BRCA1 epimutations contribute significantly to triple-negative breast cancer development. *Genome Med.* 15, 104.
37. Ruiz-De La Cruz, M., Martínez-Gregorio, H., Estela Díaz-Velásquez, C., Ambriz-Barrera, F., Resendiz-Flores, N.G., Gitler-Weingarten, R., Rojo-Castillo, M.P., Pradda, D., Oliver, J., Perdomo, S., et al. (2024). Methylation marks in blood DNA reveal breast cancer risk in patients fulfilling hereditary disease criteria. *npj Precis. Oncol.* 8, 136.
38. Ronckers, C.M., Erdmann, C.A., and Land, C.E. (2005). Radiation and breast cancer: a review of current evidence. *Breast Cancer Res.* 7, 21–32.
39. Little, M.P., Bazyka, D., Berrington de Gonzalez, A., Brenner, A.V., Chumak, V.V., Cullings, H.M., Daniels, R.D., French, B., Grant, E., Hamada, N., et al. (2024). A Historical Survey of Key Epidemiological Studies of Ionizing Radiation Exposure. *Radiat. Res.* 202, 432–487.
40. Ibrahim, E.M., Abouelkhair, K.M., Kazkaz, G.A., Elmasri, O.A., and Al-Foheidi, M. (2012). Risk of second breast cancer in female Hodgkin's lymphoma survivors: a meta-analysis. *BMC Cancer* 12, 197.
41. Veiga, L.H., Curtis, R.E., Morton, L.M., Withrow, D.R., Howell, R.M., Smith, S.A., Weathers, R.E., Oeffinger, K.C., Moskowitz, C.S., Henderson, T.O., et al. (2019). Association of Breast Cancer Risk After Childhood Cancer With Radiation Dose to the Breast and Anthracycline Use: A Report From the Childhood Cancer Survivor Study. *JAMA Pediatr.* 173, 1171–1179.
42. Brenner, A.V., Preston, D.L., Sakata, R., Sugiyama, H., Berrington de Gonzalez, A., French, B., Utada, M., Cahoon, E.K., Sadakane, A., Ozasa, K., et al. (2018). Incidence of Breast Cancer in the Life Span Study of Atomic Bomb Survivors: 1958–2009. *Radiat. Res.* 190, 433–444.
43. Aghaee, S., Laurent, C.A., Deardorff, J., Ferrara, A., Greenspan, L.C., Quesenberry, C.P., Kushi, L.H., and Kubo, A. (2019). Associations of Maternal Gestational Weight Gain and Obesity With the Timing of Pubertal Onset in Daughters. *Am. J. Epidemiol.* 188, 1262–1269.
44. Gelboin, H.V.T., and P, O.P. (1978). Polycyclic Hydrocarbons and Cancer. 1 Environment, Chemistry, and Metabolism (Academic Press, Inc).
45. Lin, T.-Y., Sree, U., Tseng, S.H., Chiu, K.H., Wu, C.H., and Lo, J.G. (2004). Volatile organic compound concentrations in ambient air of Kaohsiung petroleum refinery in Taiwan. *Atmos. Environ.* 38, 4111–4122.
46. Dumanoglu, Y., Kara, M., Altioğlu, H., Odabasi, M., Elbir, T., and Bayram, A. (2014). Spatial and seasonal variation and source apportionment of volatile organic compounds (VOCs) in a heavily industrialized region. *Atmos. Environ.* 98, 168–178.
47. Dodson, R.E., Levy, J.I., Spengler, J.D., Shine, J.P., and Bennett, D.H. (2008). Influence of basements, garages, and common hallways on indoor residential volatile organic compound concentrations. *Atmos. Environ.* 42, 1569–1581.
48. Rudel, R.A., Ackerman, J.M., Attfield, K.R., and Brody, J.G. (2014). New exposure biomarkers as tools for breast cancer epidemiology, bio-monitoring, and prevention: a systematic approach based on animal evidence. *Environ. Health Perspect.* 122, 881–895.
49. Russo, I.H., and Russo, J. (1996). Mammary gland neoplasia in long-term rodent studies. *Environ. Health Perspect.* 104, 938–967.
50. Miyata, M., Kudo, G., Lee, Y.H., Yang, T.J., Gelboin, H.V., Fernandez-Salguero, P., Kimura, S., and Gonzalez, F.J. (1999). Targeted disruption of the microsomal epoxide hydrolase gene. Microsomal epoxide hydrolase is required for the carcinogenic activity of 7,12-dimethylbenz[a]anthracene. *J. Biol. Chem.* 274, 23963–23968.
51. Xue, W., and Warshawsky, D. (2005). Metabolic activation of polycyclic and heterocyclic aromatic hydrocarbons and DNA damage: a review. *Toxicol. Appl. Pharmacol.* 206, 73–93.
52. Shimada, T., and Fujii-Kuriyama, Y. (2004). Metabolic activation of polycyclic aromatic hydrocarbons to carcinogens by cytochromes P450 1A1 and 1B1. *Cancer Sci.* 95, 1–6.
53. Shimizu, Y., Nakatsuru, Y., Ichinose, M., Takahashi, Y., Kume, H., Mimura, J., Fujii-Kuriyama, Y., and Ishikawa, T. (2000). Benzo[a]pyrene carcinogenicity is lost in mice lacking the aryl hydrocarbon receptor. *Proc. Natl. Acad. Sci. USA* 97, 779–782.
54. Buters, J.T., Sakai, S., Richter, T., Pineau, T., Alexander, D.L., Savas, U., Doehmer, J., Ward, J.M., Jefcoate, C.R., and Gonzalez, F.J. (1999). Cytochrome P450 CYP1B1 determines susceptibility to 7, 12-dimethylbenz[a]anthracene-induced lymphomas. *Proc. Natl. Acad. Sci. USA* 96, 1977–1982.
55. Russo, J., Gusterson, B.A., Rogers, A.E., Russo, I.H., Wellings, S.R., and van Zwieten, M.J. (1990). Comparative study of human and rat mammary tumorigenesis. *Lab. Invest.* 62, 244–278.
56. Russo, J., and Russo, I.H. (2000). Atlas and histologic classification of tumors of the rat mammary gland. *J. Mammary Gland Biol. Neoplasia* 5, 187–200.
57. Plante, I. (2021). Chapter 2 - Dimethylbenz(a)anthracene-induced mammary tumorigenesis in mice. In *Methods in Cell Biology*, L. Galluzzi and A. Buqué, eds. (Academic Press), pp. 21–44.
58. Abba, M.C., Zhong, Y., Lee, J., Kil, H., Lu, Y., Takata, Y., Simper, M.S., Gaddis, S., Shen, J., and Aldaz, C.M. (2016). DMBA induced mouse mammary tumors display high incidence of activating Pik3caH1047 and loss of function Pten mutations. *Oncotarget* 7, 64289–64299.
59. Paine, I.S., and Lewis, M.T. (2017). The Terminal End Bud: the Little Engine that Could. *J. Mammary Gland Biol. Neoplasia* 22, 93–108.
60. Kenney, N.J., Smith, G.H., Lawrence, E., Barrett, J.C., and Salomon, D.S. (2001). Identification of Stem Cell Units in the Terminal End Bud and Duct of the Mouse Mammary Gland. *J. Biomed. Biotechnol.* 1, 133–143.
61. Samuelson, E., Nilsson, J., Walentinsson, A., Szpirer, C., and Behboudi, A. (2009). Absence of Ras mutations in rat DMBA-induced mammary tumors. *Mol. Carcinog.* 48, 150–155.
62. Naruse, M., Ishigami, R., and Imai, T. (2021). The Unique Genetic and Histological Characteristics of DMBA-Induced Mammary Tumors in an Organoid-Based Carcinogenesis Model. *Front. Genet.* 12, 765131.
63. Reinhardt, K., Stückrath, K., Hartung, C., Kaufhold, S., Uleer, C., Hanf, V., Lantzsich, T., Peschel, S., John, J., Pöhler, M., et al. (2022). PIK3CA-mutations in breast cancer. *Breast Cancer Res. Treat.* 196, 483–493.

64. Cancer Genome Atlas Network (2012). Comprehensive molecular portraits of human breast tumours. *Nature* 490, 61–70.
65. el-Bayoumy, K., Chae, Y.H., Upadhyaya, P., Rivenson, A., Kurtzke, C., Reddy, B., and Hecht, S.S. (1995). Comparative tumorigenicity of benzo[a]pyrene, 1-nitropyrene and 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine administered by gavage to female CD rats. *Carcinogenesis* 16, 431–434.
66. Shan, L., Yu, M., Schut, H.A.J., and Snyderwine, E.G. (2004). Susceptibility of rats to mammary gland carcinogenesis by the food-derived carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) varies with age and is associated with the induction of differential gene expression. *Am. J. Pathol.* 165, 191–202.
67. Internal Agency for Research on Cancer (IARC) (1993). Some naturally occurring substances: food items and constituents, heterocyclic aromatic amines and mycotoxins. In IAC monographs on the evaluation of carcinogenic risks to humans, p. 56.
68. Snyderwine, E.G. (1998). Diet and mammary gland carcinogenesis. *Recent Results Cancer Res.* 152, 3–10.
69. Agency for Toxic Substances and Disease Registry (ATSDR) (1995). In Toxicological Profile for Polyaromatic Hydrocarbons (PAHs) (U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Agency for Toxic Substances and Disease Registry).
70. Kazerouni, N., Sinha, R., Hsu, C.H., Greenberg, A., and Rothman, N. (2001). Analysis of 200 food items for benzo[a]pyrene and estimation of its intake in an epidemiologic study. *Food Chem. Toxicol.* 39, 423–436.
71. Boström, C.E., Gerde, P., Hanberg, A., Jernström, B., Johansson, C., Kyrklund, T., Rannug, A., Törnqvist, M., Victorin, K., and Westerholm, R. (2002). Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air. *Environ. Health Perspect.* 110, 451–488.
72. Plante, I. (2021). Dimethylbenz(a)anthracene-induced mammary tumorigenesis in mice. *Methods Cell Biol.* 163, 21–44.
73. Menichini, E., Bertolaccini, M., Taggi, F., Falleni, F., and Monfredini, F. (1999). A 3-year study of relationships among atmospheric concentrations of polycyclic aromatic hydrocarbons, carbon monoxide and nitrogen oxides at an urban site. *Sci. Total Environ.* 241, 27–37.
74. Sun, L., Ai, X., Yao, X., An, Q., Liu, X., Yakovleva, E., Zhang, L., Sun, H., Zhang, K., and Zang, S. (2023). Relationship between atmospheric pollution and polycyclic aromatic hydrocarbons in fresh snow during heavy pollution episodes in a cold city, northeast China. *Ecotoxicol. Environ. Saf.* 260, 115091.
75. von Stackelberg, K., Buonocore, J., Bhawe, P.V., and Schwartz, J.A. (2013). Public health impacts of secondary particulate formation from aromatic hydrocarbons in gasoline. *Environ. Health.* 12, 19.
76. Parikh, P.V., and Wei, Y. (2016). PAHs and PM2.5 emissions and female breast cancer incidence in metro Atlanta and rural Georgia. *Int. J. Environ. Health Res.* 26, 458–466.
77. Gammon, M.D., Sagiv, S.K., Eng, S.M., Shantakumar, S., Gaudet, M.M., Teitelbaum, S.L., Britton, J.A., Terry, M.B., Wang, L.W., Wang, Q., et al. (2004). Polycyclic aromatic hydrocarbon-DNA adducts and breast cancer: a pooled analysis. *Arch. Environ. Health* 59, 640–649.
78. White, A.J., Bradshaw, P.T., Herring, A.H., Teitelbaum, S.L., Beyea, J., Stellman, S.D., Steck, S.E., Mordukhovich, I., Eng, S.M., Engel, L.S., et al. (2016). Exposure to multiple sources of polycyclic aromatic hydrocarbons and breast cancer incidence. *Environ. Int.* 89–90, 185–192.
79. Mordukhovich, I., Beyea, J., Herring, A.H., Hatch, M., Stellman, S.D., Teitelbaum, S.L., Richardson, D.B., Millikan, R.C., Engel, L.S., Shantakumar, S., et al. (2016). Vehicular Traffic-Related Polycyclic Aromatic Hydrocarbon Exposure and Breast Cancer Incidence: The Long Island Breast Cancer Study Project (LIBCSP). *Environ. Health Perspect.* 124, 30–38.
80. Ronco, A.L., De Stefani, E., Correa, P., Deneo-Pellegrini, H., Boffetta, P., Acosta, G., and Mendilaharsu, M. (2011). Dietary benzo [a] pyrene, alcohol drinking, and risk of breast cancer: a case-control study in Uruguay. *Asian Pac. J. Cancer Prev. APJCP* 12, 1463–1467.
81. Amadou, A., Praud, D., Coudon, T., Deygas, F., Grassot, L., Faure, E., Couvidat, F., Caudeville, J., Bessagnet, B., Salizzoni, P., et al. (2021). Risk of breast cancer associated with long-term exposure to benzo[a] pyrene (BaP) air pollution: Evidence from the French E3N cohort study. *Environ. Int.* 149, 106399.
82. Nie, J., Beyea, J., Bonner, M.R., Han, D., Vena, J.E., Rogerson, P., Vito, D., Muti, P., Trevisan, M., Edge, S.B., and Freudenheim, J.L. (2007). Exposure to traffic emissions throughout life and risk of breast cancer: the Western New York Exposures and Breast Cancer (WEB) study. *Cancer Causes Control* 18, 947–955.
83. Hamajima, N., Hirose, K., Tajima, K., Rohan, T., Calle, E.E., Heath, C.W., Jr., Coates, R.J., Liff, J.M., Talamini, R., Chantarakul, N., et al. (2002). Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br. J. Cancer* 87, 1234–1245.
84. Bjerkaas, E., Parajuli, R., Weiderpass, E., Engeland, A., Maskarinec, G., Selmer, R., and Gram, I.T. (2013). Smoking duration before first childbirth: an emerging risk factor for breast cancer? Results from 302,865 Norwegian women. *Cancer Causes Control* 24, 1347–1356.
85. Gaudet, M.M., Gapstur, S.M., Sun, J., Diver, W.R., Hannan, L.M., and Thun, M.J. (2013). Active smoking and breast cancer risk: original cohort data and meta-analysis. *J. Natl. Cancer Inst.* 105, 515–525.
86. Gram, I.T., Park, S.Y., Kolonel, L.N., Maskarinec, G., Wilkens, L.R., Henderson, B.E., and Le Marchand, L. (2015). Smoking and Risk of Breast Cancer in a Racially/Ethnically Diverse Population of Mainly Women Who Do Not Drink Alcohol: The MEC Study. *Am. J. Epidemiol.* 182, 917–925.
87. Jones, M.E., Schoemaker, M.J., Wright, L.B., Ashworth, A., and Swerdlow, A.J. (2017). Smoking and risk of breast cancer in the Generations Study cohort. *Breast Cancer Res.* 19, 118.
88. Russo, J., and Russo, I.H. (1997). Toward a unified concept of mammary tumorigenesis. *Prog. Clin. Biol. Res.* 396, 1–16.
89. Wellings, S.R., Jensen, H.M., and Marcum, R.G. (1975). An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions. *J. Natl. Cancer Inst.* 55, 231–273.
90. Tabár, L., Dean, P.B., Tucker, F.L., Yen, A.M.F., Fann, J.C.Y., Lin, A.T.Y., Smith, R.A., Duffy, S.W., and Chen, T.H.H. (2022). Breast cancers originating from the terminal ductal lobular units: In situ and invasive acinar adenocarcinoma of the breast, AAB. *Eur. J. Radiol.* 152, 110323.
91. Figueroa, J.D., Pfeiffer, R.M., Brinton, L.A., Palakal, M.M., Degnim, A.C., Radisky, D., Hartmann, L.C., Frost, M.H., Stallings Mann, M.L., Papatthomas, D., et al. (2016). Standardized measures of lobular involution and subsequent breast cancer risk among women with benign breast disease: a nested case-control study. *Breast Cancer Res. Treat.* 159, 163–172.
92. de Bel, T., Litjens, G., Ogony, J., Stallings-Mann, M., Carter, J.M., Hilton, T., Radisky, D.C., Vierkant, R.A., Broderick, B., Hoskin, T.L., et al. (2022). Automated quantification of levels of breast terminal duct lobular (TDLU) involution using deep learning. *npj Breast Cancer* 8, 13.
93. MacMahon, B., Cole, P., Lin, T.M., Lowe, C.R., Mirra, A.P., Ravnihar, B., Salber, E.J., Valaoras, V.G., and Yuasa, S. (1970). Age at first birth and breast cancer. *Bull. World Health Organ.* 43, 209–221.
94. Hilakivi-Clarke, L. (2007). Nutritional modulation of terminal end buds: its relevance to breast cancer prevention. *Curr. Cancer Drug Targets* 7, 465–474.
95. Nichols, H.B., Schoemaker, M.J., Cai, J., Xu, J., Wright, L.B., Brook, M.N., Jones, M.E., Adami, H.O., Baglietto, L., Bertrand, K.A., et al. (2019). Breast Cancer Risk After Recent Childbirth: A Pooled Analysis of 15 Prospective Studies. *Ann. Intern. Med.* 170, 22–30.

96. Faupel-Badger, J.M., Arcaro, K.F., Balkam, J.J., Eliassen, A.H., Hassiotou, F., Lebrilla, C.B., Michels, K.B., Palmer, J.R., Schedin, P., Stuebe, A.M., et al. (2013). Postpartum remodeling, lactation, and breast cancer risk: summary of a National Cancer Institute-sponsored workshop. *J. Natl. Cancer Inst.* **105**, 166–174.
97. Figueroa, J.D., Pfeiffer, R.M., Patel, D.A., Linville, L., Brinton, L.A., Gierach, G.L., Yang, X.R., Papathomas, D., Visscher, D., Mies, C., et al. (2014). Terminal duct lobular unit involution of the normal breast: implications for breast cancer etiology. *J. Natl. Cancer Inst.* **106**, dju286.
98. Borges, V.F., Lyons, T.R., Germain, D., and Schedin, P. (2020). Postpartum Involution and Cancer: An Opportunity for Targeted Breast Cancer Prevention and Treatments? *Cancer Res.* **80**, 1790–1798.
99. Niehoff, N.M., Terry, M.B., Bookwalter, D.B., Kaufman, J.D., O'Brien, K.M., Sandler, D.P., and White, A.J. (2022). Air Pollution and Breast Cancer: An Examination of Modification By Underlying Familial Breast Cancer Risk. *Cancer Epidemiol. Biomarkers Prev.* **31**, 422–429.
100. Shen, J., Liao, Y., Hopper, J.L., Goldberg, M., Santella, R.M., and Terry, M.B. (2017). Dependence of cancer risk from environmental exposures on underlying genetic susceptibility: an illustration with polycyclic aromatic hydrocarbons and breast cancer. *Br. J. Cancer* **116**, 1229–1233.
101. Jones, C. (1999). Benzo[a]pyrene downregulation of BRCA1. *Breast Cancer Res.* **2**, 66638.
102. Sahay, D., Lloyd, S.E., Rivera, J.A., Jezioro, J., McDonald, J.D., Pitirangon, M., Yan, B., Szabolcs, M., Terry, M.B., and Miller, R.L. (2021). Prenatal polycyclic aromatic hydrocarbons, altered ER $\alpha$  pathway-related methylation and expression, and mammary epithelial cell proliferation in offspring and grandoffspring adult mice. *Environ. Res.* **196**, 110961.
103. Yu, B., Yuan, Z., Yu, Z., and Xue-song, F. (2022). BTEX in the environment: An update on sources, fate, distribution, pretreatment, analysis, and removal techniques. *Chem. Eng. J.* **435**, 134825.
104. Zaveri, R.A., Berkowitz, C.M., Brechtel, F.J., Gilles, M.K., Hubbe, J.M., Jayne, J.T., Kleinman, L.I., Lasking, A., Madronich, S., Onasch, T.B., et al. (2010). Nighttime chemical evolution of aerosol and trace gases in a power plant plume: Implications for secondary organic nitrate and organosulfate aerosol formation, NO<sub>3</sub> radical chemistry, and N<sub>2</sub>O<sub>5</sub> heterogeneous hydrolysis. *J. Geophys. Res.* **115**.
105. Zahed, M.A., Salehi, S., Khoei, M.A., Esmaeili, P., and Mohajeri, L. (2024). Risk assessment of Benzene, Toluene, Ethyl benzene, and Xylene (BTEX) in the atmospheric air around the world: A review. *Toxicol. Vitro* **98**, 105825.
106. Hazrati, S., Rostami, R., Farjaminezhad, M., and Fazlzadeh, M. (2016). Preliminary assessment of BTEX concentrations in indoor air of residential buildings and atmospheric ambient air in Ardabil, Iran. *Atmos. Environ.* **132**, 91–97.
107. Janjani, H., Yunesian, M., Yaghmaeian, K., Aghaei, M., Yousefian, F., Alizadeh, B., and Fazlzadeh, M. (2023). BTEX in indoor air of barbershops and beauty salons: Characterization, source apportionment and health risk assessment. *Chemosphere* **345**, 140518.
108. Kamani, H., Baniyasi, M., Abdipour, H., Mohammadi, L., Rayegannakhost, S., Moein, H., and Azari, A. (2023). Health risk assessment of BTEX compounds (benzene, toluene, ethylbenzene and xylene) in different indoor air using Monte Carlo simulation in zahedan city, Iran. *Heliyon* **9**, e20294.
109. Huang, Y., Ho, S.S.H., Ho, K.F., Lee, S.C., Yu, J.Z., and Louie, P.K.K. (2011). Characteristics and health impacts of VOCs and carbonyls associated with residential cooking activities in Hong Kong. *J. Hazard Mater.* **186**, 344–351.
110. Grosse, Y., Baan, R., Straif, K., Secretan, B., El Ghissassi, F., Bouvard, V., Altieri, A., and Coglian, V.; WHO International Agency for Research on Cancer Monograph Working Group (2007). Carcinogenicity of 1,3-butadiene, ethylene oxide, vinyl chloride, vinyl fluoride, and vinyl bromide. *Lancet Oncol.* **8**, 679–680.
111. Macedo, V.C., Daemme, L.C., Penteado, R., da Motta, H.N., and Corrêa, S.M. (2017). BTEX emissions from flex fuel motorcycles. *Atmos. Pollut. Res.* **8**, 1160–1169.
112. Tsai, J.-H., Ko, Y.L., Huang, C.M., and Chiang, H.L. (2019). Effects of Blending Ethanol with Gasoline on the Performance of Motorcycle Catalysts and Airborne Pollutant Emissions. *Aerosol Air Qual. Res.* **9**, 2781–2792.
113. Kazemiparkouhi, F., Alarcon Falconi, T.M., MacIntosh, D.L., and Clark, N. (2022). Comprehensive US database and model for ethanol blend effects on regulated tailpipe emissions. *Sci. Total Environ.* **812**, 151426.
114. Heibati, B., Pollitt, K.J.G., Karimi, A., Yazdani Charati, J., Ducatman, A., Shokrzadeh, M., and Mohammadyan, M. (2017). BTEX exposure assessment and quantitative risk assessment among petroleum product distributors. *Ecotoxicol. Environ. Saf.* **144**, 445–449.
115. Sirotkin, A.V., and Harrath, A.H. (2017). Influence of oil-related environmental pollutants on female reproduction. *Reprod. Toxicol.* **71**, 142–145.
116. Bolden, A.L., Kwiatkowski, C.F., and Colborn, T. (2015). New Look at BTEX: Are Ambient Levels a Problem? *Environ. Sci. Technol.* **49**, 5261–5276.
117. Liao, Q., Zhang, Y., Ma, R., Zhang, Z., Ji, P., Xiao, M., Du, R., Liu, X., Cui, Y., Xing, X., et al. (2022). Risk assessment and dose-effect of co-exposure to benzene, toluene, ethylbenzene, xylene, and styrene (BTEXS) on pulmonary function: A cross-sectional study. *Environ. Pollut.* **310**, 119894.
118. Loomis, D., Guyton, K.Z., Grosse, Y., El Ghissassi, F., Bouvard, V., Benbrahim-Tallaa, L., Guha, N., Vilahur, N., Mattock, H., and Straif, K.; International Agency for Research on Cancer Monograph Working Group (2017). Carcinogenicity of benzene. *Lancet Oncol.* **18**, 1574–1575.
119. Madrigal, J.M., Pruitt, C.N., Fisher, J.A., Liao, L.M., Graubard, B.I., Gierach, G.L., Silverman, D.T., Ward, M.H., and Jones, R.R. (2024). Carcinogenic industrial air pollution and postmenopausal breast cancer risk in the National Institutes of Health AARP Diet and Health Study. *Environ. Int.* **197**, 108985.
120. Harati, B., Shahtaheri, S.J., Karimi, A., Azam, K., Ahmadi, A., Rad, M.A., and Harati, A. (2016). Cancer risk analysis of benzene and ethyl benzene in painters. *Basic Clin. Cancer Res.* **8**, 22–28.
121. Asekamini, M.D., Moolala, R., Gulumian, M., and Brouwer, D. (2018). Risk Assessment of Benzene, Toluene, Ethyl Benzene, and Xylene Concentrations from the Combustion of Coal in a Controlled Laboratory Environment. *Int. J. Environ. Res. Public Health* **16**, 95.
122. Sapouckey, S.A., Kassotis, C.D., Nagel, S.C., and Vandenberg, L.N. (2018). Prenatal Exposure to Unconventional Oil and Gas Operation Chemical Mixtures Altered Mammary Gland Development in Adult Female Mice. *Endocrinology* **159**, 1277–1289.
123. McCormack, V.A., and dos, S.S.I. (2006). Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol. Biomarkers Prev.* **15**, 1159–1169.
124. Boyd, N.F., Guo, H., Martin, L.J., Sun, L., Stone, J., Fishell, E., Jong, R.A., Hislop, G., Chiarelli, A., Minkin, S., and Yaffe, M.J. (2007). Mammographic density and the risk and detection of breast cancer. *N. Engl. J. Med.* **356**, 227–236.
125. Bodewes, F.T.H., van Asselt, A.A., Dorrius, M.D., Greuter, M.J.W., and de Bock, G.H. (2022). Mammographic breast density and the risk of breast cancer: A systematic review and meta-analysis. *Breast* **66**, 62–68.
126. Pettersson, A., Graff, R.E., Ursin, G., Santos Silva, I.D., McCormack, V., Baglietto, L., Vachon, C., Bakker, M.F., Giles, G.G., Chia, K.S., et al. (2014). Mammographic density phenotypes and risk of breast cancer: a meta-analysis. *J. Natl. Cancer Inst.* **106**, dju078.
127. Davidson, C.J., Svenson, D.W., Hannigan, J.H., Perrine, S.A., and Bowen, S.E. (2022). A novel preclinical model of environment-like combined benzene, toluene, ethylbenzene, and xylenes (BTEX) exposure: Behavioral and neurochemical findings. *Neurotoxicol. Teratol.* **91**, 107076.

128. Wei, Y., Davis, J., and Bina, W.F. (2012). Ambient air pollution is associated with the increased incidence of breast cancer in US. *Int. J. Environ. Health Res.* 22, 12–21.
129. Khorrami, Z., Pourkhosravani, M., Karamoozian, A., Jafari-Khounigh, A., Akbari, M.E., Rezapour, M., Khorrami, R., Taghavi-Shahri, S.M., Amini, H., Etemad, K., and Khanjani, N. (2024). Ambient air pollutants and breast cancer stage in Tehran, Iran. *Sci. Rep.* 14, 3873.
130. Heck, J.E., He, D., Wing, S.E., Ritz, B., Carey, C.D., Yang, J., Stram, D.O., Le Marchand, L., Park, S.L., Cheng, I., and Wu, A.H. (2024). Exposure to outdoor ambient air toxics and risk of breast cancer: The multiethnic cohort. *Int. J. Hyg Environ. Health* 259, 114362.
131. Cassidy-Bushrow, A.E., Burmeister, C., Birbeck, J., Chen, Y., Lamerato, L., Lemke, L.D., Li, J., Mor, G., O'Leary, B.F., Peters, R.M., et al. (2021). Ambient BTEX exposure and mid-pregnancy inflammatory biomarkers in pregnant African American women. *J. Reprod. Immunol.* 145, 103305.
132. Grivennikov, S.I., Greten, F.R., and Karin, M. (2010). Immunity, inflammation, and cancer. *Cell* 140, 883–899.
133. Coussens, L.M., and Werb, Z. (2002). Inflammation and cancer. *Nature* 420, 860–867.
134. Danforth, D.N. (2021). The Role of Chronic Inflammation in the Development of Breast Cancer. *Cancers* 13, 3918.
135. Godfrey, K.M., Reynolds, R.M., Prescott, S.L., Nyirenda, M., Jaddoe, V.W.V., Eriksson, J.G., and Broekman, B.F.P. (2017). Influence of maternal obesity on the long-term health of offspring. *Lancet Diabetes Endocrinol.* 5, 53–64.
136. Zhang, C.X.W., Candia, A.A., and Sferruzzi-Perri, A.N. (2024). Placental inflammation, oxidative stress, and fetal outcomes in maternal obesity. *Trends Endocrinol. Metabol.* 35, 638–647.
137. de Assis, S., Khan, G., and Hilakivi-Clarke, L. (2006). High birth weight increases mammary tumorigenesis in rats. *Int. J. Cancer* 119, 1537–1546.
138. Zhang, X., de Oliveira Andrade, F., Zhang, H., Cruz, I., Clarke, R., Gaur, P., Verma, V., and Hilakivi-Clarke, L. (2020). Maternal obesity increases offspring's mammary cancer recurrence and impairs tumor immune response. *Endocr. Relat. Cancer* 27, 469–482.
139. CDC (2010). How Tobacco Smoke Causes Disease: The Biologic and Behavioral Basis for Smoking-Attributable Disease: a Report of the Surgeon General (Centers for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US)).
140. Schatzkin, A. (2006). Sir Richard Doll on chance and genetic susceptibility in carcinogenesis, or, why not all smokers get lung cancer. *Cancer Epidemiol. Biomarkers Prev.* 15, 1420.
141. de Assis, S., Warri, A., Cruz, M.I., Laja, O., Tian, Y., Zhang, B., Wang, Y., Huang, T.H.M., and Hilakivi-Clarke, L. (2012). High-fat or ethinyl-oestradiol intake during pregnancy increases mammary cancer risk in several generations of offspring. *Nat. Commun.* 3, 1053.
142. Nguyen, N.M., de Oliveira Andrade, F., Jin, L., Zhang, X., Macon, M., Cruz, M.I., Benitez, C., Wehrenberg, B., Yin, C., Wang, X., et al. (2017). Maternal intake of high n-6 polyunsaturated fatty acid diet during pregnancy causes transgenerational increase in mammary cancer risk in mice. *Breast Cancer Res.* 19, 77.
143. Andrade, F.d.O., Nguyen, N.M., Warri, A., and Hilakivi-Clarke, L. (2019). Reversal of increased mammary tumorigenesis by valproic acid and hydralazine in offspring of dams fed high fat diet during pregnancy. *Sci. Rep.* 9, 20271.
144. Andrade, F.d.O., Liu, F., Zhang, X., Rosim, M.P., Dani, C., Cruz, I., Wang, T.T.Y., Helferich, W., Li, R.W., and Hilakivi-Clarke, L. (2021). Genistein Reduces the Risk of Local Mammary Cancer Recurrence and Ameliorates Alterations in the Gut Microbiota in the Offspring of Obese Dams. *Nutrients* 13, 201.
145. Hilakivi-Clarke, L., Cho, E., Raygada, M., and Kenney, N. (1997). Alterations in mammary gland development following neonatal exposure to estradiol, transforming growth factor alpha, and estrogen receptor antagonist ICI 182,780. *J. Cell. Physiol.* 170, 279–289.
146. Walker, C.L., and Ho, S.M. (2012). Developmental reprogramming of cancer susceptibility. *Nat. Rev. Cancer* 12, 479–486.
147. Peral-Sanchez, I., Hojeij, B., Ojeda, D.A., Steegers-Theunissen, R.P.M., and Willaime-Morawek, S. (2021). Epigenetics in the Uterine Environment: How Maternal Diet and ART May Influence the Epigenome in the Offspring with Long-Term Health Consequences. *Genes* 13, 31.
148. Zuccarello, D., Sorrentino, U., Brasson, V., Marin, L., Piccolo, C., Capalbo, A., Andrisani, A., and Cassina, M. (2022). Epigenetics of pregnancy: looking beyond the DNA code. *J. Assist. Reprod. Genet.* 39, 801–816.
149. Galley, J.D., Bailey, M., Kamp Dush, C., Schoppe-Sullivan, S., and Christian, L.M. (2014). Maternal obesity is associated with alterations in the gut microbiome in toddlers. *PLoS One* 9, e113026.
150. Cerdó, T., Ruiz, A., Jáuregui, R., Azaryah, H., Torres-Espínola, F.J., García-Valdés, L., Teresa Segura, M., Suárez, A., and Campoy, C. (2018). Maternal obesity is associated with gut microbial metabolic potential in offspring during infancy. *J. Physiol. Biochem.* 74, 159–169.
151. Gilley, S.P., Ruebel, M.L., Sims, C., Zhong, Y., Turner, D., Lan, R.S., Pack, L.M., Piccolo, B.D., Chintapalli, S.V., Abraham, A., et al. (2022). Associations between maternal obesity and offspring gut microbiome in the first year of life. *Pediatr. Obes.* 17, e12921.
152. Nieto-Ruiz, A., Cerdó, T., Jordano, B., Torres-Espínola, F.J., Escudero-Marín, M., García-Ricobaraza, M., Bermúdez, M.G., García-Santos, J.A., Suárez, A., and Campoy, C. (2023). Maternal weight, gut microbiota, and the association with early childhood behavior: the PREOBE follow-up study. *Child Adolesc. Psychiatr. Ment. Health* 17, 41.
153. Ludwig, T., Chapman, D.L., Papaioannou, V.E., and Efstratiadis, A. (1997). Targeted mutations of breast cancer susceptibility gene homologs in mice: lethal phenotypes of *Brca1*, *Brca2*, *Brca1/Brca2*, *Brca1/p53*, *Brca2/p53* nullizygous embryos. *Genes Dev.* 11, 1226–1241.
154. Smith, S.A., Easton, D.F., Evans, D.G., and Ponder, B.A. (1992). Allele losses in the region 17q12-21 in familial breast and ovarian cancer involve the wild-type chromosome. *Nat. Genet.* 2, 128–131.
155. Maxwell, K.N., Wubbenhorst, B., Wenz, B.M., De Sloover, D., Pluta, J., Emery, L., Barrett, A., Kraya, A.A., Anastopoulos, I.N., Yu, S., et al. (2017). BRCA locus-specific loss of heterozygosity in germline BRCA1 and BRCA2 carriers. *Nat. Commun.* 8, 319.
156. Coignard, J., Lush, M., Beesley, J., O'Mara, T.A., Dennis, J., Tyrer, J.P., Barnes, D.R., McGuffog, L., Leslie, G., Bolla, M.K., et al. (2021). A case-only study to identify genetic modifiers of breast cancer risk for BRCA1/BRCA2 mutation carriers. *Nat. Commun.* 12, 1078.
157. Liu, X., Holstege, H., van der Gulden, H., Treur-Mulder, M., Zevenhoven, J., Velds, A., Kerkhoven, R.M., van Vliet, M.H., Wessels, L.F.A., Peterse, J.L., et al. (2007). Somatic loss of BRCA1 and p53 in mice induces mammary tumors with features of human BRCA1-mutated basal-like breast cancer. *Proc. Natl. Acad. Sci. USA* 104, 12111–12116.
158. de Assis, S., Warri, A., Benitez, C., Helferich, W., and Hilakivi-Clarke, L. (2011). Protective effects of prepubertal genistein exposure on mammary tumorigenesis are dependent on BRCA1 expression. *Cancer Prev. Res.* 4, 1436–1448.
159. Nakamura, Y., Kubota, J., Nishimura, Y., Nagata, K., Nishimura, M., Daino, K., Ishikawa, A., Kaneko, T., Mashimo, T., Kokubo, T., et al. (2022). *Brca1*(L63X) (+) rat is a novel model of human BRCA1 deficiency displaying susceptibility to radiation-induced mammary cancer. *Cancer Sci.* 113, 3362–3375.
160. Palli, D., Masala, G., Mariani-Costantini, R., Zanna, I., Saieva, C., Sera, F., Decarli, A., and Ottini, L. (2004). A gene-environment interaction between occupation and BRCA1/BRCA2 mutations in male breast cancer? *Eur. J. Cancer* 40, 2474–2479.
161. Guo, J., Xu, Y., Ji, W., Song, L., Dai, C., and Zhan, L. (2015). Effects of exposure to benzo [a] pyrene on metastasis of breast cancer are mediated through ROS-ERK-MMP9 axis signaling. *Toxicol. Lett.* 234, 201–210.

162. Malik, D.-e.-s., David, R.M., and Gooderham, N.J. (2018). Mechanistic evidence that benzo [a] pyrene promotes an inflammatory microenvironment that drives the metastatic potential of human mammary cells. *Arch. Toxicol.* **92**, 3223–3239.
163. Wang, H., Liu, B., Chen, H., Xu, P., Xue, H., and Yuan, J. (2023). Dynamic changes of DNA methylation induced by benzo(a)pyrene in cancer. *Gene Environ.* **45**, 21.
164. Bukowska, B., and Sicińska, P. (2021). Influence of Benzo(a)pyrene on Different Epigenetic Processes. *Int. J. Mol. Sci.* **22**.
165. Santodonato, J. (1997). Review of the estrogenic and antiestrogenic activity of polycyclic aromatic hydrocarbons: relationship to carcinogenicity. *Chemosphere* **34**, 835–848.
166. Kay, J.E., Brody, J.G., Schwarzman, M., and Rudel, R.A. (2024). Application of the Key Characteristics Framework to Identify Potential Breast Carcinogens Using Publicly Available *In Vivo*, *In Vitro*, and *In Silico* Data. *Environ. Health Perspect.* **132**, 17002.
167. Gozgit, J.M., Nestor, K.M., Fasco, M.J., Pentecost, B.T., and Arcaro, K.F. (2004). Differential action of polycyclic aromatic hydrocarbons on endogenous estrogen-responsive genes and on a transfected estrogen-responsive reporter in MCF-7 cells. *Toxicol. Appl. Pharmacol.* **196**, 58–67.
168. Shan, L., Yu, M., and Snyderwine, E.G. (2005). Global gene expression profiling of chemically induced rat mammary gland carcinomas and adenomas. *Toxicol. Pathol.* **33**, 768–775.
169. Ahn, J., Xia, T., Konno, H., Konno, K., Ruiz, P., and Barber, G.N. (2014). Inflammation-driven carcinogenesis is mediated through STING. *Nat. Commun.* **5**, 5166.
170. Pasqualini, C., Sarrieu, A., Dussaillant, M., Corbani, M., Bojda-Diolez, F., Rostène, W., and Kerdelhué, B. (1990). Estrogen-like effects of 7,12-dimethylbenz(a)anthracene on the female rat hypothalamo-pituitary axis. *J. Steroid Biochem.* **36**, 485–491.
171. Garcia-Segura, L.M., Diolez-Bojda, F., Lenoir, V., Naftolin, F., and Kerdelhué, B. (1992). Estrogen-like effects of the mammary carcinogen 7,12-dimethylbenz(alpha)anthracene on hypothalamic neuronal membranes. *Brain Res. Bull.* **28**, 625–628.
172. Buchta Rosean, C., Bostic, R.R., Ferey, J.C.M., Feng, T.Y., Azar, F.N., Tung, K.S., Dozmorov, M.G., Smirnova, E., Bos, P.D., and Rutkowski, M.R. (2019). Preexisting Commensal Dysbiosis Is a Host-Intrinsic Regulator of Tissue Inflammation and Tumor Cell Dissemination in Hormone Receptor-Positive Breast Cancer. *Cancer Res.* **79**, 3662–3675.
173. Bernardo, G., Le Noci, V., Di Modica, M., Montanari, E., Triulzi, T., Pupa, S.M., Tagliabue, E., Sommariva, M., and Sfondrini, L. (2023). The Emerging Role of the Microbiota in Breast Cancer Progression. *Cell* **12**, 1945.
174. Sender, R., Fuchs, S., and Milo, R. (2016). Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS Biol.* **14**, e1002533.
175. Gilbert, J.A., Blaser, M.J., Caporaso, J.G., Jansson, J.K., Lynch, S.V., and Knight, R. (2018). Current understanding of the human microbiome. *Nat. Med.* **24**, 392–400.
176. Turnbaugh, P.J., Ley, R.E., Hamady, M., Fraser-Liggett, C.M., Knight, R., and Gordon, J.I. (2007). The human microbiome project. *Nature* **449**, 804–810.
177. Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K.S., Manichanh, C., Nielsen, T., Pons, N., Levenez, F., Yamada, T., et al. (2010). A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* **464**, 59–65.
178. Eberle, F., Sirin, M., Binder, M., and Dalpke, A.H. (2009). Bacterial RNA is recognized by different sets of immunoreceptors. *Eur. J. Immunol.* **39**, 2537–2547.
179. Simonov, D., Swift, S., Blenkiron, C., and Phillips, A.R. (2016). Bacterial RNA as a signal to eukaryotic cells as part of the infection process. *Discoveries* **4**, e70.
180. Sonnenburg, J.L., Xu, J., Leip, D.D., Chen, C.H., Westover, B.P., Weath-erford, J., Buhler, J.D., and Gordon, J.I. (2005). Glycan foraging *in vivo* by an intestine-adapted bacterial symbiont. *Science* **307**, 1955–1959.
181. Chung, H., Pamp, S.J., Hill, J.A., Surana, N.K., Edelman, S.M., Troy, E.B., Reading, N.C., Villablanca, E.J., Wang, S., Mora, J.R., et al. (2012). Gut immune maturation depends on colonization with a host-specific micro-biota. *Cell* **149**, 1578–1593.
182. Singh, R.K., Chang, H.W., Yan, D., Lee, K.M., Ucmak, D., Wong, K., Ab-rouk, M., Farahnik, B., Nakamura, M., Zhu, T.H., et al. (2017). Influence of diet on the gut microbiome and implications for human health. *J. Transl. Med.* **15**, 73.
183. Cani, P.D. (2018). Human gut microbiome: hopes, threats and promises. *Gut* **67**, 1716–1725.
184. Donaldson, G.P., Lee, S.M., and Mazmanian, S.K. (2016). Gut biogeog-raphy of the bacterial microbiota. *Nat. Rev. Microbiol.* **14**, 20–32.
185. Claus, S.P., Guillou, H., and Ellero-Simatos, S. (2016). The gut micro-biota: a major player in the toxicity of environmental pollutants? *NPJ Bio-films Microbiomes* **2**, 16003.
186. Leeming, E.R., Johnson, A.J., Spector, T.D., and Le Roy, C.I. (2019). Ef-fect of Diet on the Gut Microbiota: Rethinking Intervention Duration. *Nu-trients* **11**, 2862.
187. Yatsunenko, T., Rey, F.E., Manary, M.J., Trehan, I., Dominguez-Bello, M.G., Contreras, M., Magris, M., Hidalgo, G., Baldassano, R.N., Anokhin, A.P., et al. (2012). Human gut microbiome viewed across age and geog-raphy. *Nature* **486**, 222–227.
188. Koppel, N., and Balskus, E.P. (2016). Exploring and understanding the biochemical diversity of the human microbiota. *Cell Chem. Biol.* **23**, 18–30.
189. Wilde, J., Slack, E., and Foster, K.R. (2024). Host control of the micro-biome: Mechanisms, evolution, and disease. *Science* **385**, eadi3338.
190. Zheng, L., Kelly, C.J., and Colgan, S.P. (2015). Physiologic hypoxia and oxygen homeostasis in the healthy intestine. A Review in the Theme: Cellular Responses to Hypoxia. *Am. J. Physiol., Cell. Physiol.* **309**, C350–C360.
191. Byndloss, M.X., Olsan, E.E., Rivera-Chávez, F., Tiffany, C.R., Cevallos, S.A., Lokken, K.L., Torres, T.P., Byndloss, A.J., Faber, F., Gao, Y., et al. (2017). Microbiota-activated PPAR-gamma signaling inhibits dysbi-otic Enterobacteriaceae expansion. *Science* **357**, 570–575.
192. Diard, M., Bakkeren, E., Lentsch, V., Rocker, A., Bekele, N.A., Hoces, D., Aslani, S., Arnoldini, M., Böhi, F., Schumann-Moor, K., et al. (2021). A rationally designed oral vaccine induces immunoglobulin A in the murine gut that directs the evolution of attenuated Salmonella variants. *Nat. Mi-crobiol.* **6**, 830–841.
193. Wu, G.D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y.Y., Keilbaugh, S.A., Bewtra, M., Knights, D., Walters, W.A., Knight, R., et al. (2011). Link-ing long-term dietary patterns with gut microbial enterotypes. *Science* **334**, 105–108.
194. Turnbaugh, P.J., Quince, C., Faith, J.J., McHardy, A.C., Yatsunenko, T., Niazi, F., Affourtit, J., Egholm, M., Henrissat, B., Knight, R., and Gordon, J.I. (2010). Organismal, genetic, and transcriptional variation in the deeply sequenced gut microbiomes of identical twins. *Proc. Natl. Acad. Sci. USA* **107**, 7503–7508.
195. Goodrich, J.K., Waters, J.L., Poole, A.C., Sutter, J.L., Koren, O., Blekh-man, R., Beaumont, M., Van Treuren, W., Knight, R., Bell, J.T., et al. (2014). Human genetics shape the gut microbiome. *Cell* **159**, 789–799.
196. Goodrich, J.K., Davenport, E.R., Beaumont, M., Jackson, M.A., Knight, R., Ober, C., Spector, T.D., Bell, J.T., Clark, A.G., and Ley, R.E. (2016). Genetic Determinants of the Gut Microbiome in UK Twins. *Cell Host Microbe* **19**, 731–743.
197. Vilchez-Vargas, R., Skieceviciene, J., Lehr, K., Varkalaite, G., Thon, C., Urba, M., Morkūnas, E., Kucinskas, L., Bauraitė, K., Schanze, D., et al. (2022). Gut microbial similarity in twins is driven by shared environment and aging. *EBioMedicine* **79**, 104011.

198. Valles-Colomer, M., Blanco-Míguez, A., Manghi, P., Asnicar, F., Dubois, L., Golzato, D., Armanini, F., Cumbo, F., Huang, K.D., Manara, S., et al. (2023). The person-to-person transmission landscape of the gut and oral microbiomes. *Nature* 614, 125–135.
199. Zhang, Y., Shen, Y., Liufu, N., Liu, L., Li, W., Shi, Z., Zheng, H., Mei, X., Chen, C.Y., Jiang, Z., et al. (2023). Transmission of Alzheimer's disease-associated microbiota dysbiosis and its impact on cognitive function: evidence from mice and patients. *Mol. Psychiatr.* 28, 4421–4437.
200. Norton, M.C., Smith, K.R., Østbye, T., Tschanz, J.T., Corcoran, C., Schwartz, S., Piercy, K.W., Rabins, P.V., Steffens, D.C., Skoog, I., et al. (2010). Greater risk of dementia when spouse has dementia? The Cache County study. *J. Am. Geriatr. Soc.* 58, 895–900.
201. Parada Venegas, D., De la Fuente, M.K., Landskron, G., González, M.J., Quera, R., Dijkstra, G., Harmsen, H.J.M., Faber, K.N., and Hermoso, M.A. (2019). Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. *Front. Immunol.* 10, 277.
202. De la Cuesta-Zuluaga, J., Mueller, N.T., Álvarez-Quintero, R., Velásquez-Mejía, E.P., Sierra, J.A., Corrales-Agudelo, V., Carmona, J.A., Abad, J.M., and Escobar, J.S. (2018). Higher Fecal Short-Chain Fatty Acid Levels Are Associated with Gut Microbiome Dysbiosis, Obesity, Hypertension and Cardiometabolic Disease Risk Factors. *Nutrients* 11, 51.
203. Louis, P., Hold, G.L., and Flint, H.J. (2014). The gut microbiota, bacterial metabolites and colorectal cancer. *Nat. Rev. Microbiol.* 12, 661–672.
204. Louis, P., and Flint, H.J. (2017). Formation of propionate and butyrate by the human colonic microbiota. *Environ. Microbiol.* 19, 29–41.
205. Derrien, M., Vaughan, E.E., Plugge, C.M., and de Vos, W.M. (2004). *Akkermansia muciniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. *Int. J. Syst. Evol. Microbiol.* 54, 1469–1476.
206. Shuoker, B., Pichler, M.J., Jin, C., Sakanaka, H., Wu, H., Gascueña, A.M., Liu, J., Nielsen, T.S., Holgersson, J., Nordberg Karlsson, E., et al. (2023). Sialidases and fucosidases of *Akkermansia muciniphila* are crucial for growth on mucin and nutrient sharing with mucus-associated gut bacteria. *Nat. Commun.* 14, 1833.
207. Schirmer, M., Kumar, V., Netea, M.G., and Xavier, R.J. (2018). The causes and consequences of variation in human cytokine production in health. *Curr. Opin. Immunol.* 54, 50–58.
208. Sun, M., Wu, W., Liu, Z., and Cong, Y. (2017). Microbiota metabolite short chain fatty acids, GPCR, and inflammatory bowel diseases. *J. Gastroenterol.* 52, 1–8.
209. Morrison, D.J., and Preston, T. (2016). Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* 7, 189–200.
210. Schonfeld, P., and Wojtczak, L. (2016). Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. *J. Lipid Res.* 57, 943–954.
211. Jackson, D.N., and Theiss, A.L. (2020). Gut bacteria signaling to mitochondria in intestinal inflammation and cancer. *Gut Microbes* 11, 285–304.
212. Yuille, S., Reichardt, N., Panda, S., Dunbar, H., and Mulder, I.E. (2018). Human gut bacteria as potent class I histone deacetylase inhibitors in vitro through production of butyric acid and valeric acid. *PLoS One* 13, e0201073.
213. Li, M., van Esch, B.C.A.M., Henricks, P.A.J., Folkerts, G., and Garssen, J. (2018). The Anti-inflammatory Effects of Short Chain Fatty Acids on Lipopolysaccharide- or Tumor Necrosis Factor alpha-Stimulated Endothelial Cells via Activation of GPR41/43 and Inhibition of HDACs. *Front. Pharmacol.* 9, 533.
214. Licciardi, P.V., Ververis, K., and Karagiannis, T.C. (2011). Histone deacetylase inhibition and dietary short-chain fatty acids. *ISRN Allergy* 2011, 869647.
215. Jaye, K., Chang, D., Li, C.G., and Bhuyan, D.J. (2022). Gut Metabolites and Breast Cancer: The Continuum of Dysbiosis, Breast Cancer Risk, and Potential Breast Cancer Therapy. *Int. J. Mol. Sci.* 23, 9490.
216. Stanislawski, M.A., Dabelea, D., Wagner, B.D., Sontag, M.K., Lozupone, C.A., and Eggesbø, M. (2017). Pre-pregnancy weight, gestational weight gain, and the gut microbiota of mothers and their infants. *Microbiome* 5, 113.
217. Quintanilla-Mena, M., Vega-Arreguin, J., Del Río-García, M., Patiño-Suárez, V., Peraza-Echeverría, S., and Puch-Hau, C. (2021). The effect of benzo[a]pyrene on the gut microbiota of Nile tilapia (*Oreochromis niloticus*). *Appl. Microbiol. Biotechnol.* 105, 7935–7947.
218. DeBofsky, A., Xie, Y., Challis, J.K., Jain, N., Brinkmann, M., Jones, P.D., and Giesy, J.P. (2021). Responses of juvenile fathead minnow (*Pimephales promelas*) gut microbiome to a chronic dietary exposure of benzo[a]pyrene. *Environ. Pollut.* 278, 116821.
219. Stagaman, K., Alexiev, A., Sieler, M.J., Hammer, A., Kasschau, K.D., Truong, L., Tanguay, R.L., and Sharpton, T.J. (2024). The zebrafish gut microbiome influences benzo[a]pyrene developmental neurobehavioral toxicity. *Sci. Rep.* 14, 14618.
220. Ribière, C., Peyret, P., Parisot, N., Darcha, C., Déchelotte, P.J., Barnich, N., Peyretailade, E., and Boucher, D. (2016). Oral exposure to environmental pollutant benzo[a]pyrene impacts the intestinal epithelium and induces gut microbial shifts in murine model. *Sci. Rep.* 6, 31027.
221. Garcia, W.L., Miller, C.J., Lomas, G.X., Gaither, K.A., Tyrrell, K.J., Smith, J.N., Brandvold, K.R., and Wright, A.T. (2022). Profiling How the Gut Microbiome Modulates Host Xenobiotic Metabolism in Response to Benzo[a]pyrene and 1-Nitropyrene Exposure. *Chem. Res. Toxicol.* 35, 585–596.
222. Imaida, K., Lee, M.S., Land, S.J., Wang, C.Y., and King, C.M. (1995). Carcinogenicity of nitropyrenes in the newborn female rat. *Carcinogenesis* 16, 3027–3030.
223. el-Bayoumy, K., Rivenson, A., Upadhyaya, P., Chae, Y.H., and Hecht, S.S. (1993). Induction of mammary cancer by 6-nitrochrysene in female CD rats. *Cancer Res.* 53, 3719–3722.
224. Alderete, T.L., Jones, R.B., Chen, Z., Kim, J.S., Habre, R., Lurmann, F., Gilliland, F.D., and Goran, M.I. (2018). Exposure to traffic-related air pollution and the composition of the gut microbiota in overweight and obese adolescents. *Environ. Res.* 161, 472–478.
225. Lee, S.H., Yun, Y., Kim, S.J., Lee, E.J., Chang, Y., Ryu, S., Shin, H., Kim, H.L., Kim, H.N., and Lee, J.H. (2018). Association between Cigarette Smoking Status and Composition of Gut Microbiota: Population-Based Cross-Sectional Study. *J. Clin. Med.* 7, 282.
226. Antinozzi, M., Giffi, M., Sini, N., Gallè, F., Valeriani, F., De Vito, C., Liguori, G., Romano Spica, V., and Cattaruzza, M.S. (2022). Cigarette Smoking and Human Gut Microbiota in Healthy Adults: A Systematic Review. *Biomedicine* 10, 510.
227. Järup, L. (2003). Hazards of heavy metal contamination. *Br. Med. Bull.* 68, 167–182.
228. Zhao, Y., Li, X., Bao, H., and Nan, J. (2024). Effects of biochar-derived dissolved organic matter on the gut microbiomes and metabolomics in earthworm *Eisenia fetida*. *Environ. Res.* 245, 117932.
229. Indest, K.J., Everman, S.J., Lindsay, J.H., Jung, C.M., Smith, J.C., and Newell, S.B. (2018). Effects of acute exposures of 2,4,6-trinitrotoluene and inorganic lead on the fecal microbiome of the green anole (*Anolis carolinensis*). *PLoS One* 13, e0208281.
230. Chen, S., and Parmigiani, G. (2007). Meta-analysis of BRCA1 and BRCA2 penetrance. *J. Clin. Oncol.* 25, 1329–1333.
231. Chen, J., Bae, E., Zhang, L., Hughes, K., Parmigiani, G., Braun, D., and Rebeck, T.R. (2020). Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis. *JNCI Cancer Spectr.* 4, pkaa029.
232. Hilakivi-Clarke, L., and de Assis, S. (2006). Fetal origins of breast cancer. *Trends Endocrinol. Metabol.* 17, 340–348.

233. Hilakivi-Clarke, L. (2014). Maternal exposure to diethylstilbestrol during pregnancy and increased breast cancer risk in daughters. *Breast Cancer Res.* *16*, 208.
234. Rodgers, K.M., Udesky, J.O., Rudel, R.A., and Brody, J.G. (2018). Environmental chemicals and breast cancer: An updated review of epidemiological literature informed by biological mechanisms. *Environ. Res.* *160*, 152–182.
235. Cardona, B., Rodgers, K.M., Trowbridge, J., Buren, H., and Rudel, R.A. (2024). Breast Cancer-Related Chemical Exposures in Firefighters. *Toxics* *12*, 707.
236. Li, C.I., Malone, K.E., Daling, J.R., Potter, J.D., Bernstein, L., Marchbanks, P.A., Strom, B.L., Simon, M.S., Press, M.F., Ursin, G., et al. (2008). Timing of Menarche and First Full-Term Birth in Relation to Breast Cancer Risk. *Am. J. Epidemiol.* *167*, 230–239.