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Editorial Comment

PAH, genetic susceptibility and breast cancer risk: An update from the Long Island Breast Cancer Study Project

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In 2002 and 2004[1,2] we reported a 29–35% increase associated with the risk of developing breast cancer in relation to polycyclic aromatic hydrocarbon (PAH)-DNA adducts measured in lymphocytes. Our findings from the Long Island Breast Cancer Study Project (LIBCSP) are based on the largest epidemiologic investigation conducted to date on this issue, and are consistent with smaller studies.[3–5]

PAH are ubiquitous chemical carcinogens, mainly formed by incomplete combustion of fossil fuels.[6] Higher PAH exposures occur among select occupations, such as firefighters,[7,8] and coke oven, aluminum, and foundry workers.[9] Non-occupational exposure sources include: tobacco smoke;[10] charred, smoked, and broiled foods, and leafy vegetables;[11] wood and coal burning stoves;[12] and air pollution.[13]

PAH are known carcinogens in humans (to the lung, for example), causing direct genotoxic effects, or indirectly through oxidative stress.[6] PAH are lipophilic,[14] have oestrogenic properties,[15] and have been shown to cause mammary tumours in laboratory animals,[16,17] but the carcinogenic effects on the human breast are still not clear.[18]

The human body responds to PAH exposure through metabolism/detoxification pathways, but if the exposure is high or the metabolic/detoxification pathway is insufficient (in part due to genetic variations), PAH-DNA adducts are formed.[19] Persistence of these adducts occur because natural DNA repair mechanisms are inadequate, which again is influenced by genetic variation. The biomarker therefore reflects exposure and response to PAH. In the LIBCSP, cigarette smoking was associated with adduct formation among the control women.[20] However, we found that among those with increased exposure to PAH sources, the effect estimates for the adducts was not further elevated.[2] Thus, the biomarker appears to better reflect host response to PAH exposure, rather than exposure amount.

To improve our understanding of the observed link between PAH and breast cancer risk, our multi-disciplinary group is currently focused on estimating the effects on breast cancer associated with: (A) ambient PAH sources (including cigarette smoking, environmental tobacco smoke (ETS), grilled and smoked foods, and air pollution from vehicular traffic); and (B) inter-individual genetic variations in PAH-related pathways (including metabolism/detoxification, oxidative stress, p53, and DNA repair). The article by Shen and other LIBCSP colleagues reported in this issue[21] is an example of our efforts in this latter arena.

Our research has been undertaken utilising the resources of the LIBCSP, which includes a population-based bank of DNA samples for 1052 women with and 1098 women without

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breast cancer, for whom we have multi-level exposure data on PAH sources and measured PAH-DNA adduct levels. The LIBCSP was conducted in response to U.S. Congressional federal legislation mandating that an epidemiologic case-control study be undertaken to identify environmental factors for breast cancer among women on Long Island, New York.[22] Our specific aims were to determine whether breast cancer risk is associated with: (1) the organochlorine pesticide DDT, its metabolite DDE, or the polycholinated polychlorinated byphenyls (PCBs);[23] and (2) PAH-DNA adduct levels in peripheral blood.[1,2] In addition, whether breast cancer risk is associated with electromagnetic fields (EMF), assessed using multiple exposure measures, has also been examined in an LIBCSP ancillary study.[24,25] Although some investigations have inconsistently observed elevated risks for PCBs among genetically susceptible subgroups,[26–28] DDT exposure during early life,[29] and ambient EMF exposure,[30] overall, little or no effect has been reported in most epidemiologic studies focused on these organochlorine compounds (for examples, see[23,31,32]) or residential EMF (for examples, see[24,25,33,34]). Thus, PAH-DNA adducts are among the few environmentally related factors that have been consistently linked to breast cancer risk (An example of an established environmental risk factor for breast cancer risk is radiation exposure[35]).

Below we very briefly review the epidemiologic evidence linking breast cancer risk and PAH sources, and possible interactions between PAH, PAH sources and genetic polymorphisms, with a special emphasis on the research conducted using data from the LIBCSP.

1. PAH sources and breast cancer

1.1. *Active cigarette smoking*

Active cigarette smoking has been inconsistently linked to breast cancer in population studies.[36,37] More consistently positive findings have been reported in studies that consider: long-term ETS exposure,[38] including those from the LIBCSP;[39] or genetic susceptibility.[40]

1.2. *Grilled/smoked food intake*

Population studies focused on meat intake, or meat doneness, have yielded inconclusive results.[41–43] In the LIBCSP, we observed a 47% increase among postmenopausal women in relation to a lifetime average of grilled/smoked foods, that was more pronounced among those who also consumed low levels of fruits and vegetables.[44]

1.3. *Air pollution*

Bonner and colleagues at Buffalo, New York[45] reported an odds ratio (OR) of 2.4 for the association between breast cancer and early life exposure to PAHs, using total suspended particulates as a surrogate. In addition, based on models of PAH estimates attributed to vehicular traffic,[46] this same Buffalo research group reported over a two-fold increase in risk for exposures during several critical time periods for breast cancer (e.g. menarche and first live birth). To the best of our knowledge, these are the only publications on this issue. In the LIBCSP, estimates on historical exposure to ambient PAH have been developed,[47] and our risk analyses are underway.

2. Genetic susceptibility, PAH and breast cancer

2.1. *Xenobiotic metabolism/detoxification*

Results from two small studies on breast cancer have observed elevated risks among those women with higher PAH adducts and the variant alleles of several GST genetic polymorphisms.[48,49] Further, LIBCSP findings indicate that smokers with the *GSTA1* (AG/GG) genotypes had an 89% increased breast cancer risk compared to nonsmokers with the homozygous major genotype.[50] However, results from two recent meta-analyses differed, with one reporting no association with individual GST single nucleotide polymorphisms (SNPs) as well as a lack of interaction with smoking, and the other meta-analyses reported a positive association with *GSTT1* wildtype and *GSTM1* null among smokers.[40,51]

2.2. *Tumour suppressor gene P53*

Cigarette smoking as well as other PAH exposures have been shown to be associated with the *p53* mutational spectra of breast tumour tissue.[52] Common germline polymorphisms have been discovered within *TP53,* but have not been strongly associated with breast cancer risk among adequately powered studies (for example, see[53]). Few studies have considered potential gene-environment interactions. In the LIBCSP, although we found no evidence for an interaction with PAH-DNA adducts, we observed a decreased risk among current smokers with the minor alleles for the IVS6 + 62 A > G SNP (rs1625895) and the IVS3 INDEL polymorphism (rs17878362) (OR = 0.49, 95% CI 0.27–0.90; OR = 0.42, 95% CI 0.22–0.78, respectively).[54]

2.3. *DNA repair*

The *nucleotide excision repair (NER) pathway* repairs DNA damage from ultraviolet-induced photo-products, cross-links, and bulky chemical adducts, such as PAH-DNA adducts,[55] and the *xeroderma pigmentosum* group proteins are involved in this multi-step process. *XPD* (also called *ERCC2*) SNPs have been extensively studied, and the results for breast cancer are inconsistent.[56] For example, in the LIBCSP, we found a modest 21% increased risk associated with carrying one variant *Gln* allele at codon 751 of *XPD*.[57] Risk increased among those homozygous for the minor allele in relation to PAH-DNA adduct levels above the median (OR, 1.61; 95% CI, 0.99–2.63), and to current smoking (OR, 1.97; 95% CI 1.02–3.81). Another study,[58] with a similarly large sample size to the LIBCSP, found a nonsignificant elevation in the ORs among African Americans, but not whites, for the homozygous variant allele (Gln/Gln), and for smoking among whites and African Americans with the *XPD* 751 Lys/Lys genotype.

The *base-excision repair (BER) pathway* repairs 'non-bulky' DNA adducts, oxidative DNA damage and DNA damage attributable to ionising radiation.[56] SNPs involved in DNA glycosylase and BER core protein genes have been associated with cancer risk in humans, including breast cancer.[40,56] Other

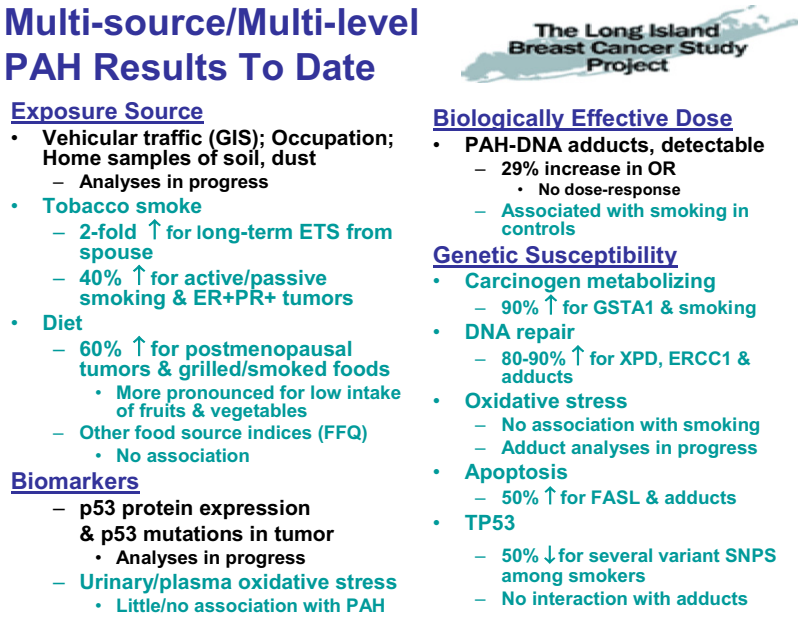

Fig. 1 – Summary of the PAH-related findings to date of the Long Island Breast Cancer Study Project (LIBCSP).

than SNPs in the *X-ray repair cross-complementing group 1* (XRCC1), which have been inconsistently linked to breast cancer in population studies[56] including the LIBCSP,[59] few BER-related SNPs have been well studied.[56]

2.4. *Oxidative stress*

Manganese SOD (MnSOD) is a mitochondrial enzyme that protects cells against damage from superoxide free radicals, and is encoded by *SOD2*.[60] *MnSOD* genotypes are frequently examined oxidative stress variants for breast cancer;[40] the summary OR, which includes LIBCSP data,[61] was 1.5 among long-term smokers with the variant allele.[51]

2.5. *Apoptosis*

Alterations in apoptosis genes may affect cancer risk by influencing individual susceptibility to environmental carcinogens. *FAS* and FAS ligand (*FASL*) play key roles in apoptotic signalling and down-regulation of this pathway may facilitate tumuorigenesis. However, breast cancer risk has been inconsistently linked to variant SNPs in this pathway.[62–64] To date we are the only group to consider interactions between genetic polymorphisms in this pathway and environmental exposures; we observed a 36% increase in breast cancer risk in relation to PAH-DNA adducts only among those carrying a *FAS1377 genetic* variant.[64]

2.6. *PAH and multiple genes/haplotypes*

Few epidemiologic studies have considered interactions among multiple SNPs in relation to breast cancer risk,[65,66] particularly with regard to PAH exposures.[40] A number of recent studies (for examples, see[58,67]), as well as data from the LIBCSP,[68–70] show stronger positive associations with variants in xenobiotic metabolism, oxidative stress and DNA repair polymorphisms when considered jointly rather than individually. For example, in the LIBCSP, when we considered the joint role of multiple at-risk genotypes in GSTs,[68] we observed nearly a 2-fold increase in breast cancer risk. However, published studies utilising this approach are not consistent and several have been underpowered.[40] Thus, whether the association of breast cancer and PAH is modified by two or more interacting genotypes has only been infrequently explored.

3. Summary

PAH are ubiquitous environmental carcinogens that induce mammary tumours in laboratory-based studies. Although PAH-DNA adducts have been consistently linked with breast cancer in epidemiologic studies, sources of ambient PAH have not. Thus, whether PAH are associated with breast cancer in humans is unclear. As we have found in the LIBCSP, it is possible that a PAH-related effect on breast cancer is evident when measures of biologically effective dose are considered, or among those that are genetically susceptible to the effects of PAH, as summarised in Fig. 1. The long-term goal of the LIBCSP collaborative group has been to characterise the association of breast cancer risk with PAH-DNA adducts and multiple PAH sources, utilising a multi-level approach, and to identify the genetic profiles associated with PAH-DNA adducts, PAH sources and breast cancer. This strategy may help to identify subgroups that are susceptible to the carcinogenic effects of PAH on the breast. Our most informative approach to date has been to consider several SNPs within the same gene or pathway,[65,66] as we do in the LIBCSP article by Shen et al.[21] in this issue.

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