SEX DISPARITY IN BENZO(a)PYRENE [B(a)P] - INDUCED COLON CARCINOGENESIS

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Abstract: Colorectal cancer (CRC) is the third most common diagnosed cancer and the third leading cause of cancer-related mortalities in the United States. While it has been reported that colon cancer incidence and death rates are higher in men than woman, a mechanistic link to show the factors that underlie the sex-specific differences in CRC initiation and progression is lacking. Benzo(a)pyrene [B(a)P], a prototypical member of the polycyclic aromatic hydrocarbon (PAH) family of compounds is a combustion toxicant that has been reported to induce sporadic colon cancer. This study aims to elucidate the sex-specific differences in B(a)P-induced colon cancer in adult Polyposis In the Rat Colon (PIRC) model. We hypothesize that sex-specific differences in B(a)P biotransformation modulates the formation of colon tumors in PIRC rats. Groups of female and male PIRC rats (n = 8) received sub-chronic exposure to 25, 50 and 100 µg B(a)P/kg body wt. via oral gavage for 60 days. Female and male rats that received no [B(a)P] treatment served as controls. [B(a)P] was shown to have no significant effect on body weight of these rats. Female PIRC rats that received 25, 50 and 100 µg B(a)P/kg body wt. showed significant decrease in total polyp count and size when compared to males with respective treatments. Histopathological analysis of colon polyps revealed that female animals exhibited low-grade to no dysplasia while high-grade dysplasia was recorded in male animals treated with corresponding doses. The Phase 1 biotransformation enzyme, Cytochrome P450 isoform 1A1 (CYP1A1), & 1B1 (CYP1B1) and Phase 2 enzyme, Sulfotransferase (SULT) Family 1A Member 1 (SULT1A1), were downregulated in colon tissue of female PIRC rats receiving 25, 50 and 100 µg B(a)P/kg body wt. when compared to male counterparts. On the other hand, another Phase 2 enzyme, the Glutathione-S-transferase (GST) showed an increased expression in female rats compared to their male counterparts. Our findings thus far indicate that increased detoxification of B(a)P in females render a protective effect. Our ongoing studies focus on assaying the expression of a phase 2 enzyme uridine diphosphate glucuronosyltransferase (UDPGT), estrogen receptors (α & β) along with measuring circulating estrogen levels, and analyzing [B(a)P] metabolite profile. Once these studies are completed, we expect to gain an insight into the role of estrogen receptor in protecting the females from developing colon cancer.

Key words: Benzo(a)pyrene, PIRC rats, colon tumors, estrogen, biotransformation

Acknowledgements: This research was supported by funding from the NIH grants 5R25GM059994-11, 5U54CA163069-04 and 5RO1CA142845-05.