Report

Sulfotransferase 1A1 (SULT1A1) polymorphism, PAH-DNA adduct levels in breast tissue and breast cancer risk in a case-control study

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Summary

Gene–environment interactions are hypothesized to be major contributors to susceptibility to environmental carcinogens and interindividual variability in cancer risk. We present findings on associations between genetic susceptibility due to inherited polymorphisms of the Phase II detoxification enzyme sulfotransferase 1A1 (SULT1A1), breast cancer risk, and polycyclic aromatic hydrocarbon (PAH)-DNA adducts. A hospital based case-control study was conducted at the New York-Presbyterian Medical Center (NYPMC). The study utilized two control groups: one comprised of women with benign breast disease (BBD) and the other comprised of women visiting NYPMC for routine gynecologic checkups (healthy controls). Blood samples were collected from cases and controls; and breast tissue from pathology blocks was collected from cases (tumor and non-tumor tissue) and BBD controls (benign tissue). PAH-DNA adduct levels were measured by immunohistochemistry in breast tissue samples, and the SULT1A1 (Arg/His) polymorphism at codon 213 was determined by PCR RFLP analyses using DNA from white blood cells. Increasing number of His alleles was modestly associated with breast cancer case-control status, when cases were compared to healthy controls ($p$ for trend $= 0.08$), when cases were compared to BBD controls ($p$ for trend $= 0.08$) and when cases were compared to both control groups combined ($p$ for trend $= 0.07$). Contrary to our hypothesis PAH-DNA adduct levels in breast tissue were not associated with SULT1A1 genotype. Our findings are consistent with a prior report that the Arg/His polymorphism in SULT1A1 is associated with breast cancer risk.

Introduction

Breast cancer is a major cause of morbidity and mortality among women in industrialized nations. In the United States, an estimated 203,500 new cases of invasive breast cancer will be diagnosed in the year 2002 and approximately 39,600 women will die from breast cancer [1]. There is growing evidence that environmental carcinogens may play a role in breast cancer development [2–5].

Genetic polymorphisms in enzymes which metabolize carcinogenic compounds have been suggested as a factor contributing to interindividual variation in susceptibility to cancer risk [6–8]. Sulfonate conjugation is an important pathway in the metabolism of a variety of potential mammary carcinogens of endogenous and exogenous origin, including estrogens, heterocyclic amines, and polycyclic aromatic hydrocarbons (PAH) [8–12]. This reaction is catalyzed by the sulfotransferase (SULT) superfamily of multifunctional enzymes. Members of the SULT enzyme family have considerable overlap in both amino acid sequence identity and substrate specificity [9–11]. Enzyme activity studies have demonstrated a large inter-individual variation in human SULT activity and polymorphisms in sulfotransferase enzymes are
well characterized [9–11]. Molecular pharmacogenetic studies of SULT1A1 have identified common polymorphisms encoding three allozymes with differing biochemical properties [13, 14]. A common G-A polymorphism at nucleotide 638 in the coding region of SULT1A1 appears to explain a large portion of the variability in enzyme activity. The base change in the gene sequence results in an arginine to histidine substitution at codon 213. Individuals homozygous for the His allele have approximately 15% of the sulfotransferase activity of those with the Arg/Arg and Arg/His genotypes [13]. SULT1A1 has multiple substrates relevant to mammary carcinogenesis. SULT1A1 catalyzes the sulfonation of estrogens to form water-soluble, biologically inactive estrogen sulfates, reducing the exposure of target tissues to estrogen [9, 10]. Thus the less active His allele is hypothesized to be associated with higher levels of unconjugated estrogens and increased breast cancer risk. Consistent with this hypothesis a recent study has shown that the His allele is associated with an increased risk of breast cancer. Compared to the Arg/Arg genotype the Arg/His genotype had an OR of 1.4 (0.9–2.2) and the His/His genotype had an OR of 1.8 (1.0–3.2, \( p = 0.03 \)) [8].

In contrast to its detoxifying role in estrogen metabolism, SULT1A1 is involved in the bioactivation of procarcinogens, including such compounds as heterocyclic amines and polycyclic aromatic hydrocarbons (PAH) [11, 12]. PAH are a class of human carcinogens that are widespread in the ambient environment. PAH are generated by incomplete combustion processes and are found in industrial emissions, tobacco smoke and foods such as charred and broiled meat [15, 16]. A number of PAH are potent mammary carcinogens in experimental bioassays [2, 17]. In vitro studies show that human breast epithelial tissue has the ability to metabolize PAH to their ultimate mutagenic/carcinogenic moieties capable of forming PAH-DNA adducts in human breast tissue. Due to the formation of sulfuric acid ester metabolites, sulfonation of PAH yields a reactive metabolite that can form PAH-DNA adducts [11, 21, 22]. Thus, the less active His allele would be hypothesized to confer lower risk of PAH-related carcinogenesis. Carcinogen-DNA adducts are considered a necessary, but not sufficient, event in the development of malignancy [23]. We have previously shown that PAH-DNA adducts can be measured in breast tissue and that malignant tissue has higher levels of adducts than breast tissue from women with benign conditions [3, 5]. Li and colleagues have similarly shown higher levels of aromatic-DNA adducts in non-tumor breast from cases compared to normal tissue from reduction mammoplasty specimens [4].

Given the role of SULT1A1 in the metabolism of estrogens, we hypothesized that the SULT1A1 His allele, which is less efficient at detoxifying estrogens, would be associated with increased risk of breast cancer. Additionally because of its reduced ability to activate PAH, we hypothesized that the His variant would be associated with reduced PAH-DNA adduct levels. Thus, we hypothesized that the SULT1A1 polymorphism would act as an inverse confounder in analyses of PAH-DNA adduct levels and breast cancer, obscuring associations between adducts and case-control status.

Materials and methods

Study population and sample collection

This study used tissue and blood samples from a hospital-based case-control study of breast cancer that has been previously described [5, 7, 24]. Women referred for breast surgery for a suspected breast cancer were enrolled prior to surgery. Patients whose subsequent diagnosis was of ductal carcinoma in situ (DCIS), or invasive ductal or invasive lobular cancer, were defined as cases \( (n = 119) \). Patients with a diagnosis of benign breast disease without atypia were defined as cases \( (n = 119) \). Patients with a diagnosis of benign breast disease without atypia were defined as benign breast disease controls (BBD controls, \( n = 108 \)). The patients took part in a structured interview covering established reproductive breast cancer risk factors, active and passive smoking, dietary practices, other environmental and occupational exposures. Blood samples were drawn prior to surgery and tissue specimens from the pathology blocks were retrieved after diagnosis.

A healthy control group was enrolled from among women coming to CPMC for routine GYN checkups. Physicians who referred their patients to the CPMC breast service for breast related complaints were chosen for participation in the study. Enrolled women signed a consent form, donated blood samples, and were interviewed \( (n = 142) \). Healthy control patients were matched to cases on age by 10-year age groups. The study protocol was approved by the CPMC Institutional Review Board and by the Columbia Comprehensive Cancer Center’s Review Board. Blood samples (30 ml) were drawn from all women at