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Microsomal epoxide hydrolase genotype and risk of myocardial infarction

Marilyn C. Cornelis[1], Ahmed El-Sohemy[1] and Hannia Campos[2, 3]

(1) Department of Nutritional Sciences, University of Toronto, Room 350, 150 College St, M5S 3E2 Toronto, ON, Canada

(2) Department of Nutrition, Harvard School of Public Health, Boston, MA, USA

(3) Centro Centroamericano de Poblacion, Universidad de Costa Rica, San Pedro, de Montes de Oca, Costa Rica

Ahmed El-Sohemy
Email: a.el.sohemy@utoronto.ca

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Abstract DNA damage caused by mutagens found in tobacco smoke may contribute to the development of coronary heart disease (CHD). Microsomal epoxide hydrolase (EPHX1) is involved in the metabolism of tobacco smoke mutagens and an amino acid substitution (H139R) in exon 4 of the *EPHX1* gene is associated with increased enzyme activity. The objective of this study was to investigate the effect of *EPHX1* genotype on risk of myocardial infarction (MI) and to determine whether smoking interacts with genotype to modify risk. Cases (n = 2,022) with a first acute non-fatal MI and population-based controls (n = 2,022) living in Costa Rica, matched for age, sex and area of residence were genotyped by RFLP-PCR. Smoking status was determined by questionnaire. The frequency of the *R139* allele was 17% for both cases and controls. *EPHX1* genotype was not associated with risk of MI, regardless of smoking status. Compared to individuals with the *HH* genotype, the multivariate adjusted odds ratio (95% confidence interval) for risk of MI was 0.95 (0.81–1.11) for individuals with the *HR* genotype and 1.18 (0.79–1.76) for those with the *RR* genotype. These results suggest that EPHX1 does not play a significant role in the development of CHD.

Keywords Microsomal epoxide hydrolase - DNA damage - Genotype - Smoking - Myocardial infarction

Introduction

Atherosclerosis is a major cause of myocardial infarction (MI), one of the leading causes of cardiovascular deaths in the world (Ross *1993*). Although smoking is a well-established risk factor for atherosclerosis the mechanism remains unclear. One of the proposed mechanisms is that mutagens found in tobacco smoke increase the formation of DNA adducts, which lead to genetic alterations in blood vessels and the heart (Benditt and Benditt *1973*; Penn *1990*; Murry et al. *1997*; Botto et al. *2001*; Ross et al. *2001*). Animal studies show that tobacco smoke mutagens such as polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines directly increase the development of atherosclerotic lesions (Albert et al. *1977*; Penn and Snyder *1988*; Randerath et al. *1988*). Humans and animals exposed to tobacco smoke have elevated levels of mutagen-DNA adducts in various organs, especially in the lungs, heart and aorta (Randerath et al. *1988*; Izzotti et al. *1994*; van Schooten et al. *1998*; Zhang et al. *1998*). Moreover, the levels of these DNA adducts in arterial tissue of patients with atherosclerosis correlate with the number of cigarettes smoked and with disease severity (Izzotti et al. *1995*; van Schooten et al. *1998*; Zhang et al. *1998*).

The extent to which mutagens found in tobacco smoke bind to DNA is partly determined by the balance between mutagen activation and detoxification, reactions that are catalyzed by xenobiotic-metabolizing enzymes. Polymorphisms of these enzymes contribute to individual differences in the biotransformation of mutagens and might, therefore, alter susceptibility to smoking-related coronary heart disease (CHD) (Li et al. *2000*; Wilson et al. *2000*; Salama et al. *2002*; Wang et al. *2002a*, *b*; Tamer et al. *2004*; Doney et al. *2005*). Microsomal epoxide hydrolase (EPHX1, also referred to as mEH) is a xenobiotic-metabolizing enzyme involved in the biotransformation of reactive intermediates and is expressed in several human tissues including the heart and blood vessels (Farin and Omiecinski *1993*). Thus, EPHX1 is capable of modulating the levels of DNA damage in these tissues, which may contribute to the development of CHD. This enzyme catalyzes the hydrolysis of arene, alkene, and aliphatic epoxides derived from PAHs and aromatic amines (Sims et al. *1974*; Guengerich *1982*). Hydrolysis is generally a detoxification reaction because less reactive and more water-soluble trans-dihydrodiols are produced, which are then excreted from the body (Oesch *1973*). Some of these metabolites, however, may be subsequently activated by cytochrome P450 (CYP)s to produce highly mutagenic diol epoxides (Sims et al. *1974*). The human *EPHX1* gene is located on chromosome 1q42.1 and consists of nine exons. An A to G polymorphism in exon 4 of the *EPHX1* gene results in a histidine (H) to arginine (R) substitution at codon 139 (Hassett et al. *1994a*). In vitro analyses of the 139R variant shows a 25–30% increase in expression, possibly caused by an alteration in protein stability (Gaedigk et al. *1994*; Hassett et al. *1994a*, *b*).

While recent evidence suggests that genetic variability in xenobiotic-metabolizing enzymes, such as glutathione *S*-transferases (GSTs), CYP1A1 and CYP2E1, play a role in CHD development (Li et al. *2000*; Wilson et al. *2000*; Salama et al.

2002; Wang et al. 2002a, b; Tamer et al. 2004; Doney et al. 2005), no study has examined the effect of the *EPHX1 H139R* polymorphism on risk of MI. The purpose of this study was to investigate the effects of *EPHX1* genotype on risk of MI in a large population-based case-control study and to determine whether smoking interacts with genotype to modify risk.

Materials and methods

Study design and participants

Details of the study design and participants have been described elsewhere (Cornelis et al. 2006). Briefly, the catchment area for this study was comprised of 7,071 km^2 and 2,057,000 individuals living in Costa Rica who are self-described Hispanic Americans. This area included 36 counties in the Central Valley of Costa Rica that covered a full range of socioeconomic levels, as well as urban, peri-urban, and rural lifestyles. Medical services in this area were covered by six large hospitals, which are part of the National Social Security System. Eligible cases were men and women who were survivors of a first acute MI as diagnosed by a cardiologist at any of the six recruiting hospitals in the catchment area between 1994 and 2004. All cases were confirmed by two independent cardiologists according to the World Health Organization criteria for MI, which require typical symptoms plus either elevation in cardiac enzyme levels or diagnostic change in electrocardiogram (Tunstall-Pedoe et al. 1994). Cases were ineligible if they died during hospitalization, were ≥75 years of age on the day of their first MI, were physically or mentally unable to answer the questionnaire, or had a previous hospital admission related to cardiovascular disease. One control for each case, matched for age (±5 years), sex and area of residence (county), was randomly selected using information available at the National Census and Statistics Bureau of Costa Rica. Controls were ineligible if they were physically or mentally unable to answer the questionnaires or if they had a previous hospital admission related to MI or other cardiovascular disease. Participation for eligible cases and controls was 98 and 88%, respectively. All data were collected by trained fieldworkers during an interview using two questionnaires consisting of closed-ended questions regarding smoking, socio-demographic characteristics, socioeconomic status, physical activity, diet, and medical history including use of medication and personal history of diabetes and hypertension. Subjects were grouped into three categories of smoking status; nonsmoker (never + past smoker), smoking 1–19 cigarettes per day or smoking ≥20 cigarettes per day. Cases and controls gave written informed consent and the study was approved by the Ethics Committees of the Harvard School of Public Health and the University of Costa Rica, the Office of Protection from Research Risk at the NIH, and the Ethics Review Committee at the University of Toronto.

Genotyping

Blood samples were collected in the morning at the subject's home after an overnight fast and were centrifuged to separate the plasma and leukocytes for DNA isolation by standard procedures. The *EPHX1 H139R* polymorphism (rs2292566) was detected as previously described (Hassett et al. *1994a*) using restriction-fragment length polymorphism (RFLP)-PCR, without knowledge of case-control status. Primers were synthesized by ACGT (Toronto, Canada) and included the forward 5′-GGGGTACCAGAGCCTGACCGT-3′ and reverse 5′-AACACCGGGCCCACCCTTGGC-3′ primers. Approximately 1 ng of DNA was amplified by thermal cycling using the HotStar™ DNA polymerase kit (Qiagen, Mississauga, Canada) with PCR buffer containing 1.5 mM $MgCl_2$, 0.2 mM of each dNTP, 0.5 U Taq, and 8 pmol of each primer. PCR conditions included an initial denaturation at 95°C for 15 min, followed by 40 cycles of 94°C for 1 min, 68°C or 30 s, and 72°C for 1 min, with a final extension at 72°C for 7 min. PCR products were digested with 2 U of *RsaI*, resolved by 2% agarose gel electrophoresis and stained with ethidium bromide. Bands were visualized using a FluorChem™ UV imaging system (Alpha Innotech, San Leandro, CA, USA). The primers amplify a 357 bp band with a nonpolymorphic restriction site that produces 295 and 62 bp fragments. The 295 bp fragment is further cut into 174 and 121 bp fragments with the G allele (*139R*).

Statistical analyses

All data were analyzed using SAS version 8.2 (SAS Institute, Cary, NC, USA). DNA was available from 4,369 subjects (2,113 cases and 2,256 controls). A total of 325 subjects were excluded because they had missing data on confounders (26 cases, 22 controls), they could not be genotyped (61 cases, 73 controls), or they became unmatched because of missing data (4 case, 139 controls) leaving 2,022 matched case-control pairs for the final analysis. Because of the matched design, significant differences in the distribution of categorical variables between cases and controls were tested using McNemar's test and continuous variables using the paired *t* test. Odds ratios (ORs) and 95% confidence intervals (95% CI) were estimated by conditional logistic regression to determine the effect of *EPHX1* genotype on risk of MI. Potential confounders included in the final models were smoking (never + past, 1–19 cigarettes/day, and ≥20 cigarettes/day), history of diabetes (yes/no), history of hypertension (yes/no), and quintiles of the continuous variables waist-to-hip ratio, physical activity, and income. We evaluated potential gene-smoking interactions by determining the relation between genotype and the risk of MI for each smoking category using conditional or unconditional logistic regression (with matching variables in the model) and by comparing −2 log (likelihood) ratios from a model with gene and smoking main effects only, and another that included their interaction term. Smoking status was not adjusted for when analyses were stratified by smoking status. Because results for conditional and unconditional logistic regression were similar for stratified analyses we report only the data from unconditional analyses to maximize the number of subjects.

Results

Demographic and risk factor characteristics of subjects based on case-control status are presented in Table 1. Cases had a significantly higher waist-to-hip ratio, lower income, were less physically active, and were more likely to be current smokers and to have a history of diabetes or hypertension.

Table 1 Subject characteristics

Characteristic	Cases (*n* = 2022)	Controls (*n* = 2022)
Age (years)	58.0 ± 11.3	58.4 ± 11.1
Male	1488 (74)	1488 (74)
Urban residence	1495 (74)	1495 (74)
Waist-to-hip ratio[a]	0.97 ± 0.07	0.95 ± 0.07
Current smokers[a]	807 (40)	429 (21)
Income (US $/month)[a]	498 ± 389	568 ± 422
Physical activity, METS[ab]	1.51 ± 0.69	1.56 ± 0.70
History of hypertension[a]	783 (39)	597 (30)
History of diabetes[a]	490 (24)	283 (14)

Values are mean ± standard deviation for continuous variables and number (%) for categorical variables

[a] $P < 0.05$ for cases compared to controls

[b]METS: metabolic equivalents

EPHX1 genotype distribution among controls was in Hardy–Weinberg equilibrium (HWE) ($P = 0.95$). Seventy, 27, and 3% of controls had the *HH*, *HR*, and *RR* genotypes, respectively. Corresponding frequencies among cases were 70, 26, and 4%. *EPHX1* genotype was not associated with risk of MI. Compared to individuals with the *HH* genotype, the OR (95% CI) for MI was 0.97 (0.85–1.12) for those with the *HR* genotype and 1.26 (0.88–1.80) for those with the *RR* genotype. Corresponding multivariate adjusted ORs (95% CI) were 0.95 (0.81–1.11) and 1.18 (0.79–1.76). We next determined the risk of MI associated with *EPHX1* genotype among different categories of smoking (Table 2), but no significant *EPHX1*-smoking interaction was observed ($P > 0.05$). Similar results were observed when subjects were stratified by age (above/below median age) and sex (data not shown).

Table 2 *EPHX1 H139R* genotype and risk of MI by smoking status

	Cases	Controls	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)
	n (%)			
Never + past smokers				
HH	848 (70)	1101 (69)	1.00	1.00
HR	322 (26)	447 (28)	0.94 (0.79–1.11)	0.94 (0.79–1.11)
RR	45 (4)	45 (3)	1.29 (0.85–1.98)	1.30 (0.84–2.02)
1–19 cigarettes/day				
HH	225 (69)	207 (74)	1.00	1.00
HR	91 (28)	63 (23)	1.28 (0.88–1.87)	1.30 (0.87–1.91)
RR	8 (2)	8 (3)	0.88 (0.32–2.42)	1.02 (0.36–2.88)
≥20 cigarettes/day				
HH	343 (71)	108 (72)	1.00	1.00
HR	120 (25)	38 (25)	0.99 (0.64–1.51)	0.97 (0.62–1.51)
RR	20 (4)	5 (3)	1.19 (0.43–3.25)	1.14 (0.40–3.23)

[a]Adjusted for age, sex, area of residence

[b]Adjusted for age, sex, area of residence, waist-to-hip ratio, income, physical activity, and history of diabetes and hypertension

Discussion

There is growing evidence that DNA damage caused by mutagens found in tobacco smoke may accelerate the development of atherosclerosis (Ross et al. *2001*). The level of DNA damage caused by environmental mutagens is determined, in part, by the balance between mutagen activation and detoxification by xenobiotic-metabolizing enzymes. Depending on the substrate, EPHX1 can be considered either activating or detoxifying (Sims et al. *1974*; Guengerich *1982*). To our knowledge, the present study is the first to examine the association between the *EPHX1 H139R* polymorphism and risk of MI. A previous study (Salama et al. *2002*) involving 120 cases and 90 controls, who were all smokers reported an increased risk of atherosclerosis among carriers of at least one *139R* allele. Atherosclerosis, however, was not clearly defined in that study. Using a large case-control study design we found that the *EPHX1 H139R* polymorphism did not modify risk of MI, regardless of smoking status. Whether this polymorphism alters other CHD endpoints or progression of the disease merits further investigation.

The functional significance of the *EPHX1 H139R* polymorphism is currently based on in vitro studies (Gaedigk et al. *1994*; Hassett et al. *1994a*; Hassett et al.

1994b). Since it is possible that this polymorphism does not affect enzyme activity in vivo, we cannot exclude the possibility that other functional *EPHX1* polymorphisms modify the risk of MI. A second polymorphism in the *EPHX1* gene resulting in a tyrosine to histidine substitution at codon 113 (*T113H*) in exon 3 has also been associated with altered enzyme activity (Gaedigk et al. 1994; Hassett et al. 1994b). Wilson et al. examined this polymorphism and found no association between genotype and risk of MI, regardless of smoking status (Wilson et al. 2000). Although the *EPHX1 T113H* genotype distribution in that study was in HWE, previous studies that have examined this polymorphism by RFLP-PCR report distributions that are not in HWE (Hassett et al. 1994a; Zhou et al. 2001; Tranah et al. 2004). A single nucleotide substitution close to the polymorphic site and within the sequence of the downstream primer appears to cause a reduction in amplification efficiency (Kelcho et al. 2001). When we examined the *EPHX1 T113H* polymorphism by RFLP-PCR as previously described (Zhou et al. 2001), the genotype distribution was not in HWE (data not shown) and, therefore, this data was not presented.

EPHX1 is only one of many xenobiotic-metabolizing enzymes involved in the biotransformation of mutagens. Thus, genetic variability in this enzyme may modify risk of MI only in the presence of susceptibility alleles of other xenobiotic-metabolizing enzymes. Polymorphisms of other activating and detoxifying enzymes, including CYP1A1, CYP2E1 and GSTs, have been associated with risk of CHD, but the effects have been inconsistent (Li et al. 2000; Wilson et al. 2000; Salama et al. 2002; Wang et al. 2002a, b; Tamer et al. 2004; Doney et al. 2005). Future studies examining the role of DNA damage in the development of CHD may need to consider the combined effect of genetic polymorphisms of a number of enzymes mediating the biotransformation of mutagens. In summary, our results suggest that EPHX1 does not appear to play a major role in the development of CHD, regardless of smoking status.

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