Smoking and Aldosterone Synthase Polymorphism

To the Editor:

Hautanen and colleagues1 claim that dyslipidemic middle-aged men from the Helsinki Heart Study with the aldosterone synthase (CYP11B2, –344T/C) CC genotype who smoked were ≈5 times more likely to suffer a nonfatal myocardial infarction than nonsmokers of the same genotype during a follow-up period of 8.5 years. I think that this finding is likely to be spurious and result from artefactual control matching. The cases included 75% of patients who had a nonfatal myocardial infarction; those who suffered cardiac death comprised one-fifth of the total cardiac event population and were excluded from analyses. This selection bias might have accounted for the relatively low frequency of the T allele in this study (0.48) compared with other reports (0.54 to 0.60).2,3

Whether subjects with the T allele were more likely to suffer cardiac death could not be known. Importantly, there were more smokers across the genotype sequence of TT>CT>CC in the controls and less smokers in the same direction for cases. Thus, the differences in smoking frequencies between cases and controls across the sequence resulted in 0.01%, 67.13%, and 125.80% more smokers within the case cohorts, respectively. Unsurprisingly, the TT genotype was found not to relate to smoking for nonfatal myocardial infarction because there was an equal number of smokers in cases and controls compared with other genotypes.

The question of whether smoking interacts with any particular genotype cannot be resolved by the retrospective case-control methodology used in this study. However, the data might still be reanalyzed with a pooled study population stratified according to different genotypes. Using this method with the available data, the case/smoker percentages for each genotype were as follows: TT, 28.4%/38.5%; CT, 35.9%/44.2%; and CC, 37.5%/41.67% (χ²=0.481, P=0.786). As suspected, with this breakdown, there was no significant interaction between smoking and the aldosterone synthase steriodogenic factor-1 (CYP11B2, –344T/C) binding-site genetic polymorphism.

Pitt O. Lim, MD
Lecturer in Cardiology
Department of Cardiology
Wales Heart Research Institute
University of Wales College of Medicine
Heath Park
Cardiff CF14 4XN
United Kingdom


Response

Lim is concerned that our study1 is biased because it did not include subjects who suffered fatal myocardial infarction (MI). This limitation was imposed by the fact that blood samples for DNA were collected at the end of a follow-up period. However, this problem applied only to genotyping; for all other putative risk factors (ie, HDL cholesterol, systolic blood pressure, and smoking), we had baseline measurements and could compare odds ratios obtained through different study designs. For example, the MI risk from smoking could be compared using the following: (1) cohort analysis including all 241 MIs; (2) cohort analysis among survivors, including those with 141 nonfatal MIs; and (3) case-control analysis of the 141 nonfatal MIs (ie, the same design as in our article). The odds ratios with 95% confidence intervals were almost identical for each of these 3 analyses. The first provided an odds ratio of 2.56 and a 95% confidence interval of 1.96 to 3.33; the second resulted in 2.48 (1.76 to 3.49) and the third in 2.50 (1.62 to 3.37). These findings argue strongly against any selection bias in our case-control design.

Lim is also concerned about the low frequency of the T allele among cases in our study population. However, in a cumulative-incidence case-control study, neither cases nor controls represent the general population. If increased MI risk is associated with the C allele, then the frequency of that allele should be increased among cases, and the frequency of the T allele will, accordingly, decrease. Because the controls were selected from a population devoid of cases during follow-up, they should have the opposite trend in allele frequencies. Similarly, there should be more smokers among cases than among controls and, if smoking and genotype interact as risk factors for MI, there should be a higher percentage of smokers among cases with the genotype CC but a lower percentage among controls. The findings in Table 1 from our article1 are completely consistent with the hypothesis of such an interaction. When analyzed in the context of conditional logistic regression analysis by considering differences of the log likelihood statistic,2 the P value for interaction was close to significant (P=0.064), despite the fact that this test for interaction has low power.

Lim’s method of testing for interaction is not valid in a case-control study because essential information on interactions will be lost by pooling cases and controls. No post hoc test can reproduce the information inherent in the subjects with fatal MI who were missing from this study, but we think that our conclusions concerning smoking, genotype, and nonfatal MI in this population are well founded.
Smoking and Aldosterone Synthase Polymorphism
Pitt O. Lim

Circulation. 2000;102:e183
doi: 10.1161/01.CIR.102.24.e183

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/102/24/e183

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/