Tobacco Use and Increased Colorectal Cancer Risk in Patients With Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome)

Patrice Watson, PhD; Ramesh Ashwathnarayan, MD; Henry T. Lynch, MD; Hemant K. Roy, MD

Background: The marked variability in age at onset of colorectal cancer (CRC) in patients with hereditary nonpolyposis colorectal cancer (HNPCC) makes management decisions difficult. Environmental factors governing the phenotypic variability of cancer-associated syndromes such as HNPCC have not been elucidated.

Methods: We determined whether tobacco use would alter CRC risk in carriers of HNPCC-associated mutations, using a retrospective cohort study of germline mutation (hMLH1 or hMSH2) carriers from the Hereditary Cancer Institute at Creighton University, one of the oldest and largest registries of HNPCC patients. The main outcome measure was age at CRC onset, estimated by means of Cox proportional hazards modeling.

Results: Tobacco use, hMLH1 mutation carriage (as opposed to hMSH2), and male sex were significantly associated with increased risk of CRC (hazard ratios, 1.43, 2.07, and 1.58, respectively). Alcohol use did not alter CRC risk.

Conclusions: Smoking cessation should be an integral part of HNPCC management. This study underscores the gene × environment interactions in cancer development.

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The pathogenesis of the phenotypic variability in HNPCC is poorly understood. To date, the most compelling arguments for environmental modulation have been geographic differences in cancer rates. For instance, in Korea, where sporadic gastric cancer is endemic secondary to dietary practices, HNPCC patients have a much higher incidence of gastric cancer than comparable Dutch families. Tobacco use is a biologically plausible modulator of the CRC risk in HNPCC because smoking predominantly potentiates MSI-high colon cancer. In the general population, 12% of all CRC fatalities are attributable to smoking. The 43% increased hazard ratio seen in this study is the first evidence, to our knowledge, of an environmental modulation of cancer risk in HNPCC. This appeared to be unrelated to the amount of total exposure. The lack of a dose-response effect may reflect a threshold effect, in which environmental effects are seen at lower levels of exposure in the highly susceptible group. However, speculation needs to be tempered by the limited number of subjects available and by the limitations inherent in any observational study. The lack of a dose-response effect may indicate that the association between tobacco use and colon cancer is noncausal and a result of confounding, which (although unlikely) is impossible to rule out in an observational study. The lack of association between alcohol use and CRC risk is consistent with several reports that suggest that alcohol predominantly augments distal CRC, which is unlikely to be MSI-high. Indeed, the one report of a minimal increase in MSI-high tumors with alcohol use was noted for liquor consumption, but not wine or beer. Taken together, the evidence suggests that alcohol-induced CRC evolves through a molecular pathway distinct from HNPCC-related CRC. Although we did not explore the mechanisms through which tobacco use might increase CRC risk, it is most likely a result of the numerous carcinogens in cigarette smoke. Given the deficiency of DNA mismatch repair in HNPCC, these patients may be particularly susceptible to mutagenic effects of tobacco-induced DNA adducts.

To our knowledge, this is the first report that hMLH1 mutation carriers had a higher risk of developing CRC than hMSH2 carriers. Previous reports from the Netherlands and Australia yielded discordant trends for CRC risk in hMLH1 and hMSH2 mutation carriers, but in neither case was the trend statistically significant. Both studies were

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**Table 1. Characteristics of 360 Hereditary Nonpolyposis Colorectal Cancer Mutation Carriers Studied**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hMLH1</td>
<td>175 (48.6)</td>
</tr>
<tr>
<td>Female sex</td>
<td>196 (54.4)</td>
</tr>
<tr>
<td>Tested</td>
<td>300 (83.3)</td>
</tr>
<tr>
<td>Dead</td>
<td>91 (25.3)</td>
</tr>
<tr>
<td>CRC history</td>
<td>159 (44.2)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>182 (50.6)</td>
</tr>
<tr>
<td>Year of birth, median</td>
<td>1947 (1882-1984)</td>
</tr>
<tr>
<td>Age at CRC diagnosis, median</td>
<td>43.6 (16-76)</td>
</tr>
</tbody>
</table>

Abbreviation: CRC, colorectal cancer.

*Data are given as frequency (percentage) unless otherwise indicated.

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**Table 2. Maximum Likelihood Estimates From Cox Proportional Hazards Modeling**

<table>
<thead>
<tr>
<th>Variables Included (in Decreasing Order of Risk Category)</th>
<th>Variable</th>
<th>Estimate ± SE</th>
<th>P Value*</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men vs women</td>
<td>0.46 ± 0.17</td>
<td>.006</td>
<td>1.58</td>
<td></td>
</tr>
<tr>
<td>hMLH1 vs hMSH2</td>
<td>0.73 ± 0.16</td>
<td>&lt;.001</td>
<td>2.07</td>
<td></td>
</tr>
<tr>
<td>Born before vs during or after 1948</td>
<td>0.25 ± 0.19</td>
<td>.20</td>
<td>1.28</td>
<td></td>
</tr>
<tr>
<td>Tobacco user vs nonuser</td>
<td>0.36 ± 0.17</td>
<td>.01</td>
<td>1.43</td>
<td></td>
</tr>
</tbody>
</table>

*The probability associated with the Wald χ² test that the regression coefficient is equal to zero. All regression coefficients are adjusted for the other variables in the model.

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In patients who smoked cigarettes and provided data on amount smoked (113 of 182 smokers), the mean consumption was 24 pack-years. Cox proportional hazards modeling failed to demonstrate a significant correlation between CRC risk and increasing pack-years of use. Alcohol use information was available in 271 carriers, of whom 83 (30.6%) were classified as nonsmokers. Cox proportional hazards modeling failed to show a significant association between alcohol use and CRC risk (P=.40). A second analysis of these cases that included tobacco use and a tobacco use × alcohol use interaction term in the model also showed no significant association between alcohol use or the interaction term and CRC risk.

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**Results**

We identified 596 mutation carriers from 62 HNPCC families. Of these carriers, 360 had information on tobacco use (so that they could be classified as users or nonusers) and were included in our study. Characteristics of this group are given in Table 1.

The results of Cox proportional hazards modeling are given in Table 2. Tobacco users had a higher incidence of CRC than nonusers, reflected in a hazard ratio of 1.43 (P<.04). In addition, hMLH1 carriers (vs hMSH2 carriers) and men (vs women) were at a statistically significant increased risk of CRC. Year of birth cohort was not associated with an altered hazard ratio for CRC. Substituting the year of birth for the year of birth cohort in the model did not improve the model fit. Including terms for sex, gene, or time (from birth) interactions with tobacco use also did not improve the model fit, indicating that the Cox proportional hazards model was appropriate for these data.
smaller than the present study. We confirm the previously reported increase in CRC hazard ratio in men vs women.24,26,27 Sex differences may result from genetic and environmental factors (estrogens are clearly protective against CRC).28

There are several limitations inherent in our retrospective study. The incomplete smoking data raise concerns about bias, including selection bias (carriers with tobacco use data may be unrepresentative of carriers as a whole) and response bias (patients with CRC might be more likely to remember or report tobacco use). However, post hoc comparisons of carriers with and without smoking data argued against important selection bias, showing no differences in sex ratio, year of birth, or proportion with CRC. Our inclusion of inferred carriers should also mitigate selection bias. Biased reporting of tobacco or alcohol use may occur in subjects with cancer, but because CRC is not widely believed to be a smoking-related tumor, we do not think that this is plausible. Future studies of the relationship between tobacco use and CRC in HNPCC should include more detailed tobacco use history information (unavailable for most cases in this study), to obtain more accurate estimates of the strength of the association and to study its temporal pattern.

In summary, we report for the first time (to our knowledge) that an exogenous factor, tobacco use, appears to modulate the penetrance of a genetic CRC susceptibility disorder caused by germline mismatch repair mutations. We also believe that this is the first demonstration of a statistically significant difference in CRC risk between the 2 most common loci for germline mutations in HNPCC, hMLH1 and hMSH2. These data underscore the complex genetic and environmental factors in the pathogenesis of CRC. Our results suggest that cigarette smoking cessation should be an integral part of the management of patients with HNPCC. Furthermore, this study may serve as a paradigm for risk stratification of patients with an inherited predisposition for cancers to implement optimal prevention strategies.

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Disclaimer: The results reported in this article are solely the responsibility of the authors and do not necessarily represent the official views of the state of Nebraska or the Nebraska Department of Health and Human Services.

REFERENCES