Smoking Increases the Risk for Colorectal Adenomas in Patients With Lynch Syndrome

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BACKGROUND & AIMS: Individuals with Lynch syndrome have a high risk of developing colorectal carcinomas and adenomas at a young age, due to inherited mutations in mismatch repair genes. We investigated whether modifiable lifestyle factors, such as smoking and alcohol intake, increase this risk. **METHODS:** Using data from the GeoLynch cohort study, a prospective analysis of 386 subjects with Lynch syndrome, we calculated hazard ratios for the association between smoking and alcohol intake and development of colorectal adenoma. We used robust variance estimates in the calculation of 95% confidence intervals to account for dependency within families and adjusted for confounding by age, sex, smoking (in the analyses of alcohol intake), number of colonoscopies during the follow-up, colonic resection, and body mass index. **RESULTS:** During a median follow-up of 10 months, 58 subjects developed a histologically confirmed colorectal adenoma. The hazard ratio for current smokers was 6.13 (95% confidence interval, 2.84−13.22) and for former smokers was 3.03 (95% confidence interval, 1.49−6.16) compared with never smokers. Among ever smokers, a higher number of pack-years was associated with an increased risk for colorectal adenoma (P for trend = .03). There was a trend of alcohol intake increasing the risk of colorectal adenomas, although this was not statistically significant; the hazard ratio for the highest tertile of intake (median, 22 g/day) vs the lowest tertile (median, 0.4 g/day) was 1.56 (95% confidence interval, 0.71−3.43). **CONCLUSIONS: Among people with Lynch syndrome, current smokers have an increased risk of colorectal adenomas. Former smokers have a lower risk than current smokers, but greater risk than never smokers. Individuals with Lynch syndrome should be encouraged to avoid smoking.**

Keywords: Genetic; Hereditary Nonpolyposis Colorectal Cancer; Cox Regression; Colon Cancer.

Individuals with Lynch syndrome have a 20%–70% risk of developing colorectal cancer before the age of 70 years,[1–4] have a higher risk for developing colorectal adenomas at a younger age,[5] and manifest rapid progression from colorectal adenoma to carcinoma.[6] It is estimated that 1%–3% of all colorectal cancer is caused by Lynch syndrome.[7] The increased risk of colorectal cancer in those with Lynch syndrome is caused by pathogenic germline mutations in genes involved in DNA mismatch repair, ie, MLH1, MSH2, MSH6, PMS2, or EPCAM.[7–10]

Considering the high lifetime risk of developing colorectal cancer in individuals with Lynch syndrome, it is very relevant to study whether modifiable lifestyle factors can affect the risk for developing this hereditary cancer. Several modifiable lifestyle factors affect the risk of sporadic colorectal cancer, among them are smoking[11] and alcohol consumption.[12] However, this association has been studied only sparsely in Lynch syndrome.[13–15]

So far, only retrospective studies on smoking and colorectal cancer risk in individuals with Lynch syndrome were performed,[13–15] these cohort[14,15] and case-control studies[13] showed that smoking was associated with an increased risk of colorectal cancer. Due to the retrospective nature, the information on smoking history was limited in one of these studies,[15] as it had to be obtained partly from medical records or family reports. Moreover, the case-control study[13] included persons who were not all confirmed carriers of a mismatch repair gene mutation. Likewise for alcohol intake, the association with colorectal cancer in Lynch syndrome has only been studied retrospectively in these studies.[13,15] Neither study detected a significant association between alcohol intake and colorectal cancer risk.

The aim of this study was to prospectively assess the association between smoking and/or alcohol intake and colorectal adenoma development in a cohort study of persons with Lynch syndrome. To our best knowledge, the association with colorectal adenomas has not been studied before, as previous studies on Lynch syndrome focused on colorectal carcinoma risk.[13–15] In the general population, smoking shows a stronger association with development of

Abbreviations used in this paper: CI, confidence interval; HR, hazard ratio.

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colorectal adenomas than with carcinoma.[11,16] For individuals with Lynch syndrome who undergo regular surveillance colonoscopies, colorectal adenomas are removed, which lowers their risks for colorectal carcinoma.[17,18] Therefore, it is very relevant to study whether the risk of developing colorectal adenomas is modifiable.

Methods

Population

Details of the prospective cohort of individuals with Lynch syndrome (the GeoLynch study) were described earlier.[19] In short, we identified subjects known to have a pathogenic mutation in one of the mismatch repair genes—as confirmed by a clinical genetics center—through the Netherlands Foundation for the Detection of Hereditary Tumors in Leiden, the Radboud University Nijmegen Medical Centre, and the University Medical Centre in Groningen, The Netherlands. Participants had to be Dutch-speaking, white, mentally competent to participate in the study, and between 18 and 80 years of age to be eligible for our study. Additionally, subjects with familial adenomatous polyposis, inflammatory bowel disease, a personal history of a complete proctocolectomy or colostomy, and those who were terminally ill were excluded.

A total of 713 eligible mutation carriers were invited to participate between July 2006 and July 2008, with the approval of their medical specialist. Of these, 73% (499 of 713) agreed to participate. Retrieval of medical and personal information was complete for 486 of 499 persons. One hundred of these 486 individuals were excluded from our analysis, as they did not have a colonoscopy during the follow-up of this study. These 100 individuals could not have been diagnosed with colorectal adenoma (the primary outcome of this study), as diagnosis requires completion of a colonoscopy. Smoking behavior and alcohol intake of these 100 individuals was comparable with the total cohort: there were 18 smokers, 38 former smokers, and 43 never smokers, and the median alcohol intake was 6 g/day (1–13 g/day). The total cohort for this study consisted of 386 subjects, who came from at least 161 families.

Approval for this study was obtained from the Medical Ethical Committee of the Radboud University Nijmegen Medical Centre. All participants provided written informed consent.

Exposure Assessment

Using structured questionnaires, we collected detailed self-reported information on smoking and possible confounding factors, eg, physical activity level, height, and weight. Smoking information included smoking status at recruitment (current, former, ever), duration of smoking, type of tobacco product (cigarettes, pipe, cigar), and number of cigarettes smoked per day. Because 224 of the 245 ever smokers in the cohort smoked cigarettes, we did not distinguish between type of tobacco in our analyses.

Information on alcohol intake was extracted from a self-administered, validated food frequency questionnaire.[20,21] In this questionnaire, subjects reported type and frequency of intake of alcoholic drinks during the past month. From this information, in combination with data from the Dutch food composition table,[22] we calculated intake of alcohol in grams per day. We used the data of all persons in the cohort to create tertiles of alcohol intake. Moreover, we evaluated whether the alcohol intake was below the recommendations set by the World Cancer Research Fund[12] of ≤1 glass per day for women (≤10 g alcohol) and of ≤2 glasses per day for men (≤20 g alcohol).

Outcome Data

Medical information was gathered via the participating centers. From the medical records, we extracted information on date and number of colonoscopies, colon operations, and incidence of cancer and adenomatous polyps before recruitment and during follow-up until July 2009. We ascertained detailed information about location, size, and histology for all documented polyps that occurred during follow-up from pathology records.

Data Analysis

The outcome of our analysis was the time to diagnosis of the first pathology-confirmed colorectal adenomatous polyp. Person-time started at the date participants had completed the questionnaires. For the subjects without an adenoma diagnosis, we censored the person-time at the date of diagnosis of colorectal or extracolonic cancer, metastasis or death, the date of the last colonoscopy during follow-up, whichever came first.

We used Cox proportional hazard regression to assess hazard ratios (HR) for the association between smoking and/or alcohol intake and development of colorectal adenomas. We used robust estimates of variance in the calculation of the 95% confidence interval (CI) to account for dependency of observations within families. The proportional hazard assumption was not violated, as evaluated by the goodness-of-fit test using Schoenfeld residuals ($P > .05$).

In additional analyses on number of cigarettes smoked per day, number of years smoked, and pack-years of smoking, we combined current and former smokers and excluded the never smokers. In test for trend analyses on those smoking variables, we assigned the median score for each tertile of the different smoking variables to each individual in this tertile. This new variable was included in the Cox model as a continuous variable.

To assess whether associations differed for prevalent vs incident colorectal adenoma cases, we stratified our analysis for history of colorectal adenomas or carcinomas. To assess multiplicative interaction between smoking and alcohol intake, we created categories based on both smoking (never, current, former smokers) and alcohol intake (low vs high intake, based on median split). We assessed the HR for development of colorectal adenomas within each category vs "never smokers and low alcohol intake" as reference category. To test for multiplicative interaction, we used a log likelihood ratio test that compared a model with interaction terms of alcohol × smoking to a model without these interaction terms.

We assessed whether the following variables affected the associations between smoking, alcohol, and colorectal adenomas: age (continuous), sex, history of colorectal adenomas or carcinomas (yes/no), number of colonoscopies during follow-up (continuous), colonic resection (yes/no), body mass index (continuous), nonsteroidal anti-inflammatory drug use (more or less than 1 time/week), education (categorical: high vs lower educated), type of gene mutation, physical activity level (categorical: high vs lower physically active), energy intake (continuous), red and processed meat intake (continuous), smoking (categorical: never/former/current, in the analyses of alcohol), alcohol (continuous, in the analyses of smoking). Covariates were included in multivariate models if correlated with the exposure (smoking or alcohol) and the outcome (colorectal adenomas) in univariate analyses; using backward elimination, covariates remained in the final models if they produced changes in the HR of ≥10%, while age, sex and number of colonoscopies were always included in the models. To test baseline differences between individuals with

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