Effects of Smoking and Antioxidant Micronutrients on Risk of Colorectal Cancer

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BACKGROUND & AIMS: **Antioxidant intake has been reported to increase the risk of colorectal cancer (CRC) for smokers, yet reduce the risk for nonsmokers. We investigated the association between tobacco smoking and risk of colon or rectal cancer, and whether dietary and supplemental intake of the antioxidant vitamins A, C, E, β-carotene, selenium, zinc, and manganese affects the risk of CRC among smokers.**

METHODS: **Data on smoking habits and antioxidant intake were analyzed for 54,208 participants in the Danish Prospective Diet, Cancer and Health Study. Of these participants, 642 were diagnosed with colon cancer and 348 were diagnosed with rectal cancer. Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazard models. Principal components were used to analyze intake of combinations of antioxidants.**

RESULTS: **Ever smoking increased the risk for CRC (hazard ratio, 1.19; 95% confidence interval, 1.03–1.37), especially for rectal cancer. Smoking for at least 20 years was associated with a 26% increase in risk of CRC, compared with never smokers, and smoking 20 g tobacco or more each day was associated with a 30% increase in risk. Smoking for more than 30 years, or more than 20 g tobacco each day, was associated with a 48% increase in risk of rectal cancer. We did not observe an interaction between smoking and antioxidant consumption on risk of CRC.**

CONCLUSIONS: **Tobacco smoking increases the risk for CRC. We did not observe that consumption of antioxidant micronutrients modulates the effects of smoking on CRC risk.**

Keywords: Cancer Risk Factor; Vitamins; Minerals; Cohort Study; Denmark.

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Consumption of dietary antioxidant carotenoids may modulate the effect of smoking on colorectal cancer (CRC) risk[1,2] and incident[3] or recurrent[4] colorectal adenomas, but results are inconsistent.[5,6]

Higher levels of reactive oxygen species (ROS) are observed in CRC tissue and adenomas than in adjacent healthy tissue.[7] When the amount of ROS exceeds the capacity of the antioxidant defense system in cells, oxidative stress may cause oxidative DNA damage[8] and initiate and promote carcinogenesis. Levels of DNA damages[9] and antioxidant enzyme activity[10] are systemically higher among patients with CRC or adenomas compared with healthy individuals. Hence, oxidative stress plays an important role in the pathogenesis of CRC. Tobacco smoking causes CRC[11] and adenomas.[12] Tobacco smoke is a rich source of ROS.[13]

The antioxidant enzymes glutathione peroxidase and superoxide dismutase are an essential part of the defense system against accumulation of ROS in all cellular compartments and extracellularly. Optimal glutathione peroxidase and superoxide dismutase enzyme activities are dependent on selenium,[14,15] zinc,[16] and manganese[17] intake.

Fruit and vegetable consumption reduces CRC risk,[18] possibly due to constituent parts as the antioxidants vitamin A, C, E, and β-carotene[9] scavenging free radicals, and thereby providing a diet-dependent protection system by preventing oxidative DNA damage in the epithelial cells of the intestinal tract. In addition, intake of antioxidant micronutrients decreases the level of inflammation,[19,20] an effect that may be modulated by smoking.[21] Systemic inflammation may be involved in the development of colorectal adenomas.[22]

Smoking is associated with a lower circulating concentration of antioxidants in the blood,[23] not only because of a lower

Abbreviations used in this paper: CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; PC, principal component; ROS, reactive oxygen species.

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dietary and supplemental antioxidant intake among smokers than among never smokers, but also because of smoke-induced oxidative stress resulting in an increased degradation or transformation of the circulating antioxidant micronutrients into biologically inactive components[2,24] or even into pro-oxidants.[1,25]

We investigated in a large prospective cohort whether smoking is associated with CRC risk, colon cancer risk, and rectal cancer risk, and if dietary and supplemental intake of 7 antioxidant micronutrients individually or in combination modulates an effect of smoking on CRC risk.

Materials and Methods

Study Population

The present study was approved by the Regional Ethical Committees on Human Studies (KF-01-345/93) and by the Danish Data Protection Agency (J. number 2008-41-2878). The Diet Cancer and Health study design has been described previously.[26] In brief, 57,053 individuals with no previous cancer diagnosis were recruited. At enrollment in 1993 to 1997, a detailed questionnaire of information on diet and lifestyle was collected. Cancer cases diagnosed between April 1995 and December 2009 were identified in the nationwide Danish Cancer Registry and the Danish Pathology Data Bank.

Exposure Variables

The following smoking variables were analyzed: status at enrollment; smoking of cigarettes, cigars, cheroots, and pipe exclusively or mixed; lifetime average smoking intensity; age when started smoking; and smoking duration. For former smokers, smoking cessation was a minimum of 1 year before enrollment. Participants with smoking cessation before the age of 20 were defined as former smokers with a null value for all smoking variables. Smoking duration was calculated as the time between age at which smoking started and age at smoking cessation for former smokers and age at enrollment for current smokers, excluding smoking pauses exceeding 1 year. Smoking intensity was reported for 4 periods of life: ages 20 to 29, 30 to 39, 40 to 49, and 50 years until enrollment. Lifetime average smoking intensity was calculated as a mean for smoking intensity at the 4 time periods, taking into account age of smoking start and cessation, enrollment age, and smoking pauses exceeding 1 year. A cigarette was equivalent to 1 g tobacco, a pipe or cheroot was equivalent to 3 g, and a cigar was equivalent to 4.5 g.

The following antioxidant micronutrients were analyzed: total, dietary, and supplemental intake of vitamins A, C, and E, β-carotene, selenium, zinc, and manganese. At baseline, participants reported an average intake of 192 different food items the year preceding enrollment within 12 possible categories ranging from never to 8 times or more per day. For each participant the average daily intake of dietary micronutrients and minerals was calculated by means of the software program Food Calc (Lauritsen J, Danish Cancer Society, Copenhagen, Denmark).[27] Supplement use was assessed through questions on brands, doses, and consumption frequency.

Statistical Analysis

Hazard ratios (HRs) for CRC, colon cancer, and rectal cancer were estimated by the Cox proportional hazards model. To control for differences between men and women, we allowed the models to have different baseline hazard functions for each sex. Age was the underlying time-scale by delayed entry (ie, each person contributed with person-time from age at baseline until age of event [CRC diagnosis]) or censoring (another cancer diagnosis than CRC, death, emigration, loss to follow-up evaluation, or end of follow-up period, whichever came first). For each potential predictor of the events, 2-sided 95% confidence intervals (CIs) and *P* values were calculated. Significant predictors were identified by means of the Wald test. Interactions between smoking and intake of each antioxidant micronutrient were compared and tested against models with only main effects using the likelihood-ratio test. The cut-off points for antioxidant micronutrients into high and low intake were the median value for intake of each antioxidant among the noncases. Heterogeneity between smoking or antioxidant intake and colon and rectal cancer risk was tested using a competing risk model based on the Lunn–McNeil approach. A significance level of 5% was applied. The statistical software program R (version 2.11.1; available at http://www.r-project.org) was used for all analyses.

Risk estimates were calculated as crude and adjusted for the following potential confounders: body mass index, physical activity during work and leisure time, use of nonsteroidal anti-inflammatory drugs, education, intake of red and processed meat, and alcohol consumption. Analyses on the association between smoking and CRC, colon cancer risk, and rectal cancer risk also included adjustments for dietary fiber, fruits, and vegetables; whereas analyses on antioxidant intake and CRC, colon cancer risk, and rectal cancer risk included adjustments for smoking. Body mass index refers to time at enrollment. The remaining confounders refer to the average over the year preceding enrollment into the cohort. Confounders selected are based on CRC risk factors established in the literature.

For all continuous predictors, the hypothesis of a linear association with risk of CRC was visualized using restricted cubic splines and tested by comparing models with linear effects with models with higher-order polynomials. All variables were associated linearly with CRC. The proportional hazard assumption was validated by means of test and graphic examination of the scaled Schoenfel residuals on function of time.[28]

To avoid redundancy provided by the correlated intake of the micronutrients, principal component (PC) analysis was applied, in which each PC is a linear combination of total, dietary, and supplemental intake, respectively, as described in the Supplementary Materials and Methods.

Results

Among the participants, 570 (1%) were diagnosed with cancer before enrollment. In addition, 2275 participants (4% of the cohort) were excluded because of missing or nonconcurrent information on smoking habits, intake of antioxidants, potential confounders, or date of cancer diagnosis. The excluded group of participants had the same distribution of sex, age, and