

## Current and Past Smoking Increases Risk for Colorectal Cancer

Hannan LM, Jacobs EJ, Thun MJ. The association between cigarette smoking and risk of colorectal cancer in a large prospective cohort from the United States. *Cancer Epidemiol Biomarkers Prev* 2009;18:3362–7.

### Study Overview

**Objective.** To evaluate the relationship between cigarette smoking and incident colorectal cancer, controlling for screening and multiple risk factors.

**Design.** Prospective cohort study.

**Setting and participants.** This study examined participants in the Cancer Prevention Study II (CPS-II) Nutrition Cohort, a prospective study examining the impact of environmental and lifestyle factors on cancer incidence and mortality in 184,187 American men and women. The CPS-II Nutrition Cohort is a subgroup of the CPS-II, a prospective mortality study of 1.2 million participants established in 1982 by the American Cancer Society. Participants in the CPS-II mortality cohort residing in 21 states with state cancer registries, aged 50 to 74 years in 1992, were invited to participate in the Nutrition Cohort. Subjects completed a mailed questionnaire upon entry regarding demographic, behavioral, environmental, occupational, medical, and dietary risk factors. Two-year follow-up questionnaires were sent to cohort members in 1997, 1999, 2001, 2003, and 2005 to update exposure information and elucidate new health problems, including cancer. The response rate among living participants was at least 89% for each of the follow-up questionnaires. The follow-up period ended on 30 June 2005 for this particular analysis.

**Methods.** The investigators ascertained cigarette smoking status (current, past, or never) at enrollment in 1992/1993, and updated it in successive questionnaires. At the baseline sur-

vey, participants were defined as lifelong nonsmokers if they smoked fewer than 100 cigarettes in their lifetime. Smoking status responses were inconsistent for 3731 women (5.1%) and 1813 men (3.5%) who reported never having smoked on a follow-up questionnaire after previously reporting current or former smoking. These subjects were considered by the investigators to be former smokers rather than lifelong nonsmokers in subsequent analyses. Individuals who indicated being a current smoker but did not indicate current daily cigarette consumption and had reported being a lifelong nonsmoker in all previous questionnaires were considered to be lifelong nonsmokers with the assumption that they checked the incorrect answer on one survey. The authors determined smoking initiation age at baseline for all current and former smokers by combining information from the 1982 CPS-II questionnaire and the 1992/1993 questionnaire.

The authors identified incident colon cancer through survey self-report and verified them in a number of ways. Most cases were verified through medical records ( $n = 1227$ ) or linkage to state cancer registries ( $n = 422$ ). Some cases ( $n = 313$ ) were identified through linkage with the National Death Index, with only 70 unable to be linked to state cancer registries to obtain a date of diagnosis. The investigators used the date of diagnosis as the date of death in these 70 colorectal cancer deaths.

The investigators constructed hazards models to examine the association between time-varying smoking status (current, former, never) and incident colorectal cancer. Further models examined the association between colorectal cancer and increasing years of cigarette smoking duration,

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years since initiation, and years since cessation. Multivariate models were adjusted for known and potential risk factors for colorectal cancer. These covariates included body mass index, education, family history of colorectal cancer, physical activity, race, vegetable consumption, red and processed meat consumption, multivitamin use, aspirin use, alcohol use, and history of colorectal endoscopy. Models that combined men and women also adjusted for sex. Models including women adjusted for hormone replacement therapy use (estrogen only, combined, and other). History of endoscopy use was not available until the 1997 questionnaire; participants were considered to have missing endoscopy information for the period 1992 to 1997.

The authors utilized Cox proportional hazards models to examine the association between cigarette smoking and incident colorectal cancer. They ran these models after stratification by age and adjusting for potential risk factors with time since enrollment. Individuals contributed person-time to the analysis until colorectal cancer diagnosis or censoring. The investigators defined censoring as one of the following: not returning a follow-up questionnaire, providing incomplete smoking information, dying of causes other than colorectal cancer, reaching the end of the follow-up time period, reporting unverified colorectal cancer, or being diagnosed with colorectal cancer in situ or nonadenocarcinoma colorectal cancer.

**Main results.** Overall, 86,402 men and 97,785 women participated in the Nutrition Cohort. The authors excluded 10,129 (11.7%) men and 13,501 (13.8%) women who reported cancer at the initial survey, except for nonmelanoma skin cancer. A total of 2864 (3.3%) men and 2795 (2.9%) women were lost to follow-up. In sum, 73,386 women and 51,365 men were included in the analysis. The authors identified a total of 1962 verified cases of invasive colorectal cancer (1006 men, 956 women) between 1992 and 2005. At baseline, 33,029 (64.3%) men and 32,102 (43.7%) women reported ever having smoked at least 100 cigarettes in their lifetime.

The cohort was predominantly white, and current smokers attained lower education than both former smokers and never smokers. Current smokers also reported higher consumption of alcohol and of red and processed meat, less physical activity, lower fruit/vegetable/fiber intake, less multivitamin use, and lower rates of colorectal endoscopy compared with never smokers.

In the overall analyses adjusting for all measured risk factors, the incidence of colorectal cancer was 30% higher in current than never smokers (hazard ratio [HR], 1.27; 95% confidence interval [CI], 1.06–1.52). This association was attenuated, though still statistically significant, among former smokers (HR, 1.23; 95% CI, 1.11–1.36). The association with current smoking was stronger for colon cancer (HR, 1.28;

95% CI, 1.04–1.57) than rectal cancer (HR, 0.97; 95% CI, 0.63–1.47).

The association between current smoking and colorectal cancer was strongest among those who had smoked for more than 50 years (HR, 1.38; 95% CI, 1.04–1.84) but the association was not statistically significant when compared to < 40 or 40–49 years of smoking duration (*P* trend = 0.052). However, the risk of colorectal cancer was decreased with increased time since cessation (*P* trend = 0.0003) and earlier age at cessation (*P* trend = 0.0014).

**Conclusion.** In a large prospective cohort of individuals followed for over a decade and controlled for other risk factors, current and former smoking increased the risk of incident colorectal cancers.

### Commentary

Cigarette smoking is well-known to be strongly associated with increased risks of nearly all aerodigestive cancers, including oral, pharynx, larynx, lung, esophageal, stomach, and pancreatic cancer [1]. However, recent comprehensive reviews of the evidence by the U.S. Surgeon General [1] and the International Agency for Research on Cancer (IARC) [2] concluded that there is insufficient evidence to link smoking to increased risk of colorectal cancer. These reviews concluded that the associations reported in the literature may be residual confounding by factors associated with smoking (ie, high alcohol intake and low physical activity), rather than indicative of independent causative associations.

In order to elucidate the association between smoking and colon cancer, the authors performed an analysis of a large prospective cohort of Americans followed biannually for over a decade. Controlling for 13 known or proposed sociodemographic, behavioral, medical, and dietary risk factors, the authors found that the incidence of colorectal cancers was higher in current and former smokers compared with lifelong nonsmokers. Furthermore, the risk was greatest among current smokers with the longest duration of smoking (> 50 years), and decreased among former smokers with longer time since cessation or earlier age of cessation.

This study provides compelling temporal and epidemiologic evidence of an association between smoking and colorectal cancer. The study was large, prospective, and well-conducted in an older age cohort with a high current and former smoking rate. The investigators minimized loss to follow-up and missing data, and they verified all but 70 of the 1962 colorectal cancers during the study. Further, the authors did an admirable job controlling for the many known and putative colorectal cancer risk factors that they had data for in their nutrition cohort. Few studies in the field have had access to this sort of prospective, time-varying, and

detailed covariate data. Moreover, the results are in line with an analysis of the association between smoking and colorectal cancer risk in the overall CPS-II cohort (HR, 1.32–1.41) [3] as well as in a recent large meta-analysis that found similar risk ratios (1.17–1.25) [4].

While the authors went to great lengths to minimize the potential for residual confounding, the possibility for this remains given the cohort nature of the study. Given the relatively low HR (1.2–1.5), this confounding is certainly a possibility. In addition, neither smoking status nor colorectal cancer was biochemically or pathologically verified, though it is unlikely that this lack of verification contributed systematic bias toward the findings.

### Applications for Clinical Practice

Health providers and policymakers should be aware of the increasingly persuasive literature that suggests an independent association between smoking and increased risk of colorectal cancer. Primary care physicians and gastroenter-

ologists should incorporate smoking cessation counseling and treatment into their colorectal cancer screening and prevention practices.

—Review by Asaf Bitton, MD

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