Smoking and Colorectal Cancer: Different Effects by Type of Cigarettes?

Margreet Lüchtenborg, Kami K.L. White, Lynne Wilkens, Laurence N. Kolonel, and Loïc Le Marchand

Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii, Honolulu, Hawaii

Abstract

Although smoking is suggested to be a risk factor for colorectal cancer, the evidence to date is conflicting and may be confounded. Moreover, the effect of tobacco smoke may vary by time since initiation, type of tobacco product, anatomic subsites, and among ethnic groups. Data were derived from two consecutive population-based case-control studies conducted among Caucasians, Japanese, Native Hawaiians, Filipinos, and Chinese in Hawaii, including 1,959 ethnicity-, sex-, and age-matched case-control pairs. A lifetime history of smoking for different tobacco products and information on other risk factors were obtained by in-person interviews. Odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were estimated using conditional logistic regression models with adjustment for potential confounders. Subjects who ever smoked were at an increased risk of colorectal cancer compared with never smokers (OR, 1.23; 95% CI, 0.99-1.52 for men and OR, 1.27; 95% CI, 1.01-1.59 for women). Increasing quartiles of pack-years over all tobacco products showed a clear dose-dependent association in men [for the highest quartile, Q4 (>40 pack-years) versus never smokers: OR, 1.48; 95% CI, 1.12-1.96; P_{trend} = 0.002]. The dose-response trend was also present in women [for the highest quartile, Q4 (>30 pack-years) versus never smokers: OR, 1.38; 95% CI, 0.91-1.95; P_{trend} = 0.04] and each ethnic group. There was a suggestion of a difference in risk with type of tobacco product. Non-filtered cigarettes increased risk of both colon and rectal cancer [for Q4 versus never smokers: OR, 1.59; 95% CI, 1.15-2.21; P_{trend} = 0.001 and OR, 1.84; 95% CI, 1.18-2.86; P_{trend} = 0.02, respectively], whereas filtered cigarettes seemed to increase risk of rectal but not colon cancer (OR, 1.37; 95% CI, 0.88-2.13; P_{trend} = 0.06 and OR, 1.05; 95% CI, 0.79-1.39; P_{trend} = 0.98, respectively). The effect of smoking was not limited to the distant past, and accumulated pack-years of smoking seemed to be more important than the time in which smoking occurred. The data from this large study corroborate previous reports of a positive association between smoking and colorectal cancer and suggest that the association may vary by type of cigarette. (Cancer Epidemiol Biomarkers Prev 2007;16(7):1341–7)

Introduction

Burning of tobacco produces numerous genotoxic compounds, including polycyclic aromatic hydrocarbons, heterocyclic aromatic amines, and *N*-nitroso compounds (1). These tobacco carcinogens may cause irreversible damage to the colorectal mucosa via the circulation after bronchoalveolar absorption into the bloodstream or by direct contact after ingestion with saliva (2).

In epidemiologic studies, cigarette smoking has been consistently associated with small and large colorectal adenomas, which are generally accepted as being precursor lesions for colorectal cancer (reviewed in refs. 2, 3). Thus, exposure to tobacco constituents may be an initiating factor for colorectal carcinogenesis. However, the results from studies on smoking and colorectal cancer have been less compelling. One explanation for this weaker link between smoking and colorectal cancer may lie in the extensive time lag between the smoking induced pre-oncogenic transformation of the colorectal epithelium and the occurrence of an adenocarcinoma. Evidence for this explanation came from the Health Professionals and Nurses' Health studies that showed an association between smoking and colorectal cancer only 30 to 40 years after smoking initiation (4, 5). Whereas a number of studies found an association between smoking and colorectal cancer (reviewed in refs. 2, 6-10), others did not (reviewed in refs. 2, 11, 12). Thus, both IARC and the U.S. Surgeon General reports concluded that at present, there is insufficient evidence for including colorectal cancer among tobacco-related malignancies, and that the associations observed in some studies may have been the result of residual confounding by alcohol or other risk factors (13, 14).

Generally, the associations with smoking have been observed for both colon and rectal cancer. However, several studies have shown an association solely for, or more strongly with, colon cancer (8, 10), or only for, or more strongly with, rectal cancer (15, 16). In recent studies in Japan, smoking was found not to be associated with overall colorectal cancer but to possibly be confined to increasing risk of rectal cancer, as reviewed by Mizoue et al. (17).

Most studies on smoking and risk of colorectal cancer to date have been limited to Caucasians. Because susceptibility to various carcinogens may vary by ethnicity, it seems plausible that there may be differences in the strength of the association between smoking and colorectal cancer among ethnic populations. Colorectal cancer incidence rates vary 4-fold among ethnic groups in the United States. Japanese and African Americans have higher incidence of colorectal cancer than non-Hispanic Whites.

To conduct a comprehensive analysis of tobacco smoking and colorectal cancer, we pooled data from two large successive population-based case-control studies that collected detailed smoking histories among Japanese, Caucasians, Native Hawaiians, Filipinos, and Chinese in Hawaii.

Received 6/28/06; revised 3/9/07; accepted 4/13/07.

Grant support: NIH grants P01-CA33619, R01 CA60987, CA72520, and CA104132 and National Cancer Institute/U.S. Department of Health and Human Services contract N01-CN55424.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Margreet Lüchtenborg, Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii, 1236 Lauhala Street, Suite 407, Honolulu, HI 96813. Phone: 808-586-7491. E-mail: mluchten@crch.hawaii.edu

doi:10.1158/1055-9965.EPI-06-0519

Materials and Methods

Patients from two consecutive case-control studies were identified in all main hospitals on the island of Oahu, HI through the rapid-reporting system of the Hawaii Tumor Registry, a member of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute.

In both studies, eligible cases were all Oahu residents under the age of 85, who had been newly diagnosed between January 1987 and December 1991 (first study) or January 1994 and August 1997 (second study), with a first, histologically confirmed primary adenocarcinoma of the colon or rectum. Only patients who had any percentage of Hawaiian ancestry or were at least 75% Japanese, Caucasian, Filipino, or Chinese were included. An in-person interview was completed for 63% (1,960 men and women) of the eligible cases of both studies. The main reasons for non-participation were refusal (16%), death before contact (13%), severe illness (6%), and inability to locate (3%).

Controls for both studies were selected randomly from a list of Oahu residents interviewed by the Hawaii State Department of Health as part of a heath survey among a 2% random sample of state households. The second study was supplemented with controls aged ≥65 years from Health Care Financing Administration participants on Oahu. One control was matched to each case on sex, ethnicity, and age (±2.5 years). The overall participation rate for the controls for both studies was 63%. Reasons for non-participation included refusal (24%), serious illness (6%), and inability to locate or death (6%). After exclusion of one case that Hawaii Tumor Registry reclassified as a non-case, a total of 1,959 age- and sex-matched case-control pairs were available for analysis.

In-person interviews were conducted at the subjects' homes by trained interviewers. On average, cases were interviewed within 1 year of diagnosis. Members of a case-control pair were generally interviewed by the same interviewer. The questionnaire included detailed information on demographics, including country of birth, number of years spent in the United States, and ethnicity of each grandparent; a quantitative food frequency questionnaire; a lifetime history of tobacco use, including type of tobacco ever smoked and, if smoked, dose smoked for each tobacco product type, age when started smoking, and if subjects stopped smoking, when and for which period; a lifetime history of alcohol, coffee, tea, and caffeinated soda use; a history of recreational sport activities since age 18; a personal history of various relevant medical conditions; a family history of colorectal cancer; a history of constipation and laxative use; a lifetime occupational history; information on height and weight at different ages; and, for women, a history of reproductive events and hormone use. The food frequency questionnaire used in both studies has been described previously and validated in this population (18). The questionnaire was designed to include all foods commonly consumed among the five main ethnic groups in Hawaii (Japanese, Caucasian, Filipino, Chinese, and Native Hawaiian), and to capture total energy intake.

Subjects were asked if they had ever smoked any of the tobacco products (non-filtered, filtered cigarettes, cigar, or pipe) for at least 6 months and were classified as never smokers if they had not, as current smokers if they smoked daily at date of diagnosis for cases and the date of interview for controls, or as former smokers if they had stopped smoking daily before that date. Lifetime tobacco use was computed as pack-years (number of tobacco products per day / 20 × years of smoking) for non-filtered and filtered cigarettes, cigars, and pipes separately for each tobacco product, and for all tobacco products combined, assuming equivalency among products (i.e., one cigarette = one cigar = one pipe-full).

For all analyses, we applied conditional logistic regression models to compute odds ratios (OR) and 95% confidence intervals (95% CI) for indicator variables for quartiles of exposure to tobacco products using never smokers as the reference group. In a preliminary analysis considering each sex separately, we compared models with both smoking intensity and duration to a model with pack-years. Because no statistical difference between the models was observed, and because most past studies have reported the effect of smoking using this combined variable, we used pack-years of tobacco as our main exposure variable in our analyses.

For pack-years of smoking, subjects were categorized into never smokers or quartiles based on the distribution of this variable among controls who smoked, separately for each sex and combined. Cut points for pack-years of all tobacco products were based on data from all controls, whereas cut points for pack-years of filtered and non-filtered cigarettes were based on controls who ever smoked the specific products. For subjects who smoked cigars and pipes, the single cut point was based on the median value of pack-years of cigars and pipes in controls who ever smoked these products. The number of females who smoked cigars or pipes was too small to analyze separately.

Adjustment variables included those variables that were found to be associated with colorectal cancer in these studies [i.e., family history of colorectal cancer, body mass index 5 years ago (only in models that included males), lifetime hours in recreational activities (only in models that included males) and egg, total calcium, non-starch polysaccharides from vegetables, methionine (only in models that included females), and alcohol (only in models that included males)]. Missing values for the adjustment variables gave rise to slightly diminished numbers of case-control pairs in the analyses (see tables). To assess the trend, the medians of each quartile were fitted as a continuous variable in the multivariate model, and the Wald test was used to test the significance. The likelihood ratio test was used to determine the significance of interactions between independent variables with respect to colorectal cancer.

The risk associated with each specific type of tobacco product was assessed in each sex by fitting a conditional logistic regression using indicator variables for each quartile of pack-years of filtered and of non-filtered cigarettes and indicator variables for two levels (<median; >median) of pack-years of cigar and pipe smoking for males, and a continuous variable for combined cigar and pipe pack-years for females. To test for differential risk associated with filtered and non-filtered cigarettes, a Wald test compared the variable estimates for the trend variables of pack-years for the two types of cigarettes, while controlling for cigar and pipe pack-years and other adjustment variables.

A similar analysis was carried out successively in Japanese, Caucasian, and Native Hawaiian participants. The numbers of Chinese and Filipino case-control pairs were too small to be analyzed separately. The risk associated with smoking was also assessed separately for colon and rectal cancer by fitting two separate conditional regression models to pairs where the case was diagnosed with cancer of the specific anatomic site. Subjects with both types of cancer were excluded from this subsite analysis. Additionally, we used polytomous regression to test for a difference in the risk estimates for colon and rectal cancer for pack-years of all tobacco and filtered and non-filtered cigarettes. In this analysis, pairs were broken, and matching variables (age, sex, and ethnicity) were included as adjustment variables and subjects with both types of cancer were excluded from the analysis.

We also investigated the effect of a possible latency period in two ways. First, we reran our main logistic models further adjusting for interval (in years) between initiation of smoking and diagnosis (for cases) or interview (for controls). Second, we estimated the risk of smoking over different time periods [i.e., 10-year increments in pack-years of smoking cumulative

Table 1. Characteristics of colorectal cancer cases and controls: median (interquartile range), except where noted

	Male		Female	
	Case (n = 1,143)	Control (n = 1,143)	Case (n = 816)	Control (n = 816)
Age, y	67 (60-73)	67 (60-73)	67 (58-73)	67 (58-73)
Ethnicity*				
Japanese	605 (53)	605 (53)	447 (55)	447 (55)
Caucasian	303 (27)	303 (27)	192 (24)	192 (24)
Native Hawaiian	116 (10)	116 (10)	85 (10)	85 (10)
Filipino	70 (6)	70 (6)	50 (6)	50 (6)
Chinese	49 (4)	49 (4)	42 (5)	42 (5)
Family history*,†	158 (14)	87 (8)	129 (16)	60 (7)
Lifetime recreational activities, h	3,264 (288-10,080)	5,184 (1,008-12,348)	384 (0-2,880)	624 (0-3,384)
Body mass index 5 y ago, kg/m^2	25 (23-28)	24 (22-27)	23 (21-26)	23 (21-26)
Dietary intake‡				
Energy, kcal/d	2,338 (1,796-3,035)	2,119 (1,657-2,712)	1,756 (1,321-2,228)	1,650 (1,270-2,120)
NSP from vegetables, g/d	3.0 (1.8-4.4)	3.6 (2.2-5.0)	3.0 (2.1-4.1)	3.5 (2.3-5.0)
Total calcium§, mg/d	718 (507-1,108)	782 (543-1,460)	763 (489-2,307)	984 (510-3,998)
Alcohol, g/d	2.3 (0.1-24)	1.3 (0.1-16)	0.1 (0-0.4)	0.1 (0-0.3)
Eggs, g/d	18 (10-36)	15 (7-27)	12 (5-22)	8 (4-17)
Methionine, g/d	1.8 (1.6-2.1)	1.8 (1.6-2.1)	1.4 (1.2-1.6)	1.4 (1.3-1.6)
Smoking characteristics*				
Never smoker	298 (26)	380 (33)	489 (60)	529 (65)
Former smoker	615 (54)	584 (51)	214 (26)	185 (23)
Current smoker	230 (20)	179 (16)	113 (14)	101 (12)
Age started‖	18 (16-20)	18 (16-20)	20 (18-25)	20 (18-25)
Time since smoking commenced, y‖	48 (41-54)	48 (41-55)	42 (33-50)	41 (33-49)
Amount‖, cigarettes/pipes/cigars per day	20 (15-36)	20 (11-30)	15 (8-20)	10 (6-20)
Duration‖, y	33 (22-43)	31 (19-42)	31 (18-43)	28 (13-37)
Pack-years				
All tobacco products‖	36 (17-59)	28 (12-48)	20 (7-40)	15 (5-35)
Non-filtered cigarettes¶	16 (7-33)	11 (5-24)	9 (3-20)	5 (1,11)
Filtered cigarettes¶	28 (14-45)	23 (10-40)	19 (7-35)	16 (7-30)
Cigars¶	2 (1-6)	2 (0-5)	3 (2-3)	2 (2-4)
Pipe¶	1 (0-4)	1 (0-4)	**	**

Abbreviation: NSP, non-starch polysaccharides.
*n (%).
†Family history of colorectal cancer among parents and siblings.
‡Dietary intakes (except energy) are calorie adjusted.
§From foods and supplements.
‖Among smokers.
¶Among smokers of specific tobacco product.
**No data available, only two women reported pipe smoking.

up to defined periods (0, 5, 10, 20, 30, 40, and 50 years before diagnosis for cases or interview for controls)], using adjusted conditional logistic regression models. Models including the accumulated pack-years over a specified time period were adjusted for pack-years accumulated from that time to diagnosis or interview to account for the confounding effect of duration on time since smoking initiation. To assess risk over these periods by type of cigarette, accumulated pack-years of either type were included in a single model.

Results

Table 1 compares cases and controls by demographic characteristics and a number of dietary and smoking variables by sex. Family history of colorectal cancer among a first-degree relative was more common in cases than controls. The median caloric intake was greater in cases than controls, as was the median body mass index 5 years before the interview in men. Lifetime recreational physical activity was lower in cases than controls. Cases had a lower median intake of non-starch polysaccharide from vegetables and of calcium than controls. Male cases seemed to consume more alcohol than controls; however, overall intake was low. On average, cases consumed more eggs than controls. There were fewer never smokers among cases than controls; and among female ever smokers, cases smoked more of each tobacco product per day, and cases in both sexes smoked for a longer period of time, compared with controls.

Adjusted colorectal cancer ORs are presented for smoking status in Table 2 and show that both men and women who ever smoked tended to be at a slightly increased risk, compared with never smokers. No appreciable difference was observed between current and former smokers (likelihood ratio test comparing models with ever smoker indicator to former and current smokers indicators: P = 0.48 in men and P = 0.51 in women). In men, smoking over 30 cigarettes per day was associated with an increased risk of colorectal cancer, but there was no clear effect of duration of smoking. In women, on the other hand, smoking duration conferred a clearer risk of colorectal cancer than smoking intensity. The results presented in Table 2 do not show an increased risk of colorectal cancer with prolonged time since smoking initiation when adjusted for duration.

Table 3 shows adjusted colorectal cancer ORs for pack-years, overall and for each tobacco product, mutually adjusted for each other. Compared with never smokers, increasing quartiles of pack-years over all tobacco products showed a clear dose-dependent association in men, but a dose-response trend was less clear in women. These associations seemed to be mostly due to the effect of smoking non-filtered cigarettes (for highest quartile of pack-years of non-filtered cigarettes compared with never smokers: OR, 1.73; 95% CI, 1.27-2.34 for men and OR, 2.23; 95% CI, 1.25-3.98 for women). Smoking of cigars also contributed to the association with colorectal cancer in men. The risk of colorectal cancer associated with smoking of all tobacco products and filtered and non-filtered cigarettes did not differ between men and women ($P_{interaction}$ = 0.64 for

Table 2. Colorectal cancer risk by smoking status, intensity, duration, and latency period

	Male (1,112 case-control pairs)		Female (815 case-control pairs)	
	*n**	OR (95% CI)†	*n**	OR (95% CI)†
Never smoker (reference group)	363/282	1.00	529/489	1.00
Smoking status				
Former smoker	574/607	1.21 (0.97-1.50)	185/213	1.32 (1.02-1.71)
Current smoker	175/223	1.32 (0.99-1.76)	101/113	1.17 (0.85-1.62)
Intensity (cigarettes per day)‡				
Males Females				
1-10 1-5	175/159	0.94 (0.62-1.43)	54/64	1.88 (1.02-3.45)
11-20 6-10	275/282	1.00 (0.67-1.49)	81/66	1.06 (0.58-1.94)
21-30 11-20	140/139	0.89 (0.56-1.42)	90/110	1.68 (0.90-3.15)
>30 >20	156/247	1.51 (0.99-2.29)	61/85	1.73 (0.87-3.43)
P_{trend}§		0.007		0.33
Duration (y)‡				
1-10	84/74	1.12 (0.70-1.80)	55/53	1.74 (0.95-3.16)
11-20	130/113	0.96 (0.63-1.48)	47/44	1.56 (0.80-3.03)
21-30	153/177	1.24 (0.80-1.91)	64/65	1.76 (0.90-3.43)
31-40	168/204	1.22 (0.78-1.91)	66/71	1.80 (0.85-3.80)
>40	212/260	1.18 (0.71-1.96)	54/92	3.17 (1.40-7.19)
P_{trend}§		0.39		0.06
Time since smoking commenced (y)‖				
1-30	49/47	1.18 (0.61-2.32)	52/51	1.54 (0.75-3.13)
31-40	119/145	1.14 (0.70-1.87)	89/93	1.35 (0.74-2.46)
41-50	284/292	1.07 (0.71-1.59)	90/103	1.23 (0.68-2.24)
>50	297/344	1.05 (0.68-1.62)	55/79	1.64 (0.82-3.30)
P_{trend}§		0.86		0.32

*Number of controls/number of cases. The analysis of smoking intensity and duration gave rise to missing values for this variable in three male and one female subjects. These case-control pairs were excluded from the analysis.
†OR and 95% CI are estimated by conditional logistic regression, matched on age and ethnicity, compared with never smokers, and adjusted for family history of colorectal cancer, body mass index 5 y ago (males only), lifetime hours in recreational activities (males only) and egg, total calcium, non-starch polysaccharides from vegetables, methionine (females only), and alcohol (males only) intake. All levels of the smoking characteristics are compared against never smokers. Separate models were run for intensity, duration, and time since smoking commenced.
‡Further adjusted for smoking status.
§P_{trend} is estimated by fitting the medians of each category as a continuous variable in the multivariate model.
‖Further adjusted for smoking status and duration.

pack-years of all tobacco). Therefore, both sexes were combined in subsequent analyses.

Table 4 presents the results of the same analyses in each of the three larger ethnic groups. Similar associations with colorectal cancer were observed or suggested in Japanese, Caucasians, and Native Hawaiians for pack-years of all tobacco products and non-filtered cigarettes. A direct association with colorectal cancer was also seen with pack-years of filtered cigarettes in Caucasians. No heterogeneity in ORs was observed between ethnicity and overall pack-years

Table 3. Colorectal cancer risk by sex and quartiles of pack-years of all tobacco products and of filtered and non-filtered cigarettes

	Q1*		Q2		Q3		Q4		P_{trend}†
	n‡	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	
Males (1,109 case-control pairs)									
All tobacco	185/144	1.02 (0.76-1.36)	186/187	1.14 (0.86-1.51)	186/224	1.33 (1.00-1.76)	189/272	1.48 (1.12-1.96)	0.002
Filtered cigarettes	132/116	0.95 (0.68-1.32)	139/132	0.91 (0.67-1.26)	134/162	1.11 (0.81-1.51)	138/173	1.06 (0.79-1.42)	0.63
Non-filtered cigarettes	135/115	1.03 (0.75-1.42)	135/116	0.91 (0.65-1.28)	136/168	1.30 (0.96-1.78)	125/207	1.73 (1.27-2.34)	0.0002
Cigars	38/46	1.30 (0.96-1.78)	39/62	1.60 (1.00-2.58)					0.04
Pipes	46/44	0.89 (0.55-1.44)	34/50	0.99 (0.61-1.60)					0.98
Females (814 case-control pairs)									
All tobacco	72/74	1.33 (0.91-1.95)	73/57	0.81 (0.54-1.22)	68/95	1.48 (1.03-2.13)	73/99	1.38 (0.91-1.95)	0.04
Filtered cigarettes	62/70	1.42 (0.95-2.12)	61/45	0.69 (0.45-1.07)	62/81	1.32 (0.88-1.97)	61/85	1.17 (0.78-1.76)	0.35
Non-filtered cigarettes	27/21	0.79 (0.43-1.49)	26/32	1.06 (0.58-1.92)	27/37	1.33 (0.74-2.42)	25/55	2.23 (1.25-3.98)	0.004

NOTE: OR and 95% CI are estimated by conditional logistic regression, matched on age and ethnicity, and adjusted for family history of colorectal cancer, body mass index 5 y ago (males only), lifetime hours in recreational activities (males only) and egg, total calcium, non-starch polysaccharides from vegetables, methionine (females only), and alcohol (males only) intake. Two separate models were run in each sex, both with never smokers as the reference category: one model included indicator variables for each quartile of pack-years of all tobacco products, and the other model included indicator variables for each quartile of pack-years for each type of cigarettes (filtered and non-filtered cigarettes), and in men, levels (<median; >median) of pack-years of cigars and pipes. In women, the latter model was further adjusted for pack-years of cigars and pipes (continuous).
*Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile. Based on male controls who smoked, the quartile cut points (25th-75th percentile) for total pack-years and pack-years of filtered and non-filtered cigarettes are as follows: >0-12, >12-28.3, >28.3-48, and >48 for all tobacco; >0-10.4, >10.4-23, >23-40, and >40 for filtered cigarettes; and >0-4.8, >4.8-11, >11-24 and >24 for non-filtered cigarettes. Median cut points for pipes and cigars are 1.8 pack-years of cigars and 1.0 pack-years of pipes. Based on female controls who smoked, the quartile cut points (25th-75th percentile) for total pack-years and pack-years of filtered and non-filtered cigarettes are as follows: >0-5.3, >5.3-15, >15-34.7, and >34.7 for all tobacco; >0-7, >7-15.6, >15.6-30, and >30 for filtered cigarettes; and >0-1.4, >1.4-5, >5-11, and >11 for non-filtered cigarettes.
†P_{trend} is estimated by fitting the medians of each quartile as a continuous variable in the multivariate model.
‡Number of controls/number of cases (never smokers: 363/282 and 528/489 for men and women, respectively).

Table 4. Colorectal cancer risk by ethnicity and quartiles of pack-years of all tobacco products and of filtered and non-filtered cigarettes

	Q1*		Q2		Q3		Q4		P_{trend} †
	n ‡	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	
Japanese (1,018 case-control pairs)									
All tobacco	108/96	1.09 (0.78-1.51)	141/121	0.89 (0.65-1.21)	128/165	1.34 (0.99-1.82)	135/184	1.27 (0.94-1.74)	0.06
Filtered cigarettes	95/99	1.22 (0.85-1.75)	97/111	1.09 (0.77-1.54)	116/135	1.12 (0.80-1.57)	104/112	0.95 (0.68-1.34)	0.58
Non-filtered cigarettes	89/73	0.83 (0.57-1.21)	77/75	0.97 (0.64-1.49)	91/102	1.15 (0.78-1.69)	63/123	1.96 (1.29-2.98)	0.004
Caucasian (485 case-control pairs)									
All tobacco	76/63	1.17 (0.77-1.78)	64/77	1.50 (0.97-2.31)	70/72	1.47 (0.94-2.28)	79/123	1.92 (1.27-2.92)	0.003
Filtered cigarettes	61/44	0.74 (0.46-1.21)	56/55	0.95 (0.58-1.54)	37/46	1.35 (0.79-2.31)	54/86	1.53 (0.97-2.40)	0.04
Non-filtered cigarettes	46/42	1.06 (0.64-1.77)	48/40	1.01 (0.59-1.73)	39/54	1.54 (0.92-2.58)	63/88	1.42 (0.90-2.24)	0.09
Native Hawaiian (191 case-control pairs)									
All tobacco	30/22	0.88 (0.40-1.90)	32/32	1.08 (0.55-2.15)	33/18	0.60 (0.28-1.26)	24/51	1.99 (0.97-4.07)	0.07
Filtered cigarettes	23/20	0.94 (0.41-2.14)	33/23	0.62 (0.30-1.29)	21/25	1.06 (0.48-2.33)	26/32	1.01 (0.50-2.04)	0.77
Non-filtered cigarettes	23/19	0.94 (0.40-2.18)	17/15	0.91 (0.34-2.42)	10/17	1.92 (0.61-6.11)	13/24	2.33 (0.93-5.83)	0.05

NOTE: OR and 95% CI are estimated by conditional logistic regression, matched on age and sex, and adjusted for family history of colorectal cancer, body mass index 5 y ago, lifetime hours in recreational activities as well as egg, total calcium, non-starch polysaccharides from vegetables, methionine, and alcohol intake. Two separate models were run in each ethnicity, both with never smokers as the reference category: one model included indicator variables for each quartile of pack-years of all tobacco products, and the other model included indicator variables for each quartile of pack-years for each type of cigarettes (filtered and non-filtered) and was further adjusted for pack-years of cigars and pipes (continuous).

*Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile. Based on controls who smoked, the quartile cut points (25th-75th percentile) for total pack-years are as follows: >0-9.8, >9.8-24.6, >24.6-44, and >44; for pack-years of filtered cigarettes: >0-9.5, >9.5-21, >21-38, and >38; for pack-years of non-filtered cigarettes: >0-4, >4-10, >10-22, and >22.

†P_{trend} is estimated by fitting the medians of each quartile as a continuous variable in the multivariate model.

‡Number of controls/number of cases (never smokers: 506/452, 196/150 and 72/68 for Japanese, Caucasians, and Native Hawaiians, respectively).

($P_{interaction}$ = 0.68) or between ethnicity and pack-years of non-filtered or filtered cigarettes ($P_{interaction}$ = 0.50 and 0.52, respectively).

As presented in Table 5, the ORs for total pack-years seemed greater for the rectum than the colon in men and women combined. This pattern was observed in both sexes and all ethnic groups (data not shown). However, a polytomous regression analysis showed that the difference in OR by colorectal subsite treating total pack-years as a continuous variable was not significant (P = 0.52). There was also no difference in risk for proximal versus distal colon tumors (P = 0.16). When considering type of tobacco product and risk of colon and rectal cancer, an effect of pack-years of filtered cigarettes was suggested for the risk of rectal but not colon cancer. The risk associated with pack-years of non-filtered cigarettes seemed to be similar for colon and rectal cancer (Table 5). Polytomous regression analysis showed absence of heterogeneity between the risk of colon and rectal cancer (P = 0.82 for pack-years of non-filtered cigarettes and P = 0.71 for pack-years of filtered cigarettes).

Our data suggest a difference in the risk conferred by smoking filtered or non-filtered cigarettes. Because subjects could smoke either or both types of cigarettes, a careful examination of the results is warranted. The percentage of smokers consuming both types of cigarettes was substantial (45% of smokers). However, the correlation between pack-years of filtered and non-filtered cigarettes in smokers was low (r = 0.08 in men and r = 0.03 in women). The risk associated with filtered and non-filtered cigarettes was found to be significantly different in the models in Table 3 for men (P = 0.005) and women (P = 0.03).

Because non-filtered cigarettes were smoked in the more distant past, we explored whether the time elapsed since smoking initiation could explain the observed difference between the types of cigarette smoked. Because the correlations between time since smoking initiation and pack-years were low (r = 0.01 and r = 0.12 for filtered cigarettes and r = 0.33 and r = 0.32 for non-filtered cigarettes in men and women, respectively), we further adjusted all models assessing risk of pack-years by type of cigarette for this variable. The

Table 5. Colorectal cancer risk by anatomical subsite and quartiles of pack-years of all tobacco products and of filtered and non-filtered cigarettes

	Q1*		Q2		Q3		Q4		P_{trend} †
	n ‡	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	
Colon (1,349 case-control pairs)									
All tobacco	175/154	1.14 (0.87-1.50)	197/171	0.92 (0.70-1.20)	179/199	1.18 (0.90-1.54)	191/278	1.39 (1.07-1.81)	0.01
Filtered cigarettes	134/139	1.20 (0.89-1.62)	154/137	0.87 (0.65-1.16)	134/157	1.08 (0.79-1.46)	145/172	1.05 (0.79-1.39)	0.98
Non-filtered cigarettes	129/108	0.90 (0.66-1.23)	115/99	0.92 (0.65-1.31)	109/148	1.38 (1.00-1.92)	111/176	1.59 (1.15-2.21)	0.001
Rectum (573 case-control pairs)									
All tobacco	76/64	1.13 (0.75-1.69)	63/85	1.78 (1.18-2.70)	86/92	1.41 (0.97-2.07)	72/121	2.12 (1.43-3.14)	0.0003
Filtered cigarettes	62/47	0.71 (0.44-1.13)	49/66	1.25 (0.80-1.96)	66/78	1.14 (0.74-1.75)	51/76	1.37 (0.88-2.13)	0.06
Non-filtered cigarettes	42/50	1.55 (0.93-2.56)	42/51	1.57 (0.93-2.65)	42/46	1.37 (0.80-2.34)	54/89	1.84 (1.18-2.86)	0.02

NOTE: OR and 95% CI are estimated by conditional logistic regression, matched on age, sex and ethnicity, and adjusted for family history of colorectal cancer, body mass index 5 y ago, lifetime hours in recreational activities as well as egg, total calcium, non-starch polysaccharides from vegetables, methionine, and alcohol intake. Two separate models were run for each subsite, both with never smokers as the reference category: one model included indicator variables for each quartile of for pack-years of all tobacco products, and the other model included indicator variables for each quartile of pack-years for each type of cigarettes (filtered and non-filtered) and was further adjusted for pack-years of cigars and pipes (continuous).

*Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile. Based on controls who smoked, the quartile cut points (25th-75th percentile) for total pack-years are as follows: >0-9.8, >9.8-24.6, >24.6-44, and >44; for pack-years of filtered cigarettes: >0-9.5, >9.5-21, >21-38, and >38; for pack-years of non-filtered cigarettes: >0-4, >4-10, >10-22, and >22.

†P_{trend} is estimated by fitting the medians of each quartile as a continuous variable in the multivariate model.

‡Number of controls/number of cases (never smokers: 607/547 and 276/211 for males and females, respectively).

Table 6. Colon and rectal cancer risk by time period before diagnosis for cases and interview for controls

Pack-years, cumulative up to	OR* (95% CI)		
	All tobacco products	Filtered cigarettes	Non-filtered cigarettes
Colon (1,349 case-control pairs)			
0 y ago	1.05 (1.01-1.08)	1.00 (0.97-1.05)	1.12 (1.05-1.19)
5 y ago	1.05 (1.01-1.09)	1.01 (0.96-1.06)	1.11 (1.04-1.19)
10 y ago	1.06 (1.01-1.10)	1.01 (0.95-1.08)	1.11 (1.04-1.19)
20 y ago	1.05 (1.00-1.11)	0.98 (0.90-1.07)	1.11 (1.03-1.20)
30 y ago	1.04 (0.96-1.13)	0.90 (0.79-1.03)	1.09 (0.99-1.20)
40 y ago	1.03 (0.91-1.17)	0.75 (0.57-0.98)	1.04 (0.90-1.19)
50 y ago	1.08 (0.84-1.38)	0.84 (0.40-1.74)	0.98 (0.76-1.27)
Rectum (573 case-control pairs)			
0 y ago	1.10 (1.05-1.16)	1.10 (1.03-1.17)	1.11 (1.03-1.19)
5 y ago	1.10 (1.03-1.16)	1.09 (1.00-1.19)	1.09 (1.00-1.18)
10 y ago	1.10 (1.03-1.17)	1.11 (0.78-1.59)	1.07 (0.99-1.17)
20 y ago	1.09 (1.00-1.18)	1.08 (0.93-1.24)	1.08 (0.98-1.20)
30 y ago	1.05 (0.94-1.17)	0.96 (0.76-1.20)	1.07 (0.94-1.21)
40 y ago	1.00 (0.85-1.18)	0.86 (0.56-1.32)	1.01 (0.84-1.21)
50 y ago	1.05 (0.76-1.43)	0.85 (0.23-3.15)	1.05 (0.75-1.47)

*OR and 95% CI are estimated using conditional logistic regression and represent the risk associated with an increment of 10 pack-years in the specified time period, and are adjusted for pack-years accumulated from that time to diagnosis or interview, as well as for family history of colorectal cancer, body mass index 5 y ago, lifetime hours in recreational activities and egg, total calcium, non-starch polysaccharides from vegetables, methionine and alcohol intake, and matched on age, sex, and ethnicity. Fourteen separate models were run for each subsite (seven for pack-years of all tobacco products and seven for pack-years of filtered and non-filtered cigarettes), which were modeled together.

adjusted ORs for pack-years of filtered and non-filtered cigarettes remained virtually unchanged, and likelihood ratio tests comparing the adjusted models to the unadjusted models revealed no significant differences (overall $P = 0.97$).

Finally, to investigate further whether a lag time effect exists for the risk of smoking on colorectal cancer in our data, the adjusted ORs for colon and rectal cancer for increments of 10 pack-years for various time periods cumulative from the date of interview (for controls) or diagnosis (for cases) up to time of smoking initiation are shown in Table 6. For colon cancer, the ORs were significantly elevated in all tobacco products and in all time periods except for the ones in the most remote past. A similar pattern was observed in rectal cancer with ORs that were slightly stronger. Very similar gradually increasing risk estimates were found with the more recent time periods of smoking non-filtered cigarettes for colon cancer. Pack-years of both types of cigarettes were associated with an increased risk of rectal cancer in the more recent time periods.

Discussion

We observed an increased risk of colorectal cancer with increasing numbers of pack-years smoked in a large data set that combined two consecutive case-control studies carried out in the ethnically diverse population of Hawaii. Overall, risk did not differ significantly between subsites of the colorectum. However, there was the suggestion of a difference in risk by type of tobacco. Non-filtered cigarettes and possibly cigars increased risk of both colon and rectal cancers, whereas filtered cigarettes only slightly increased the risk of rectal cancer.

Controversy over whether or not tobacco smoking should be considered as a risk factor for colorectal cancer is ongoing. Recent expert reviews judged the currently available evidence for smoking and colorectal cancer to be equivocal (13, 14). It was argued that generally, low risk ratios are reported, and there is potential for confounding by consumption of alcohol or other established risk factors for colorectal cancer (14, 19). In our analysis, we adjusted for intake of alcohol in men, which led to attenuated risk estimates for quartiles of pack-years of smoking all tobacco products. The OR for highest quartile of pack-years versus never smokers in men, not adjusted for alcohol, was 1.64 (95% CI, 1.25-2.15), whereas the OR adjusted for alcohol was 1.49 (95% CI, 1.13-1.97). Because alcohol intake is reasonably well measured by food frequency questionnaires (20), it is unlikely that residual confounding by alcohol intake would explain the association with smoking in our data. Indeed, the consumption of alcohol in women was low in our population, and the association with pack-years in this group was of similar magnitude as in men. After adjustment for other potential confounders, such as physical activity and calcium intake, the risk estimates were still significant. Thus, tobacco smoking seems to be an appreciable risk factor for colorectal cancer.

Some limitations of the present study need to be considered. Information on dietary and lifestyle habits referred to 3 years before onset of symptoms (cases) and interview (controls) to minimize a reflection of adaptations of habits due to underlying disease. However, information on smoking habits was collected for the time up until the date of diagnosis for cases and interview date for controls. Tobacco smoking is not viewed as a risk factor for colorectal cancer by the general public; thus, although the information was obtained retrospectively, differential misclassification seems unlikely. Generally, the same interviewer interviewed both the case and the matched control, thereby also reducing the chances of differential misclassification. This analysis includes subjects from two consecutive case-control studies. The designs of these studies were very similar, thus allowing us to combine their data, and give rise to a large sample size.

The biological mechanisms underlying the association of tobacco smoking and colorectal cancer may involve the exposure of the epithelium of the large bowel to carcinogens either via the blood circulation after absorption of these chemicals in the lung or after ingestion of saliva contaminated by tobacco smoke. Tobacco smoke contains at least 50 carcinogenic components, the most genotoxic of which are thought to be the polycyclic aromatic hydrocarbons, heterocyclic aromatics amines, and *N*-nitroso compounds (21). These compounds require bioactivation before they can form adducts with DNA. Polycyclic aromatic hydrocarbons are activated mainly by extra-hepatic enzymes [e.g., cytochrome *P*450 (CYP1A1) and microsomal epoxide hydrolase (mEH)], whereas heterocyclic aromatics amines are activated in the liver by CYP1A2, and *N*-nitroso compounds are activated by hepatic CYP2E1 and CYP2A6 (22). Polymorphisms in *mEH* have been associated with colorectal cancer or adenoma in the presence of smoking and high intakes of cooked meat (23, 24), and the *Msp*I *CYP1A1* variant rare allele gives rise to increased levels of the main enzyme involved in the activation of polycyclic

aromatic hydrocarbons and was found to be related to higher risk for colon or rectal cancer (10, 25, 26). Polymorphisms in *CYP2E1* have also been associated specifically with rectal cancer, and not colon cancer, in individuals with a high exposure to *N*-nitrosamines from diet (27).

In this study, detailed information on smoking history (age started smoking, duration, age quit smoking, duration of quitting, and smoking intensity) was obtained with a questionnaire that differentiated between smoking of filtered and non-filtered cigarettes, cigars, and pipe. To our knowledge, no other studies of tobacco exposure and colorectal cancer have taken into account the type of cigarette smoked. Our data suggest that there might be a difference in the risk of colorectal cancer by type of cigarettes. In both sexes, the association of smoking with colorectal cancer was limited to non-filtered cigarettes. This difference in effect was observed for colon cancer and in Japanese and Hawaiians. However, smoking filtered cigarettes was suggested to increase risk of rectal cancer.

If confirmed, a more pronounced risk of developing colon or rectal cancer with non-filtered cigarettes, compared with filtered cigarettes, may be attributed to the greater likelihood to ingest tobacco smoke condensates from non-filtered cigarettes. Furthermore, higher exposure to carcinogenic polycyclic aromatic hydrocarbons may occur with non-filtered cigarettes due to a less complete combustion of tobacco in non-filtered than in filtered cigarettes (1). However, the change in tobacco blends and the addition of stems and ribs in the manufacturing of cigarettes that occurred in more recent decades is thought to have led to an increase in the nitrosamine content of tobacco smoke. Thus, in more recent years, cigarettes not only acquired a filter tip but resulted in increased exposure to *N*-nitroso compounds and to lower levels of polycyclic aromatic hydrocarbons (1). We found a nonsignificant positive association of filtered cigarettes with rectal cancer, but not with colon cancer, and this association was observed up to 20 years before diagnosis or interview. This may reflect the increased exposure to *N*-nitrosamines through smoking cigarettes in more recent years because a similar site specificity for rectal cancer versus colon cancer has been observed for exposure to *N*-nitrosamines from foods (28).

A reason suggested for the less clear association between tobacco smoking and risk of colorectal cancer, compared with adenoma, is that a substantial time lag (of as long as 35 years) may be required for observing a relation between smoking and colorectal cancer, which possibly reflects the time involved in the formation of a cancerous lesion (2). We did not find any evidence in support of a latency period for the effect of smoking on colorectal cancer risk. There was no trend or cutoff point observed for risk associated with time since smoking initiation. Moreover, our detailed lag analysis did not suggest that the association with pack-years was limited to smoking in the distant past. In contrast, associations were strongest in the more recent past, suggesting that total accumulated pack-years of tobacco may be more important than the time in which smoking occurred.

In summary, the data from this large study corroborate past reports of an association between smoking and colorectal cancer and suggest that there may be a difference in the risk associated with smoking of filtered and non-filtered cigarettes. More research on this point is warranted.

References

1. Hoffmann D, Hoffmann I. The changing cigarette, 1950-1995. J Toxicol Environ Health 1997;50:307–64.
2. Giovannucci E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2001;10:725–31.
3. Giovannucci E, Martinez ME. Tobacco, colorectal cancer, and adenomas: a review of the evidence. J Natl Cancer Inst 1996;88:1717–30.
4. Giovannucci E, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U S. women. J Natl Cancer Inst 1994;86:192–9.
5. Giovannucci E, Rimm EB, Stampfer MJ, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. men. J Natl Cancer Inst 1994;86:183–91.
6. Chyou PH, Nomura AM, Stemmermann GN. A prospective study of colon and rectal cancer among Hawaii Japanese men. Ann Epidemiol 1996;6:276–82.
7. Colangelo LA, Gapstur SM, Gann PH, Dyer AR. Cigarette smoking and colorectal carcinoma mortality in a cohort with long-term follow-up. Cancer 2004;100:288–93.
8. Limburg PJ, Vierkant RA, Cerhan JR, et al. Cigarette smoking and colorectal cancer: long-term, subsite-specific risks in a cohort study of postmenopausal women. Clin Gastroenterol Hepatol 2003;1:202–10.
9. Luchtenborg M, Weijenberg MP, Kampman E, et al. Cigarette smoking and colorectal cancer: APC mutations, hMLH1 expression, and GSTM1 and GSTT1 polymorphisms. American Journal Of Epidemiology 2005;161:806–15.
10. Slattery ML, Samowtiz W, Ma K, et al. CYP1A1, cigarette smoking, and colon and rectal cancer. Am J Epidemiol 2004;160:842–52.
11. Sharpe CR, Siemiatycki JA, Rachet BP. The effects of smoking on the risk of colorectal cancer. Dis Colon Rectum 2002;45:1041–50.
12. Wakai K, Hayakawa N, Kojima M, et al. Smoking and colorectal cancer in a non-Western population: a prospective cohort study in Japan. J Epidemiol 2003;13:323–32.
13. CDC. The health consequences of smoking: a report of the Surgeon General. Washington DC: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
14. IARC. Tobacco smoking and involuntary smoking. IARC Monographs on the evaluation of carcinogenic risks to humans. Lyon (France): IARC; 2004.
15. Ho JW, Lam TH, Tse CW, et al. Smoking, drinking and colorectal cancer in Hong Kong Chinese: a case-control study. Int J Cancer 2004;109:587–97.
16. Terry PD, Miller AB, Rohan TE. Prospective cohort study of cigarette smoking and colorectal cancer risk in women. Int J Cancer 2002;99:480–3.
17. Mizoue T, Inoue M, Tanaka K, et al. Tobacco smoking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol 2006;36:25–39.
18. Hankin JH, Wilkens LR, Kolonel LN, Yoshizawa CN. Validation of a quantitative diet history method in Hawaii. Am J Epidemiol 1991;133:616–28.
19. Vineis P, Alavanja M, Buffler P, et al. Tobacco and cancer: recent epidemiological evidence. J Natl Cancer Inst 2004;96:99–106.
20. Willett WC. Nutritional Epidemiology. Monographs in epidemiology and biostatistics. New York: Oxford University Press; 1998.
21. Hecht SS. Biochemistry, biology, and carcinogenicity of tobacco-specific *N*-nitrosamines. Chem Res Toxicol 1998;11:559–603.
22. Nishikawa A, Mori Y, Lee IS, Tanaka T, Hirose M. Cigarette smoking, metabolic activation and carcinogenesis. Curr Drug Metab 2004;5:363–73.
23. Cortessis V, Siegmund K, Chen Q, et al. A case-control study of microsomal epoxide hydrolase, smoking, meat consumption, glutathione *S*-transferase M3, and risk of colorectal adenomas. Cancer Res 2001;61:2381–5.
24. Ulrich CM, Bigler J, Whitton JA, Bostick R, Fosdick L, Potter JD. Epoxide hydrolase Tyr113His polymorphism is associated with elevated risk of colorectal polyps in the presence of smoking and high meat intake. Cancer Epidemiol Biomarkers Prev 2001;10:87582.
25. Sivaraman L, Leatham MP, Yee J, Wilkens LR, Lau AF, Le Marchand L. CYP1A1 genetic polymorphisms and *in situ* colorectal cancer. Cancer Res 1994;54:3692–5.
26. Le Marchand L. Meat intake, metabolic genes and colorectal cancer. IARC Sci Publ 2002;156:481–5.
27. Le Marchand L, Donlon T, Seifried A, Wilkens LR. Red meat intake, CYP2E1 genetic polymorphisms, and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2002;11:1019–24.
28. Le Marchand L, Hankin JH, Pierce LM, et al. Well-done red meat, metabolic phenotypes and colorectal cancer in Hawaii. Mutat Res 2002;506507:205–14.

Smoking and Colorectal Cancer: Different Effects by Type of Cigarettes?

Margreet Lüchtenborg, Kami K.L. White, Lynne Wilkens, et al.

Cancer Epidemiol Biomarkers Prev 2007;16:1341-1347.