Research Article

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The Increased Risk of Colon Cancer Due to Cigarette Smoking May Be Greater in Women than Men

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Abstract

Background: Smoking is a recently established risk factor for colon cancer. We wanted to explore the hypothesis that women may be more susceptible to smoking-attributed colon cancer than men as one of the possible explanations for the high colon cancer risk of Norwegian women.

Methods: We followed 602,242 participants aged 19 to 67 years at enrollment in 1972–2003, by linkage to national registries through December 2007. We used Cox proportional hazard models to estimate HRs and 95% confidence intervals (CI).

Results: During a mean follow-up of 14 years, altogether 3,998 (46% women) subjects developed colon cancer. Female ever-smokers had a 19% (HR = 1.19, 95% CI = 1.09–1.32) and male ever-smokers an 8% (HR = 1.08, CI = 0.97–1.19) increased risk of colon cancer compared with never smokers. For all the four dose–response variables examined, female ever-smokers in the most exposed category of smoking initiation, (HR = 1.48, 95% CI = 1.21–1.81), of daily cigarette consumption (HR = 1.28, 95% CI = 1.06–1.55), of smoking duration (HR = 1.47, 95% CI = 1.11–1.95), and of pack-years of smoking (HR = 1.33, 95% CI = 1.11–1.57) had a significantly increased risk of more than 20% for colon cancer overall and of more than 40% for proximal colon cancer, compared with never smokers. A test for heterogeneity by gender was statistically significant only for ever smoking and risk of proximal colon cancer (Wald χ^2, $P = 0.02$).

Conclusions: Female smokers may be more susceptible to colon cancer and especially to proximal colon cancer than male smokers.

Impact: Women who smoke are more vulnerable to colon cancer than men. *Cancer Epidemiol Biomarkers Prev; 22(5); 862–71. ©2013 AACR.*

Introduction

The International Agency for Research on Cancer concluded in their monograph on tobacco smoke and risk of cancer published in 2004 (1), that there was not enough evidence to establish smoking as a causal factor for colorectal cancer. However, in its most recent monograph on this subject published in 2012 (2), the conclusion was that the relationship between smoking and colorectal cancer may be causal.

Globally, colorectal (CRC) cancer is the third and second most common cancer in men and women, respectively. Incidence rates vary, but in all the 15 countries with the highest incidence rates, men have higher rates than women. This has also been the case in Norway during the last 50 years. However, while Norwegian men rank 13 among countries for their colon cancer incidence rate, Norwegian women rank number two. In Norway, the incidence of CRC is 43 for men and 35 for women per 100,000 person-years, when age-adjusted to the world standard population (3). This difference is mostly due to men consistently having more rectal but not more colon cancer than women. In the late 50s, the incidence rate for colon cancer was 10 per 100,000 person-years for both men and women and increased in the same way until 1980. From 1954 until 2008, the incidence rate for colon cancer has more than doubled for both men (to 26,2 per 100,000 person-years) and women (to 23,5 per 100,000 person-years; ref. 4)

During these fifty years, the prevalence for daily smoking for men has been quite different from that of women. For men, the prevalence peaked at 65% during the late 1950s, it was 50% in 1975, and 33% in 1999. For women, the corresponding figure was 23% in 1954, the peak was at

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37% in 1970, and then the prevalence of daily smokers stabilized at around 32% for the rest of the century (5). This smoking pattern is in accordance with the tobacco epidemic stages model suggested by Lopez and colleagues almost 20 years ago. The model predicts that smoking-attributed mortality for women, will rise in the same way as the smoking prevalence, lag behind that of men, and both will peak at a lower level than that of men (6).

On the basis of the above described facts, that smoking is a causal factor for colon cancer and that women in Norway have smoked less than men but have had about the same increase in colon cancer incidence, we hypothesized that a part of the explanation is that women may be more susceptible to smoking-attributed colon cancer than men.

The purpose of this study was to examine separately by gender the association between different measures of smoking exposure and risk of colon cancer overall and by tumor location in a large Norwegian cohort.

Materials and Methods

Study population

The study population included 602,242 Norwegians (302,866 women and 299,376 men), born between 1897 and 1975, recruited from several Norwegian health screening surveys initiated by the National Health Screening Service (now included in the Norwegian Institute of Public Health).

The Oslo study I

This cardiovascular health screening was conducted in 1972–1973 among men, aged 40–49 years, and a random sample of 7% of those aged 20–39 years, living in the municipality of Oslo. Participants answered a one-page questionnaire that focused on symptoms of cardiovascular disease and diabetes, smoking habits, and physical activity. The participation rate was almost 60% (7–10).

The Norwegian counties study

These surveys included participants of cardiovascular disease screening in 3 rural Norwegian counties (Finnmark, Sogn og Fjordane, and Oppland) during 3 periods: 1974–1978, 1977–1983, and 1985–1988. All residents aged 35–49 years in addition to a random sample of 10% of the general population aged 20–34 years were invited. New cohorts and previous participants were invited to a second and third screening. The present study includes data collected at enrollment. The attendance rate was 88% for the two first and 84% for the third screening (10–13).

The 40 years cohort

These surveys included about 420,000 Norwegian men and women and were carried out in all of the 19 counties of Norway from 1985–1999. Men and women aged 40–42 years were invited and in some counties also those aged 65–67 years. The participation rate was 69% (14, 15).

The CONOR study

In this survey, regional data from epidemiologic studies conducted in 1994–2003 were merged into a national database. Standardized protocols, procedures, and questionnaires were used. The response rate for the 10 surveys in the CONOR study was 58% (10, 16, 17).

Protocol health surveys

The protocols for the above described surveys were similar. All surveys had a baseline questionnaire, which included detailed assessments of smoking habits, physical activity, and other lifestyle factors. As a part of a short health examination at the screening facility, body height and weight were measured in a standardized way by a trained nurse, which allowed us to calculate body mass index (BMI, kg/m^2). In most surveys, the attendees were given another questionnaire to be completed at home and mailed back in a prestamped envelope. There were some modifications to the questionnaires, regarding smoking, alcohol consumption, physical activity, and other lifestyle factors. The present study was approved by the Regional Committee for Medical Research Ethics South-East, Norway.

Exposure information

The smoking questions were similar, but not identical, across all surveys. The questions asked about current and former daily smoking habits, smoking duration, average number of cigarettes smoked per day, and former smokers were asked about time since quitting. Only the CONOR study asked about age at smoking initiation. In the other surveys, we calculated this variable for both current (age at enrollment minus duration of smoking in years) and former (age at enrollment minus years since quitting and duration of smoking) smokers. The number of missing for the 380, 351 ever-smokers was for cigarette consumption 7,211 (<2%), years of smoking 3,702 (<1%), pack-years of smoking 21,793 (<6%), and age at smoking initiation 83,946 (<23%). We collapsed current and former smokers to ever-smokers. We further categorized ever-smokers according to the following factors: age at smoking initiation ($\leq$16, 17–19, 20–24, $\geq$25 years), numbers of cigarettes smoked per day (1–9, 10–19, $\geq$20), smoking duration in years (1–19, 20–29, 30–39, $\geq$40), and number of pack-years (i.e., number of cigarettes smoked per day, divided by 20, multiplied by the duration of smoking in years; 0–9, 10–19, $\geq$20). All subjects not being current or former smokers were classified as never smokers. They constitute the reference group throughout the article.

The subjects were categorized into 3 groups based on the level of physical activity at time of enrollment: sedentary (reading, watching television, and sedentary activity), moderate (walking, bicycling, and/or similar activities $\geq$4 hours per week), and heavy (light sports or heavy gardening $\geq$ 4 hours per week, heavy exercise, or daily competitive sports). The most recent information

regarding duration of education obtained from Statistics Norway was used to assign subjects to one of 3 categories according to the years of education: <10, 10–12, ≥13.

Follow-up and end points

The study population comprised subjects participating in one of the 4 health surveys from 1972 until 2003. We followed all participants aged from 19 to 67 years at enrollment through linkage to the Cancer Registry of Norway and the Central Population Register, using the unique 11-digit personal identification number to identify all cancer cases, emigrations and deaths, respectively. The national registries are both accurate and virtually complete (18, 19). The start of follow-up was set as 1 January, the year after completing the baseline questionnaire. Person-years were calculated from the start of follow-up to the date of colon cancer diagnosis, the date of any incident cancer diagnosis (except skin basal cell carcinoma), emigration, death, or the end of follow-up, that is, December 31, 2007, whichever occurred first.

Colon cancer was classified according to the Seventh Revision of the International Statistical Classification of Diseases, and was further categorized according to tumor location, that is, proximal (codes 153.0/153.1) and distal (codes 153.2/153.3). Tumors that were overlapping (code 153.4), specified as appendix (code 153.6), or unspecified (code 153.9) were classified as "others" and were included in the analyses for the whole colon only.

We excluded subjects who had emigrated or died before the start of follow-up ($n = 1{,}009$; 49.7% women) and those with prevalent cancer ($n = 11{,}476$; 62% women). We excluded subjects with missing information on either smoking exposure ($n = 6{,}299$; 45% women) or on any of the covariates [body mass index (BMI), physical activity, education $n = 31{,}766$ (49.8% women)]. Altogether 50,550 (48% women) subjects were excluded leaving 602,242 subjects (50,3% women) in the analytical cohort. For the excluded men and women, the overall incidence of colon cancer was 53 and 59 per 100, 000 person-years, respectively.

Statistical analysis

We conducted all analyses separately by gender. We used the t test and χ^2 test for investigating differences in the distribution of selected characteristics between cases and noncases and between ever and never smokers. The Cox proportional hazards model was used with age as the underlying time scale to estimate multivariate-adjusted HRs with 95% confidence intervals (CI) for the associations between different measures of smoking exposure [age at smoking initiation (≤16, 17–19, 20–24, ≥25 years), numbers of cigarettes smoked per day (1–9, 10–19, ≥20), smoking duration in years (1–19, 20–29, 30–39, ≥40), and number of pack-years (0–9, 10–19, ≥20)] and colon cancer overall, and according to tumor location, with never smokers as the reference group. Entry time was defined as age at enrollment and exit time was age at diagnosis of colon cancer, the date of any incident cancer diagnosis (except basal cell carcinoma), emigration, death, or the end of follow-up (31 December, 2007), whichever occurred first. We included the 8,151 (99% men) participants who reported to ever smoke only cigar or pipe as ever smokers based on a recent paper finding an increased risk of colon cancer for both groups, although it was only significant for the latter group (20). We did a sensitivity analyses among men excluding this group. The estimates did not differ from those presented in the paper (data not shown).

The possible confounders included in the final models, selected *a priori*, were age at enrollment (continuous), level of physical activity (sedentary, moderate and heavy), BMI (continuous), all at enrollment and years of education (<10, 10–12, ≥13). Tests for linear trends were obtained by creating an ordinal exposure variable with equally spaced scores and including it in the models with never smokers as the reference category. For females, heterogeneity by smoking status in the effect of smoking and risk of colon cancer overall, and by location, were tested with Wald χ^2 statistics. Likewise, heterogeneity by gender in the effect of smoking and risk of colon cancer overall, and by location, were tested with Wald χ^2 statistics. Two-sided $P < 0.05$ were considered statistically significant. All analyses were conducted using STATA version 12.0 (Stata Corp.).

Results

During the 8,613,249 person-years of observation, 3,998 histologically confirmed invasive colon cancer cases were ascertained. The overall incidence of colon cancer among men and women was 49 and 44 per 100, 000 person-years, respectively. Altogether, 63% of the subjects were ever smokers (59% among women and 67% among men).

Table 1 shows that women diagnosed with colon cancer had a shorter duration of education, were less physically active, had a higher BMI and a higher proportion of ever smokers compared with those without colon cancer ($P < 0.0001$). Women with proximal cancer were on average 63 years and 4 years older at diagnosis compared with those with a distal colon cancer ($P < 0.0001$). Men with proximal colon cancer were on average 64 years and one year older at diagnosis compared with those with a distal cancer location ($P < 0.05$; Table 1).

Table 2 shows that women who were ever smokers were on average 4 years younger at diagnosis compared with never smokers, whereas the corresponding figure for men was 3 years older at diagnosis (both $P < 0.0001$).Women who were ever smokers had a shorter education, were less physically active and were leaner compared with never smokers (all $P < 0.0001$). Similar results were found for men (Table 2).

Tables 3 and 4 show the multivariate adjusted HR estimates for colon cancer overall and by location for women and men, respectively. Table 3 shows that women who were ever smokers had a 19% (HR = 1.19 95% CI = 1.09–1.32) increased risk of colon cancer overall compared with never smokers. For all the 4 dose–response variables

Table 1. Selected characteristics of the study population (N = 602,242) at enrollment with and without colon cancer and by tumor location and by gender

	Participants with colon cancer	Participants without colon cancer	P^a	Age-adjusted HR (95% CI)	Proximal colon cancer[b]	Distal colon cancer	P^c
Men (N = 299,376)	2,152	297,224			1,048	866	
Age at enrollment (mean year)	49	44	<0.0001		50	49	0.0635
Age at diagnosis (mean year)	64				64	63	<0.05
Follow-up years (median)[d]	14	13	0.0954		14	14	0.4286
Years of education (%)							
<10	34	23		Ref	34	33	
10–12	47	54		0.99 (0.91–1.10)	46	48	
≥13	19	23	<0.0001	1.01 (0.91–1.16)	20	19	0.6870
Level of physical activity[e] (%)							
Sedentary	19	18		Ref	18	19	
Moderate	50	41		0.96 (0.86–1.08)	51	49	
Heavy	31	41	<0.0001	0.92 (0.81–1.04)	31	32	0.718
BMI (kg/m^2, mean)	26	25	<0.05	1.05 (1.03–1.07)	26	26	0.0548
Smoking status at enrollment(%)							
Never smokers	25	33			25	25	
Ever smokers	75	67	<0.0001		74	75	0.785
Women (n = 302,866)	1,846	301,020			986	654	
Age at enrollment (mean year)	50	44	<0.0001		51	50	<0.05
Age at diagnosis (mean year)	62				63	59	<0.0001
Follow-up years (median)[d]	11	12	<0.0001		12	11	<0.05
Years of education (%)							
<10	40	25		Ref	44	37	
10–12	47	55		0.99 (0.90–1.10)	45	48	
≥13	13	20	<0.0001	0.90 (0.77–1.04)	11	15	<0.05
Level of physical activity[e](%)							
Sedentary	22	18		Ref	20	24	
Moderate	57	54		0.98 (0.87–1.10)	59	54	
Heavy	21	28	<0.0001	1.05 (0.91–1.21)	20	22	0.067
BMI (kg/m^2, mean)	25	24	<0.0001	1.01 (1.00–1.02)	25	25	0.2941
Smoking status at enrollment(%)							
Never	45	41			44	45	
Ever	55	59	<0.0001		56	55	0,834

[a] *t* test or χ^2 test for difference between participants with and without primary colon cancer.
[b] The numbers of proximal and distal cancer do not sum up to 3,998 as 444 colon cancer cases are categorized as unspecified.
[c] *t* test or χ^2 test for difference between proximal and distal colon cancer cases.
[d] *P* of Wilcoxon/Mann–Whitney 2-sample test.
[e] Level of physical activity; sedentary (reading, watching television, and sedentary activity), moderate (walking, bicycling, or similar activities ≥4 hours/wk), and heavy (light sports or heavy gardening ≥4 hours/wk, heavy exercise or daily competitive sports).

examined, women in the highest category [those who initiated smoking at or before 16 years of age (HR = 1.48, 95% CI = 1.21–1.81), those who smoked 20 cigarettes or more per day (HR = 1.28, 95% CI = 1.06–1.55), those who had been smoking for 40 years (HR = 1.47, 95% CI = 1.11–1.95), and those who had a smoking history of 20 or more pack-years (HR = 1.33, 95% CI = 1.11–1.57)] revealed a significantly increased risk of more than 20% compared with never smokers. When stratified by tumor location, female ever smokers had a significantly increased risk of 31% (HR = 1.31, 95% CI = 1.15–1.49) for proximal colon cancer. Female ever smokers in the highest category of all the 4 dose–response variables examined, had a significantly increased risk for proximal colon cancer of more than 40%, compared with never smokers. Trend tests across the different exposure categories (including the reference group) for smoking status, age at smoking initiation, number of cigarettes smoked per day, smoking duration and number of pack-years all yielded significant results for colon cancer overall and

Table 2. Selected characteristics of the study population (n = 602,242) at enrollment by smoking (ever versus never) status and gender

	Men n = 299,376			Women n = 302,866		
Characteristics	**Ever smokers (n = 200,988)**	**Never smokers (n = 98,388)**	***P*[a]**	**Ever smokers (n = 179,363)**	**Never smokers (n = 123,503)**	***P*[b]**
Age at enrollment (mean, year)	44	43	<0.0001	44	45	<0.0001
Age at diagnosis among cases (mean, year)	64	61	<0.0001	60	64	<0.0001
Follow-up years(median)	14	12	<0.0001	13	12	<0.0001
Education (n%)						
≤10 years	27	13		28	20	
10–12 years	55	52		57	52	
≥13 years and more	18	35	<0.0001	15	28	<0.0001
Physical activity[c](n%)						
Sedentary	20	14		20	16	
Moderate	43	37		53	54	
High	37	49	<0.0001	27	30	<0.0001
BMI (kg/m^2, mean)	25	26	<0.0001	24	25	<0.0001
Age at smoking initiation ≤16 years (n%)	57			43		<0.0001
Number of cigarettes smoked per day ≥20 years (n%)	69			31		<0.0001
Smoking duration ≥40 years (n%)	72			28		<0.0001
Number of pack-years[d] ≥20 years (n%)	68			32		<0.0001

[a]*t* test or χ^2 test for differences between ever and never smokers in men.
[b]*t* test or χ^2 test for differences between ever and never smokers in women.
[c]Level of physical activity; sedentary(reading, watching television, and sedentary activity), moderate (walking, bicycling, or similar activities ≥4 hours/wk), and heavy (light sports or heavy gardening ≥4 hours/wk, heavy exercise or daily competitive sports).
[d]Pack-years were calculated as numbers of cigarettes smoked per day, divided by 20, and multiplied by smoking duration in years.

for proximal colon cancer (all $P_{trend} < 0.0001$, but for age at smoking initiation $P_{trend} < 0.05$; Table 3). A test for heterogeneity by tumor location did not achieve statistical significance for either ever (Wald χ^2, $P = 0.16$) or current (Wald χ^2, $P = 0.08$) smoking.

Table 4 shows that men who were ever-smokers had an increased risk for colon cancer overall of 8% (HR = 1.08, 95% CI = 0.97–1.19) that did not achieve statistical significance. Former male smokers had a significantly increased risk for colon cancer overall of 14% (HR = 1.14, 95% CI = 1.02–1.27), which also was significantly increased (HR = 1.24, 95% CI = 1.03–1.47) for distal colon cancer, compared with never smokers. Male ever smokers who had been smoking for 40 years or more showed a statistically significant increased risk of almost 30% (HR = 1.29, 95% CI = 1.05–1.59) for colon cancer overall, compared with never smokers. Trend tests across the different exposure categories (including the reference group) for number of cigarettes smoked per day, smoking duration, and number of pack-years all yielded significant results for colon cancer overall ($P_{trend} < 0.05$). For distal colon cancer only the trend test for number of cigarettes smoked per day was significant ($P_{trend} < 0.05$; Table 4).

A test for heterogeneity by gender was significant for ever smoking and risk of proximal (Wald χ^2, $P = 0.02$), but not for risk of distal or overall colon cancer.

Discussion

Our study finds that female ever-smokers have an increase in overall and, even more pronounced, proximal colon cancer risk. A causal interpretation of these results is supported by the presence of a consistent dose–response association between the 4 measures of smoking exposure (age at smoking initiation, numbers of cigarettes smoked per day, smoking duration in years, and number of pack-years), and overall and proximal colon cancer risk. Our study also shows an association between male ever-smokers and risk of colon cancer, with a dose–response association between 3 of 4 measures of smoking exposure and colon cancer risk. The difference between the genders for the association between ever-smokers and the risk of colon cancer overall and by tumor location was only statistically significant for proximal colon cancer.

Our results regarding the increased risk of colon cancer among female ever-smokers appearing to be more

Table 3. Multivariate[a] adjusted HR estimates for colon cancer with 95% CIs overall and by tumor location among women (N = 302,866) by various measures of smoking exposure at enrollment, compared with never smokers

	Colon cancer			Proximal colon cancer		Distal colon cancer	
	Cases (n = 1,846)	Person-years	HR (95% CI)	Cases (n = 986)	HR (95% CI)	Cases (n = 654)	HR (95% CI)
Smoking status							
Never	834	1,744,944	1.00 (Ref)	438	1.00 (Ref)	295	1.00 (Ref)
Former	355	824,913	1.16 (1.02–1.31)	186	1.22 (1.02–1.45)	132	1.15 (0.94–1.41)
Current	657	1,621,343	1.22 (1.10–1.36)	362	1.37 (1.18–1.59)	227	1.12 (0.93–1.34)
P_{trend}[b]			<0.0001		<0.0001		0.205
Ever	1012	2,446,256	1.19 (1.09–1.32)	548	1.31 (1.15–1.49)	359	1.13 (0.96–1.32)
Ever smokers[c]							
Age at smoking initiation, y							
≥25	240	357,101	1.19 (1.03–1.38)	133	1.24 (1.01–1.50)	85	1.22 (0.96–1.57)
20–24	234	588,736	1.14 (0.98–1.32)	119	1.19 (0.96–1.46)	94	1.19 (0.94–1.51)
17–19	173	520,173	1.22 (1.03–1.45)	106	1.60 (1.28–1.99)	50	0.88 (0.65–1.20)
≤16	117	408,782	1.48 (1.21–1.81)	60	1.72 (1.30–2.29)	40	1.18 (0.83–1.67)
P_{trend}[b]			<0.05		<0.05		0.086
Number of cigarettes smoked per day							
1–9	382	824,198	1.14 (1.00–1.28)	208	1.20 (1.02–1.42)	135	1.12 (0.91–1.37)
10–19	492	1,268,980	1.23 (1.09–1.38)	266	1.37 (1.17–1.61)	180	1.17 (0.97–1.42)
≥20	126	337,874	1.28 (1.06–1.55)	68	1.48 (1.14–1.92)	42	1.07 (0.76–1.48)
P_{trend}[b]			<0.0001		<0.0001		0.177
Smoking duration, y							
1–19	464	1,263,528	1.16 (1.04–1.31)	241	1,22 (1.04–1.44)	173	1.16 (0.96–1.41)
20–29	404	1,089,772	1.16 (1.02–1.31)	214	1,26 (1.06–1.50)	150	1.12 (0.91–1.38)
30–39	75	54,748	1.37 (1.08–1.75)	50	1,69 (1.25–1.28)	20	1.06 (0.66–1.68)
≥40	57	21,650	1.47 (1.11–1.95)	36	1.67 (1.17–2.38)	15	1.18 (0.69–2.03)
P_{trend}[b]			<0.0001		<0.0001		0.217
Number of pack-years[d]							
0–9	501	1,270,193	1.13 (1.00–1.26)	270	1.22 (1.05–1.44)	178	1.10 (0.91–1.33)
10–19	337	862,029	1.14 (1.00–1.30)	177	1.29 (1.07–1.54)	133	1.23 (1.00–1.52)
≥20	155	288,147	1.33 (1.11–1.57)	91	1.69 (1.34–2.12)	45	1.08 (0.78–1.48)
P_{trend}[b]			<0.0001		<0.0001		0.126

[a]Adjusted for age, body mass index, level of physical activity all at enrollment and duration of education.

[b]Never smokers included in the model.

[c]Total numbers of ever smokers do not equal to the total in different smoking exposures due to missing values in different smoking exposure groups.

[d]Pack-years were calculated as numbers of cigarettes smoked per day, divided by 20 and multiplied by smoking duration in years.

pronounced in the proximal than the distal colon location are in agreement with the long-term Iowa cohort study of postmenopausal women (21), and our own study among Norwegian women (22). Also, the results from the Women's Health Initiative study reported by Paskett and colleagues, showed statistically significant positive associations for cigarettes per day and duration of smoking with risk of colon cancer, and risk of proximal, but not distal tumor location (23).

In the cohort study with men and women from 10 European countries, we found that ever-smokers had a significantly increased risk of proximal, but not distal colon cancer compared with never smokers. The overall similarity to the results we find among the females in the present study may be explained by the fact that 70% of the participants in the EPIC cohort are women (24). In a meta-analysis including published cohort and case–control studies, both ever- and former smokers had a significantly increased risk for colon cancer and a non-significant increased risk of proximal, but no increased risk of distal colon cancer, when compared with never smokers (25).

We use ever smoking as our main exposure variable, as our risk estimates for colon cancer risk was similar for former and current smokers, for both genders. Likewise, the meta-analysis by Liang and colleagues revealed

Table 4. Multivariate[a] adjusted HR estimates for colon cancer with 95% CIs overall and by tumor location among men (299,376) by various measures of smoking exposure at enrollment, compared with never smokers

	Colon cancer			Proximal colon cancer		Distal colon cancer	
	Cases (N = 2,152)	Person-years	HR (95% CI)	Cases (n = 1,048)	HR (95%CI)	Cases (n = 866)	HR (95% CI)
Smoking status							
Never	534	1,369,691	1.00 (Ref)	267	1.00 (Ref)	217	1.00 (Ref)
Former	744	1,138,881	1.14 (1.02–1.27)	350	1.06 (0.90–1.24)	323	1.24 (1.03–1.47)
Current	874	1,913,477	1.03 (0.92–1.15)	431	1.02 (0.86–1.19)	326	0.95 (0.79–1.13)
P_{trend}[b]			0.789		0.902		0.368
Ever	1,618	3,052,358	1.08 (0.97–1.19)	781	1.03 (0.90–1.19)	649	1.08 (0.92–1.26)
Ever smokers[c]							
Age (years) at smoking initiation							
≥25	184	268,600	1.01 (0.85–1.20)	90	0.99 (0.77–1.25)	75	1.04 (0.80–1.36)
20–24	303	592,480	1.08 (0.94–1.25)	144	1.03 (0.83–1.25)	115	1.04 (0.82–1.30)
17–19	311	655,095	1.11 (0.97–1.28)	157	1.12 (0.92–1.38)	116	1.04 (0.82–1.30)
≤16	263	639,243	1.15 (0.99–1.34)	128	1.13 (0.91–1.40)	101	1.10 (0.86–1.40)
P_{trend}[b]			0.577		0.984		0.795
Number of cigarettes smoked per day							
1–9	359	604,421	0.99 (0.86–1.13)	168	0.91 (0.75–1.11)	147	1.02 (0.82–1.26)
10–19	760	1,526,804	1.09 (0.97–1.22)	373	1.06 (0.90–1.24)	293	1.04 (0.87–1.25)
≥20	415	832,845	1.16 (0.97–1.28)	191	1.08 (0.90–1.30)	182	1.25 (01.02–1.53)
P_{trend}[b]			<0.05		0.232		<0.05
Smoking duration, y							
1–19	495	1,250,222	1.06 (0.93–1.20)	229	0.99 (0.83–1.19)	216	1.12 (0.93–1.35)
20–29	661	1,471,526	1.06 (0.94–1.20)	322	1.04 (0.88–1.23)	257	1.02 (0.85–1.22)
30–39	278	241,385	1.09 (0.94–1.27)	134	1.03 (0.83–1.28)	110	1.10 (0.87–1.40)
≥40	159	58,133	1.29 (1.05–1.59)	80	1.16 (0.87–1.55)	62	1.40 (1.00–1.94)
P_{trend}[b]			<0.05		0.356		0.219
Number of pack-years[d]							
0–9	364	943,796	1.08 (0.94–1.23)	177	1.06 (0.87–1.28)	149	1.07 (0.87–1.32)
10–19	445	1,014,305	1.10 (0.97–1.25)	222	1.10 (0.92–1.32)	164	1.00 (0.80–1.22)
≥20	369	647,100	1.14 (0.99–1.31)	188	1.16 (0.96–1.41)	140	1.06 (0.85–1.32)
P_{trend}[b]			<0.05		0.110		0.771

[a]Adjusted for age, body mass index, level of physical activity all at enrollment and duration of education.

[b]Never smokers included in the model.

[c]Total numbers of ever smokers do not equal to the total in different smoking exposures due to missing values in different smoking exposure groups.

[d]Pack-years were calculated as numbers of cigarettes smoked per day, divided by 20 and multiplied by smoking duration in years.

almost identical results, that is, a 10% nonsignificant increase in risk of colon cancer, for current and former smokers. The former overall estimate was based on pooled risk estimates from 11 and the latter from 13 cohort studies (26).

The association between cigarette smoking and colon cancer risk has been shown to be dose-dependent (2). Our study shows the expected dose–response relationship for female ever-smokers for all the examined smoking exposures for both colon cancer overall and for proximal, but not for distal tumor location. For male ever-smokers, our data displayed a weak dose–response relationship with colon cancer, but not for all the examined measures of smoking exposure. Compared with never smokers, we also found that female ever-smokers had significantly increased risks of colon cancer for the lowest level of smoking exposure for number of cigarettes, smoking duration, and number of pack-years. Male ever-smokers that had smoked 40 years or more, had a significantly increased risk of colon cancer, compared with never smokers, whereas the increased risk in the highest exposure category for number of cigarettes and of pack-years did not achieve statistical significance.

In contrast to our findings, two Japanese cohort studies (27, 28) that analyzed the association between cigarette smoking and colon cancer separately by gender, found

that male ever (27) and former or current (28) smokers had a nonsignificantly increased risk of colon cancer, but neither study did find any association for female smokers. An explanation for this may be the small proportion of female ever-smokers, less than 20% (27) and 7% (28), and less than 200 colon cancer cases among women in those studies.

Another meta-analysis by Botteri and colleagues, confirmed the previously reported significant association between smoking and colorectal adenoma, known to be a precursor lesion for most colorectal cancers (29). Also, smoking has been shown to be associated with flat colorectal adenomas, which were located mainly in proximal colon (30). Recently, cigarette smoking has been shown to be strongly associated with molecularly defined subtypes of colorectal cancer, such as MSI-high, CIMP-positive, and *BRAF* mutation-positive, that originate through epigenetically mediated carcinogenic pathways. These subtypes are more prevalent among women and are more often located in the proximal than the distal colon (31–33). Furthermore, it was recently suggested that cigarette smoking may be a stronger risk factor for *KRAS* mutation-negative tumors located in the proximal colon than in the distal colon (34). Evidence is emerging in support of a strong association between smoking and proximal colon cancer, especially among female smokers.

Our study has several major strengths. The study is based on a large prospective cohort population from Norway comprising both men and women, who have been followed for many years, with virtually complete follow-up. We were able to examine the association with smoking according to colon tumor location. The long follow-up period resulting in a large number of cases gives us more stable risk estimates and results that are less prone to chance. We were able to stratify all the analyses according to different measures of smoking exposure and we were able to conduct all analyses separately by gender. Also, the smoking histories were obtained at enrolment and, hence, are not subject to recall bias. We have a high proportion of male and female ever-smokers. Another strength is that we focused our analyses on the comparison between ever versus never smokers. Thus, it is only never smokers that could possibly change smoking status during follow-up. As very few Norwegians start to smoke after the age of 30 and the mean age at enrolment for our study is more than 40 years, we are confident that the possible changes in smoking status among the never smokers during follow-up did not influence our risk estimates. We had information on, and were able to control for, established risk factors for colon cancer, many of which varied according to smoking status. Colon cancer screening is not yet common in Norway and was therefore unlikely to affect our results. Also, we did find the expected association between female ever-smokers and breast cancer incidence in this cohort (35).

Our study has several limitations. We lack information on the family history of colon cancer and on dietary factors, such as alcohol and red meat consumption which are, established risk factors for colon cancer. Increased consumption of alcohol and red meat are factors that partly may explain the steep increase in colon cancer incidence for both genders. The alcohol consumption is higher among men than women in Norway (36). Thus, the lack of adjustments for alcohol consumption in our analyses is likely to have inflated the estimates among men more than women and, thereby, attenuated the gender difference. If Norwegian men consumed more red meat than women, this would also have attenuated the gender difference in our study. However, we cannot rule out that alcohol and red meat consumption may have stronger effects in females than males

Similarly, information on the use of COX inhibitors, such as aspirin, which has preventive effects on colon cancer development (37), was not available. The lack of molecular data is another limitation.

We also lack detailed information on smoking exposure, such as depth of inhalation, type of cigarettes smoked, occasional, and passive smoking. Around 10% of the Norwegian population reported to be occasional smokers from 1976 to 2006 which is during our follow-up period (38). We believe that some occasional smokers may have been excluded due to insufficient smoking information, whereas others may have been included in the reference group, together with women exposed to passive smoking, which would have attenuated the associations between smoking and colon cancer. As current smokers have an increased risk of dying from any major cause during follow-up and colon cancer is assumed to take many years, competing causes of death may decrease the impact of smoking more among current than former smokers and make the association with colon cancer more similar for current and former smokers. There may be some residual confounding due to these and other unknown risk factors. Nevertheless, the dose response observed is suggestive of a causal association between smoking and colon cancer.

In conclusion, our results provide further evidence that smoking plays a role in the etiology of colon cancer in both sexes. Female smokers may be more susceptible to colon cancer and especially proximal colon cancer than male smokers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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