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Impact of smoking on patients with stage III colon cancer: Results from CALGB 89803

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Abstract

Background—Cigarette smoking has been shown to increase the risk of developing colorectal cancer, particularly smoking early in life. Little is known about the impact of tobacco use on colon cancer recurrence among colon cancer survivors.

Methods—We prospectively collected lifetime smoking history from stage III colon cancer patients enrolled in a phase III trial via self-report questionnaires during and 6 months after completion of adjuvant chemotherapy. Smoking status was defined as never, current or past. Lifetime pack-years were defined as number of lifetime packs of cigarettes. Patients were followed for recurrence or death.

Results—Data on smoking history were captured on 1,045 patients with stage III colon cancer receiving adjuvant therapy (46% never smokers; 44% past; 10% current). The adjusted hazard ratio (HR) for disease-free survival (DFS) was 0.99 (95% CI 0.70–1.41), 1.17 (95% CI 0.89–1.55)

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and 1.22 (95% CI 0.92–1.61) for lifetime pack-years 0–10, 10–20 and 20+, respectively, compared to never smoking ($p=0.16$). In a pre-planned exploratory analysis of smoking intensity early in life, the adjusted HR for 12+ pack-years before age 30 for DFS was 1.37 (95% CI 1.02–1.84) compared to never smoking ($p=0.04$). The adjusted hazard ratio (HR) for disease-free survival (DFS) was 1.18 (95% CI 0.92–1.50) for past smokers and 1.10 (95% CI 0.73–1.64) for current smokers, compared to never smokers.

Conclusion—Total tobacco usage early in life may be an important, independent prognostic factor of cancer recurrences and mortality in patients with stage III colon cancer.

Keywords

colorectal cancer; smoking; cancer recurrence; cancer survival; adjuvant chemotherapy

Introduction

Tobacco use is estimated to cause approximately 170,000 cancer deaths in 2008 in the United States¹. Worldwide, colorectal cancer is the fourth most commonly diagnosed malignancy, with an estimated 1,023,152 new cases and 529,978 deaths in 2002². Nearly 150,000 persons will be diagnosed and 50,000 will die with colorectal cancer in 2008¹. Studies attribute 11–22% of these new cases to tobacco use^{3–6}. An association between tobacco use and development of premalignant colorectal adenomas is established. In one study, smokers with a 20 to 40 cigarette pack-years history had a 5-fold increased risk of colorectal adenomas compared to nonsmokers⁷. Smoking at a younger age and for longer intervals also conveys an increased risk of adenoma^{3, 8}.

There is controversy in the literature regarding the impact of tobacco use on the incidence of colorectal cancer. This may be due to the short follow-up period in some studies^{4, 7, 9}. Recent studies have noted that the duration and total quantity of cigarette usage, particularly in smokers of at least four decades, is strongly associated with an increased incidence of colorectal cancer^{7, 10, 11}.

No data exist regarding the impact of tobacco use on patients already diagnosed with colorectal cancer. The present analysis evaluates the impact of tobacco use defined as smoking status, intensity and duration – on colon cancer recurrence in patients with stage III colon cancer.

Methods

Study population

The Cancer and Leukemia Group B led a multicenter, phase III trial (CALGB 89803) in which 1,264 patients with resected stage III adenocarcinoma of the colon were randomized to receive bolus 5-fluorouracil (5-FU)/leucovorin with or without irinotecan. Patients were also enrolled by the North Central Cancer Treatment Group, the National Cancer Institute of Canada Clinical Trials group, the Eastern Cooperative Oncology Group (ECOG), the Southwest Oncology Group, and the National Cancer Institute Cancer Trials Support Unit from May 21, 1999 through April 27, 2001. Patients with resected stage III adenocarcinoma of the colon without evidence of radiographic or surgical metastases and without prior radiation or chemotherapy were eligible for this study. Additional eligibility criteria included ECOG performance status of less than or equal to 2, normal bone marrow function and bilirubin, serum creatinine less than or equal to 1.5 times the upper limit of normal, and age 18 years and older. Patients with rectal cancers were excluded. Study treatment commenced between day 21 and 56 following surgical resection. Data and safety monitoring

was conducted by the CALGB according to the CALGB policies and procedures. Participating subjects signed informed consent, independently approved at each site's institutional review board.

Tobacco use assessment

Early in the enrollment period, the protocol was amended to include a self-administered questionnaire capturing diet and lifestyle habits midway through adjuvant therapy (four months after surgery; questionnaire 1) and, again, six months after completion of adjuvant therapy (14 months after surgery; questionnaire 2). On questionnaire 1, subjects were asked if they had smoked 20 packs of cigarettes or more in their lifetime. If they answered 'yes, currently smoke' or 'yes, smoked in past', they answered the average number of cigarettes smoked per day at age intervals of age <15, age 15–19, age 20–29, age 30–39, age 40–49, age 50–59 and age 60+. Additionally, for those that answered 'yes, smoked in past, but quit', they indicated the time since smoking cessation (<1 year, 1–2 years, 3–5 years, 6–9 years, 10+ years). Those who answered 'no' were categorized as nonsmokers for questionnaire 1. On questionnaire 2, subjects were asked if they currently smoke cigarettes; if they answered 'yes', they indicated the number of cigarettes smoked per day (1–4, 5–14, 15–24, 25–34, 35–44, 45+). If they answered 'no', they were considered nonsmokers for questionnaire 2.

Smoking status was defined as never, current, or past based on data from questionnaire 1. Lifetime pack years were defined as the estimated number of packs of cigarettes smoked per year over the subject's lifetime based on questionnaire 1. Pack-years were divided into quartiles, for overall pack-years (0, 0–10, 10–20, and 20+ pack-years), comparable to other similar studies in the literature^{3–8, 10}. Pack-years was further categorized as pack-years quartiles prior to age 30 (0, 0–4, 4–12, 12+ pack-years) and after age 30 (0, 0–1, 1–20, 20+ pack-years) to examine the impact of early smoking on outcomes as previously described^{3, 8}. Time since smoking cessation was defined by the median value of the time categories since last smoking (0.5, 1.5, 4, 7.5, and 10 years) based on questionnaire 1. In secondary analyses, we updated exposures based on data from the second questionnaire and did not observe an appreciable change in the results. As such, we present only data using the first questionnaire completed during adjuvant therapy.

Study end points

The primary endpoint for these analyses was disease-free survival, defined as time from completion of questionnaire 1 to death from any cause or recurrence of colon cancer. Secondary endpoints were overall and recurrence-free survival. Overall survival is defined as time from completion of questionnaire 1 to death from any cause. Recurrence-free survival is defined as time from completion of questionnaire 1 to recurrence of colon cancer. For recurrence-free survival, subjects who died without evidence of colon cancer recurrence were censored at the time of their last visit to their clinician. Median time from study entry to questionnaire 1 completion was 3.5 months (95% range 2.5–5.0 months). Survival endpoints were measured from completion of questionnaire 1 to event of interest, excluding events within the first 90 days to avoid biases of change in behavior due to an impending event.

Statistical analyses

A detailed description of the statistical plan for the comparison of 5-FU and leucovorin to 5-FU, leucovorin and irinotecan has been published¹². Since there was no difference in efficacy between the two treatments in the clinical trial, data for all patients were combined¹². In this secondary analysis, differences in survival outcome were calculated using Cox Proportional Hazards. The Kaplan Meier method and log rank analysis were used

to graphically represent disease-free survival, overall survival, and recurrence-free survival by smoking status and intensity. The contribution of other variables was also entered into the model as fixed covariates (age at study entry, gender, body mass index at study entry, extent of penetration through the bowel wall, number of positive lymph nodes and tumor differentiation). Covariates with missing values were coded with indicator variables in all adjusted models. Differences in baseline characteristics across smoking status and intensity groups were tested using the chi-squared test of independence for dichotomous/categorical variables and the Wilcoxon test for continuous variables. Testing for linear trends across quartiles of smoking intensity and time since smoking cessation was performed by assigning median values for each quartile then modeling this value as a continuous variable. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina). All p-values presented are two-sided, using a level of significance of 0.05 as statistically significant.

The sample size for the initial study was determined based on a comparison of the two chemotherapy regimens in the adjuvant setting for stage III colon cancer. In a post-hoc calculation of power based on the known sample size and number of events for disease-free survival for tobacco use, we had >90% power to detect step-wise increases in hazard ratios of 0.25 for each category of smoking intensity, compared to baseline 0 pack-year history, for the 3rd and 4th category (10–20 pack years and > 20 pack years). We had 80% power to detect a hazard ratio of 1.3 for past smokers and 1.5 for current smokers, both compared to never smokers.

Patient registration and clinical data collection was managed by the CALGB Statistical Center. All analyses are based on the study database frozen on March 7, 2007 and performed with the supervision of CALGB statisticians. Using Clark's C, the completeness of follow-up for this study was 83.25%¹³. Applying Wu's modification, to adjust for unreported deaths, the assessment of the completeness was 85.0%¹⁴.

Results

Baseline characteristics

Current smokers were more likely to be male, had lower body mass index (BMI), had more poorly differentiated tumors and had deeper invasion into the bowel wall at diagnosis than past or never smokers [Table 1]. Smokers did not differ from nonsmokers with regard to treatment arm, race, ECOG performance status, postoperative carcinoembryonic antigen (CEA) titers or the presence of bowel perforation at diagnosis. In regard to baseline characteristics by smoking intensity, those with higher pack-years of smoking were older, were more likely to be male and had worse performance status compared to never smokers but did not differ by treatment arm, race, postoperative CEA or the presence of bowel perforation at diagnosis.

Smoking status

The median follow-up time from the time of completion of the first questionnaire was 5.3 years. In total, 363 of the 1,045 patients experienced disease-free survival events (colon cancer recurrence and/or death) and 257 patients died from any cause (221 with cancer recurrence and 31 without evidence of recurrence at time of death). Current smokers had a non-significant increased hazard ratio of 1.30 (95% CI 0.93–1.84) for colon cancer recurrence or death from any cause compared to never smokers in adjusted analyses [Table 2; Figure 1]. After adjustment for age, gender, number of positive lymph nodes, extent of invasion through bowel wall, tumor differentiation, BMI and clinical bowel obstruction at diagnosis, the hazard ratio for disease-free survival was 1.10 (95% CI 0.73–1.64). This non-

significantly inferior disease-free survival seems to be driven by death from any cause. Compared to never smokers, current smokers had an adjusted hazard ratio for overall mortality of 1.38 (95% CI 0.87–2.18) while there was no association with recurrence-free survival (HR 0.90 [95% CI 0.58–1.41]). There were no significant differences in adjusted disease-free, recurrence-free or overall survival for past smokers compared to never smokers.

Our primary analyses were based on smoking status at time of questionnaire 1. These results did not change when considering status at questionnaire 2 (6 months after completing adjuvant therapy; data not shown). Of 968 in which we have data for smoking status during questionnaire 1 and questionnaire 2, 95% did not change their status while 3% were current smokers on questionnaire 1 and then nonsmokers on questionnaire 2 and 2% were either past or never smokers and then reported to be current smokers.

Smoking intensity

We examined whether there was a dose-response association between smoking intensity and colon cancer recurrences and overall mortality [Table 3; Figure 2A]. We initially considered total lifetime exposure using total pack-years of cigarettes. Subjects in the highest quartile of smoking intensity, 20+ pack-years, had an unadjusted hazard ratio for cancer recurrences or death from any cause of 1.34 (95% CI 1.02–1.75), compared to never smokers. In multivariate analyses, this point estimate was attenuated to HR 1.21 (95% CI 0.92–1.61). The major factor that led to the effect attenuation was gender. However, we did not detect effect modification by gender. In men, the HR for disease-free survival for 20+ pack-years compared to never smokers was 1.37 (95% CI 0.98–1.92, $p=0.06$) while in females, the HR was 1.17 (95% CI 0.70–1.95, $p=0.55$). The p for interaction by gender was 0.15. The inferior disease-free survival was primarily due to death from any cause rather than colon cancer recurrences. Compared to nonsmokers, subjects with greater than 20 pack-years history had an adjusted hazard ratio for overall mortality of 1.23 (95% CI 0.88–1.71), but an adjusted hazard ratio for colon cancer recurrences of 1.12 (95% CI 0.83–1.51).

Since published studies suggest that smoking intensity prior to age 30 may be the most predictive influence on colon cancer development^{3, 5, 7–9}, we tested the impact of smoking intensity prior to age 30 and after age 30 in subjects with established colon cancer. The only baseline characteristic that was significantly different across smoking intensity categories prior to age 30 was gender, where the rates of 4–12 pack-years and 12 or more pack-years prior to age 30 were 20% and 22% in males and 13% and 7% in females, respectively. As with overall smoking intensity, increased pack-years of smoking were associated with worse outcomes in colon cancer survivors [Table 4; Figure 2B]. For smokers with 12 or more pack-years prior to age 30, the adjusted HR for disease-free survival was 1.37 (95% CI 1.02–1.84, p trend 0.04), compared to no smoking history prior to age 30. This association remained significant after further adjustment by smoking intensity after age 30 (HR 1.41, 95% CI 1–1.97, p trend 0.05). The point estimates for recurrence-free and overall survival were similar to that seen for disease-free survival for smoking prior to age 30, though were more limited in power due to fewer events and were not statistically significant (Table 4).

Smoking intensity after age 30 was not significantly associated with any of the survival endpoints (adjusted p trend 0.21 for disease-free survival, 0.14 for overall survival and 0.48 for recurrence-free survival) [Table 4].

Time from smoking cessation

The majority of past smokers reported cessation more than 10 years prior to completing the first questionnaire. For past smokers, compared to those that reported cessation of tobacco

usage within 1 year of the first questionnaire, those that quit at least 10 years prior had an adjusted hazard ratio for disease-free survival of 0.93 (95% CI, 0.54–1.58). The p trend by number of years from cessation was 0.89. Similarly, overall survival and recurrence-free survival were not associated with number of years of cessation (adjusted p trends = 0.55 and 0.82, respectively).

Discussion

Using a cohort of patients that participated in CALGB 89803, we evaluated the impact of smoking on colon cancer recurrence and survival in the patients who participated in this clinical trial. Neither smoking status nor time since smoking cessation appeared to have a statistically significant impact on the primary endpoint of these analyses, disease-free survival, or the secondary endpoints, overall survival or recurrence-free survival. In contrast, a dose-response association was noted for smoking intensity, particularly for the risk of death or recurrence in higher quartiles of pack-years smoked before age 30 compared to nonsmokers.

The notion that a longer induction period of tobacco use may be associated with increased risk of colon cancer recurrence or death has not previously been demonstrated in a population already diagnosed with colon cancer. Giovannucci and colleagues, however, demonstrated that smoking during early adulthood was more predictive of an increased risk of adenomas than other smoking variables in two large cohort studies^{3, 8}. In a prospective study of self-reported tobacco use and risk of developing adenoma and colorectal cancer amongst 121,700 women participating in the Nurses Health Study, Giovannucci et al noted that increased smoking intensity prior to age 30 was associated with a 2-fold increased risk of rectal cancer (95% CI 1.24–3.42) and 23% increased risk of colon cancer. A long induction period (smoking prior to age 30) was associated with an increased risk of colorectal cancer after age 55 (overall RR 1.71, 95% CI 1.27–1.31, p=0.008). Similar results were noted in a companion study of 51,529 male health professionals in the Health Professionals Follow-up Study for smoking intensity prior to age 30 with a nearly 2-fold increased risk of colon cancer (RR 1.96, 95% CI 1.16–3.29, p trend 0.007).

In the present analysis, smoking intensity, particularly prior to age 30, is associated with a worse disease-free survival. It is plausible that a greater duration of exposure to tobacco leads to a more aggressive tumor. Adjustment for known clinical factors associated with a more aggressive tumor behavior (extent of invasion through bowel wall, nodal stage, grade of differentiation, presence of clinical bowel obstruction or perforation at diagnosis) did not fully attenuate our finding. Thus, while smoking intensity early in life may lead to a more aggressive cancer, it does seem to be independent of other known prognostic factors.

Observational studies are limited in elucidating the mechanism by which tobacco use is associated with risk of premalignant adenomas and colorectal cancer. However, most studies suggest that smoking intensity in early adulthood may be associated with molecular changes early in the pathogenesis of colorectal cancer. One theory of mechanism is that a deletion of a gene, GSTM1, that encodes enzymes responsible for detoxification of carcinogenic compounds found in tobacco leads to an increased risk of colorectal cancer. However, this was not supported by a case-control pooled analysis of 6 studies¹⁵. Slattery et al found a significant increase in the presence of microsatellite instability in colon tumors among subjects who smoked more than one pack per day compared to nonsmokers (odds ratio 1.6, 95% CI 1–2.5 for men; odds ratio 2.2, 95% CI 1.4–3.5 for women)¹⁶. A strong association between colon tumors with microsatellite instability and cigarette smoking was noted in a subset of heavy cigarette smokers (those who started smoking at an early age, smoked for

more than 35 years, those who were current smokers and those who stopped smoking less than 15 years prior to the diagnosis of colon cancer).

Smoking status and intensity are shown to be associated with an increase in genetic alterations in adenomas and sporadic colon cancers in some¹⁷⁻²⁰, but not all^{15, 16, 21}, studies. In a Dutch case-control study, Diergaarde et al noted an increase in p53 overexpression and the presence of transversion mutations in APC, K-ras and p53 for ever smokers compared to never smokers among 176 case subjects compared to 249 controls¹⁷. In that study, there was not a clear correlation of smoking status or intensity with the presence of microsatellite instability. Huang and colleagues reported significantly higher rates of p53 deletion mutations among smokers compared to nonsmokers²². Recently, Limsui et al showed that smoking status and intensity was linked to specific colon cancer carcinogenesis pathways in a prospective cohort of nearly 42,000 Iowa women²³. There was a statistically significant risk of the presence of BRAF mutation or CpG island methylation phenotype for women with cumulative pack-years smoked or with current smoking status.

The present study uniquely evaluates the risk of colon cancer recurrence in a cohort of patients with stage III colon cancer. However, there are limitations that should be considered. These analyses are based on self-reporting of tobacco use history. Self-report of tobacco use has been shown to be accurate for current smokers. Approximately 20% of never smokers tend to misreport their tobacco exposure;²⁴ such measurement error would bias towards the null. Patients that enroll in randomized trials may differ from the population-at-large. However, the distribution of smoking status as well as past smoking intensity is consistent with other studies in non-cancer populations^{25, 26}. Since the study included patients across North America, at community and academic centers, our findings should reflect the general population of stage III patients.

Gritz et al called for the inclusion of questions on smoking status in clinical trials to determine the impact of tobacco use on cancer treatment and outcome²⁷. The CALGB 89803 smoking analysis allows for evaluation of such an impact in colon cancer recurrence. A dose-response for lifetime total of tobacco usage exists that may impact survival outcomes in patients with stage III colon cancer, particularly for longer induction periods of tobacco usage prior to age 30. Further research on the potential interactions between molecular markers and smoking history as well as confirmation of these findings with independent datasets is warranted.

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Fig I. Disease-free and overall survival by smoking status for never, current and past smokers by time from study entry in years.

Fig II.

Disease-free and overall survival by smoking intensity (pack-years) by time from study entry in years. A = disease-free survival by overall smoking intensity; B = overall survival by time from study entry in years; C = disease-free survival by smoking intensity prior to age 30; D = overall survival by smoking intensity prior to age 30.

Table 1

Baseline patient characteristics by smoking status and intensity

	Smoking Status		Smoking Intensity			
	Never N=478	Current N=107	Past N=460	0 pyr N=478	0-10 pyr N=122	10-20 pyr N=211
Age, years						
Median	58	57	64 ^δ	58	61	60
Range	24-85	21-83	26-81	24-85	29-80	21-81
Male (%)	45%	70%	64% ^δ	45%	58%	63%
Treatment arm (%)						
5-FU + LV	51%	57%	49%	51%	48%	50%
IFL	49%	44%	51%	49%	52%	50%
Race (%)						
White	87%	90%	90%	87%	84%	92%
Black	8%	7%	6%	8%	12%	5%
Other	5%	3%	4%	5%	4%	3%
ECOG PS * (%)						
0	75%	69%	77%	75%	79%	82%
1 or 2	25%	31%	23%	25%	21%	18%
BMI at diagnosis (%)						
Median	27	26	28 ^δ	27	28	27
Range	17-50	17-38	16-52	17-50	17-43	16-50
Invasion through bowel wall (T stage) [†]						
T1-2	18%	6%	15% ^δ	18%	11%	14%
T 3-4	82%	94%	85%	82%	89%	86%
Grade of tumor differentiation						
Well/moderately	79%	68%	77% ^δ	79%	77%	77%
Poorly/undifferentiated	21%	32%	23%	21%	23%	23%
Number of nodes sampled						
Median	13	13	12 ^δ	13	12	13

	Smoking Status			Smoking Intensity			
	Never N=478	Current N=107	Past N=460	0 pyr N=478	0-10 pyr N=122	10-20 pyr N=211	20+ pyr N=205
Range	1-61	3-68	1-68	1-61	2-52	1-68	1-41
Number of positive nodes							
Median	3	3	2	3	2	2	2
Range	1-29	0-14	1-23	1-29	1-14	0-18	1-23
Postoperative CEA level							
≤5 ng/mL %	93%	90%	92%	93%	87%	92%	94%
>5 ng/mL %	7%	10%	8%	7%	13%	8%	6%
Clinical bowel obstruction at diagnosis (%)							
No	81%	72%	76%	81%	74%	76%	75%
Yes	19%	28%	24%	19%	26%	24%	25%
Clinical bowel perforation (%)							
No	97%	92%	95%	97%	94%	95%	94%
Yes	3%	8%	5%	3%	6%	5%	6%

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; IFL (irinotecan, 5-FU, leucovorin); CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index

δ
p <0.05

* Performance status: PS 0 = fully active; PS 1 = restricted in physically strenuous activity but ambulatory and able to carry out light work; PS 2 = ambulatory and capable of all self care but unable to carry out any work activities, up and about more than 50% of waking hours.

[†] T1-2 = level of invasion through the bowel wall not beyond the muscle layer; T3-4 = level of invasion through the bowel wall beyond the muscle layer.

Table II

Disease-free, overall and recurrence-free survival by smoking status

Smoking Status	Never	Current	Past
Disease-free survival			
Number of cases/at risk	152/478	42/107	169/460
HR (95% CI), unadjusted	1.00	1.30 (0.93–1.84)	1.19 (0.96–1.49)
HR (95% CI), adjusted [†]	1.00	1.10 (0.73–1.64)	1.18 (0.92–1.50)
Overall survival			
Number of cases/at risk	105/478	35/107	117/460
HR (95% CI), unadjusted	1.00	1.65 (1.12–2.42)	1.20 (0.93–1.56)
HR (95% CI), adjusted [†]	1.00	1.38 (0.87–2.18)	1.17 (0.87–1.57)
Recurrence-free survival			
Number of cases/at risk	144/478	34/107	154/460
HR (95% CI), unadjusted	1.00	1.11 (0.76–1.61)	1.15 (0.92–1.44)
HR (95% CI), adjusted [†]	1.00	0.90 (0.58–1.41)	1.15 (0.89–1.48)

HR = hazard ratio; CI = confidence interval

[†] Adjusted for age, gender, number of positive lymph nodes, extent of invasion through bowel wall, tumor differentiation, body mass index, clinical bowel obstruction at diagnosis

Table III

Disease-free, overall and recurrence-free survival by overall smoking intensity

Overall Smoking Intensity	0 pack-yr	0–10 pack-yr	10–20 pack-yr	20+ pack-yr	P trend
Disease-free survival					
Number of cases/at risk	152/478	40/122	79/211	84/205	
HR (95% CI), unadjusted	1.00	1.06 (0.75–1.50)	1.26 (0.96–1.66)	1.34 (1.02–1.75)	0.03
HR (95% CI), adjusted [†]	1.00	0.99 (0.70–1.41)	1.17 (0.89–1.55)	1.21 (0.92–1.61)	0.16
Overall survival					
Number of cases/at risk	105/478	28/122	56/211	61/205	
HR (95% CI), unadjusted	1.00	1.08 (0.72–1.65)	1.29 (0.93–1.78)	1.44 (1.05–1.97)	0.03
HR (95% CI), adjusted [†]	1.00	1.01 (0.67–1.54)	1.19 (0.86–1.65)	1.23 (0.88–1.71)	0.22
Recurrence-free survival					
Number of cases/at risk	144/478	37/122	73/211	71/205	
HR (95% CI), unadjusted	1.00	1.03 (0.72–1.48)	1.22 (0.92–1.62)	1.19 (0.89–1.58)	0.23
HR (95% CI), adjusted [†]	1.00	0.97 (0.68–1.40)	1.15 (0.86–1.53)	1.12 (0.83–1.51)	0.41

Quartiles computed via SAS v.9

[†] Adjusted for age, gender, number of positive lymph nodes, extent of invasion through bowel wall, tumor differentiation, body mass index, clinical bowel obstruction at diagnosis

Table IV

Disease-free, overall and recurrence-free survival by smoking intensity prior to and after age 30

Pack-years of smoking by age 30					
	0 pack-yr	0-4 pack-yr	4-12 pack-yr	12+ pack-yr	P trend
Disease-free survival					
Number of cases/at risk	166/520	59/173	60/167	71/160	
HR (95% CI), unadjusted	1.00	1.10 (0.82-1.48)	1.17 (0.87-1.57)	1.49 (1.13-1.97)	0.005
HR (95% CI), adjusted [†]	1.00	1.06 (0.78-1.42)	1.10 (0.81-1.49)	1.37 (1.02-1.84)	0.04
HR (95% CI), adjusted [‡]	1.00	1.06 (0.78-1.38)	1.12 (0.81-1.54)	1.41 (1.00-1.97)	0.05
Overall survival					
Number of cases/at risk	118/520	41/173	45/167	47/160	
HR (95% CI), unadjusted	1.00	1.07 (0.75-1.52)	1.24 (0.88-1.75)	1.40 (1.00-1.96)	0.04
HR (95% CI), adjusted [†]	1.00	1.03 (0.72-1.47)	1.13 (0.80-1.60)	1.27 (0.89-1.80)	0.17
HR (95% CI), adjusted [‡]	1.00	1.02 (0.71-1.46)	1.09 (0.75-1.59)	1.20 (0.80-1.81)	0.37
Recurrence-free survival					
Number of cases/at risk	156/520	54/173	56/167	60/160	
HR (95% CI), unadjusted	1.00	1.07 (0.78-1.45)	1.16 (0.85-1.57)	1.32 (0.98-1.78)	0.06
HR (95% CI), adjusted [†]	1.00	1.04 (0.76-1.42)	1.12 (0.82-1.52)	1.29 (0.91-1.76)	0.11
HR (95% CI), adjusted [‡]	1.00	1.05 (0.77-1.43)	1.17 (0.84-1.63)	1.38 (0.96-1.98)	0.08
Pack-years of smoking after age 30					
	0 pack-yr	0-1 pack-yr	1-20 pack-yr	20+ pack-yr	P trend
Disease-free survival					
Number of cases/at risk	193/599	55/147	50/129	58/145	
HR (95% CI), unadjusted	1.00	1.25 (0.92-1.68)	1.31 (0.96-1.79)	1.28 (0.95-1.71)	0.12
HR (95% CI), adjusted [†]	1.00	1.08 (0.79-1.47)	1.25 (0.91-1.71)	1.20 (0.89-1.64)	0.21
HR (95% CI), adjusted [‡]	1.00	0.95 (0.67-1.34)	1.11 (0.79-1.57)	1.00 (0.69-1.46)	0.85
Overall survival					
Number of cases/at risk	130/599	41/147	35/129	45/145	

Pack-years of smoking by age 30					
	0 pack-yr	0-4 pack-yr	4-12 pack-yr	12+ pack-yr	P trend
HR (95% CI), unadjusted	1.00	1.39 (0.98-1.98)	1.38 (0.95-2.00)	1.50 (1.07-2.10)	0.03
HR (95% CI), adjusted [†]	1.00	1.21 (0.84-1.72)	1.29 (0.89-1.88)	1.32 (0.93-1.88)	0.14
HR (95% CI), adjusted [‡]	1.00	1.16 (0.78-1.74)	1.25 (0.84-1.88)	1.26 (0.82-1.94)	0.38
Recurrence-free survival					
Number of cases/at risk	182/599	50/147	46/129	48/145	
HR (95% CI), unadjusted	1.00	1.19 (0.87-1.63)	1.27 (0.92-1.76)	1.12 (0.81-1.54)	0.49
HR (95% CI), adjusted [†]	1.00	1.07 (0.77-1.47)	1.24 (0.89-1.72)	1.11 (0.79-1.54)	0.48
HR (95% CI), adjusted [‡]	1.00	0.97 (0.68-1.40)	1.14 (0.80-1.63)	0.96 (0.64-1.45)	0.96

Quartiles computed via SAS v.9

[†] Adjusted for age, gender, number of positive lymph nodes, extent of invasion through bowel wall, tumor differentiation, body mass index, clinical bowel obstruction at diagnosis

[‡] Adjusted as above as well as smoking intensity after age 30 (in analyses of pre-age 30) or before age 30 (in analyses of post-age 30)