Review

An Updated Review of the Epidemiological Evidence that Cigarette Smoking Increases Risk of Colorectal Cancer

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Abstract

Carcinogens from tobacco reach the colorectal mucosa through either the alimentary tract or the circulatory system and could possibly damage or alter expression of important cancer-related genes. Twenty-one of 22 studies found that long-term, heavy cigarette smokers have a 2–3-fold elevated risk of colorectal adenoma. Risk of large adenomas, immediate cancer precursors, was elevated in smokers in 12 of 12 studies. The studies of smoking and colorectal cancer risk conducted earlier in the twentieth century consistently did not show any association. However, 27 studies in various countries, including the vast majority of those that have been analyzed in the past several years, now show an association between tobacco use and colorectal cancer. In the United States, 15 of 16 studies conducted after 1970 in middle-age men and elderly men and, in the 1990s, in women demonstrate an association. This temporal pattern is consistent with an induction period of three to four decades between genotoxic exposure and the diagnosis of colorectal cancer and with men as a group having begun smoking several decades earlier than women. Overall, accumulating evidence, much within the past decade, strongly supports the addition of colorectal cancer to the list of tobacco-associated malignancies and the possibility that up to one in five colorectal cancers in the United States may be potentially attributable to tobacco use.

Introduction

The burning of tobacco produces numerous genotoxic compounds, including polynuclear aromatic hydrocarbons, heterocyclic amines, nitrosamines, and aromatic amines (1–4). Smoking is associated with a higher risk of cancer (5) in various tissues, including the stomach, kidney, bladder, and pancreas, that are not in direct contact with tobacco smoke. However, although the large bowel is exposed to the same genotoxic compounds either through the circulatory system (6) or through direct ingestion (7), initial studies, encompassing a follow-up time predominantly in the 1950s and 1960s for men, did not find cigarette smoking associated with risk of colorectal cancer (8–14). Yet when colorectal adenomas, which had become established as cancer precursors (15, 16), were first studied in the 1980s and 1990s, smokers were consistently found to have an elevated risk. A possible explanation for smoking being an apparent risk factor for precursor adenomas but not for cancers was offered (17, 18): carcinogens from cigarette smoke cause irreversible genetic damage in the normal colorectal mucosa, but many years are required for completion of all of the carcinogenic events after initiation. If so, the early studies may not have considered a sufficiently long time lag between smoking exposure and time of risk.

An induction period consisting of multiple decades is consistent with the known chemical or morphological events that precede the diagnosis of colorectal cancer. Two early changes that precede adenomas are DNA adducts and aberrant crypt foci (19). Some minute adenomas (<0.5 cm) may grow to intermediate-sized adenomas (0.5–1.0 cm), and some of these may progress to large adenomas (>1 cm). Increases in adenoma size are associated with enhanced dysplasia, genetic aberrations, and malignant potential (15, 16, 20). In some advanced adenomas, carcinoma *in situ* arises, followed by cancer, which itself may be present for some years before diagnosis. A number of observations reviewed previously (21) indicate that a substantial number of years, at least several decades, is generally required for completion of all of the stages.

Since the hypothesis of smoking as an initiator of colorectal carcinogenesis was raised (17, 18, 21), a number of studies have examined this relationship. In this review, the epidemiological data examining the association between smoking and colorectal adenoma and cancer will be summarized. All of the relevant articles were identified through the Medline database up to March 2001 and also by checking references from identified articles. Key words used for the search included: cigarettes, smoking, tobacco, colorectal, colon, rectal, cancer, neoplasm, adenoma, polyps, and adenocarcinoma. All of the identified studies that at least controlled for age and presented quantitative results were included.

Cigarette Smoking and Colorectal Adenomas: Summary of Studies

Incident or Prevalent Adenomas. In the late 1980s, reports of cigarette smoking and risk for colorectal adenoma were first published. Almost all of these studies were based on the diagnosis of prevalent adenoma detected at endoscopy. Tobacco use was examined in a variety of ways, including current cigarettes/day, duration of smoking, past smoking history, and total cigarette pack-years. In almost every published study, both male and female smokers had a higher risk of colorectal adenoma (17, 18, 22–40), including large (>1 cm) adenoma (17, 18, 23, 25, 28, 30, 33–38). The studies have typically found dose-response relationships between adenoma risk with cigarettes/

Received 12/28/00; revised 4/27/01; accepted 5/2/01.
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day among current smokers, with duration of smoking, and with total cigarette pack-years. Studies have consistently shown that individuals who smoke one to two packs (20–40 cigarettes)/day or who have accumulated 20 to 40 cigarette pack-years have about a 2–3-fold and up to a 5-fold higher risk than nonsmokers. An association has been observed relatively consistently among past smokers (17, 18, 26, 28–31, 34, 38).

Although smoking intensity appears to be important, the data also indicate that duration is critical. A study by Nagata *et al.* (36) found an elevated risk among those who had smoked for 30+ years (RR[2], 1.60; 95% CI, 1.02–2.62) but not less (RR, 1.10; 95% CI, 0.69–1.84). In male health professionals (17) and female nurses (18), elevated risks for large adenoma were observed only among men or women who had smoked for at least 20 years. A study by Terry and Neugut (35) found an elevated risk for ≥40 pack-years of smoking in men (OR, 1.61; 95% CI, 1.06–2.44) and in women (OR, 4.52; 95% CI, 2.04–9.08), but not with fewer cigarette pack-years. Zahm *et al.* (30) found that in past smokers, an increased risk for adenoma was only observed among those who had smoked for 26+ years, whereas for current smokers, an increased risk was observed for 11+ years of smoking. Monnet *et al.* (31) found that 1–9 years of smoking was associated with an OR of 1.3 (95% CI, 0.5–3.26), whereas >19 years of smoking was associated with an OR of 2.5 (95% CI, 1.3–4.9).

In contrast to the 21 studies that have found an association between cigarette smoking and adenoma risk, two case-control studies found no or equivocal relationships. One of these studies (41), conducted in the United States, found a nonsignificant but suggestive increased risk in women with greater pack-years (OR, 2.13; 95% CI, 0.83–5.52), but no association was observed in men. One Japanese study, based on only 86 cases, initially had null results (42). However, an analysis of 116 additional cases that occurred in the next 2 years of follow-up in the same population yielded a positive association (28).

Recurrent Adenomas. Studies of tobacco use and risk of recurrent adenomas have been sparse. The first such study (29) was based on only 23 cases of hyperplastic and adenomatous polyps combined and, thus, provides limited information. No appreciable relationship was noted, although male current smokers had slightly higher risk of polyp recurrence. In another study (38), consisting of 186 recurrent polyp cases and 330 individuals with no adenomas at follow-up, the risk of recurrent adenomas was higher among both male and female smokers. A 30- to 40-cigarette pack-year history was associated with a 2–3-fold elevation in risk of recurrent adenomas, which persisted even after 10 years of smoking cessation, consistent with an irreversible effect of tobacco.

A study by Baron *et al.* (43) examined recurrent adenomas in men and women. In endoscopy at year 1 after initial polypectomy, only in those who smoked >60 cigarettes/day was there a suggestive increased risk of recurrent adenoma (RR, 1.55; 95% CI, 0.89–2.72). However, there is likely to be some degree of misclassification at the year 1 endoscopy, because some of the polyps diagnosed are likely to be those missed at baseline.

Of note, the recurrent adenoma study design does not directly address the question whether smoking is related to a higher risk of adenoma, and there is no *a priori* reason to expect that, even if cigarettes increase risk of adenoma, the diagnosis of a subsequent adenoma would be more likely in those with smoking-associated adenomas than those with adenomas caused by other factors.

Summary of Evidence that Smoking Causally Increases Risk of Colorectal Adenoma

The evidence that smoking increases risk for adenoma is quite strong, and the strength of the association, the dose-response pattern for measures of intensity and duration, and the consistency across studies are consistent with a causal effect (44). The smoking and adenoma association persisted in every study after controlling for potential confounders, including diet and alcohol in many studies. If an unidentified confounding factor accounted for the association, this factor would have to be a very strong risk factor of colorectal adenoma to artifactually produce 2–5-fold RRs for smoking, be very strongly and consistently related to smoking in diverse United States male and female populations and in populations in Norway, France, and Japan, and have missed detection by every investigator in the 21 positive studies.

Most studies were based on endoscopied individuals. Although this design is useful in ensuring adenoma-free controls, individuals present for endoscopy for a variety of reasons. Thus, it is theoretically possible that smokers are more likely to undergo endoscopy for indications related to an underlying polyp as compared with nonsmokers, creating a systematic bias. However, studies in which all of the individuals in the defined population are screened regardless of symptoms (28–32) or subanalyses limited to an asymptomatic screening group (17, 18) also found a higher risk of colorectal adenoma among smokers.

A possibility raised by Baron *et al.* (45) is that adenomas may be more easily detectable during endoscopy for smokers, perhaps because of a relaxing effect of nicotine on the large bowel. However, although this bias may be plausible for small adenomas, a relationship with tobacco has also been observed for large adenomas in all of the 12 studies that have assessed size (17, 18, 23, 25, 28, 30, 33–38). That this systematic bias would account for a 2–3-fold greater likelihood of observing large adenomas, mostly within the range of 1 cm to 3 cm in diameter, is implausible, because only a small percentage of these are likely to be missed. Additionally, associations have been observed consistently in past smokers, for whom the putative relaxing effect of nicotine on the large bowel would no longer be present.

Because colorectal adenomas are well-established precursor lesions for cancers (15, 16, 20), risk factors for adenoma would likely increase risk of colorectal cancer. However, it is plausible that smoking may increase the risk only of adenomas that do not have the potential for progression to malignancy (46), although no evidence supports that a risk factor can be related to adenomas that are inherently incapable of progression. The strongest evidence against this possibility is that smoking is associated with higher risk of large adenomas (17, 18, 23, 25, 28, 30, 33–38). It is unlikely that large adenomas, which have acquired many genetic alterations observed in malignancies (20), have no capacity for carcinogenic progression.

Cigarette Smoking and Colorectal Cancer: Summary of Studies

Studies in United States Men. Assuming a 35–40-year induction period between smoking and colorectal cancer risk as suggested by recent studies (17, 18), an increased risk of

[2] The abbreviations used are: RR, relative risk; CI, confidence interval; OR, odds ratio.

colorectal cancer would not have emerged until at least the 1960s or 1970s in United States men, who as a group started smoking heavily around 1920. In contrast to the generally null earlier studies that covered the 1950s and 1960s (8–14, 47–51), in published studies of United States men that had a follow-up time after 1970, results have almost universally supported an association (17, 52–61). The only recent null study (62) was specifically conducted in young men, who, because they were ages 25 to 44 years, could not have smoked for 40 or more years. A study by Sandler *et al.* (53), which encompassed 1963–1975, found a suggestive association in men (RR, 1.42; 95% CI, 0.91–2.22) for current smokers. Because the time period was as early as 1963, a substantial number of men who had not smoked for 40 or so years may have been included.

In a prospective study of United States males followed from 1980 to 1985, Wu *et al.* (52) reported an elevated risk of colorectal cancer among current smokers (RR, 1.80), past smokers who stopped <20 years (RR, 2.63), and past smokers who stopped ≥20 years (RR, 1.71), all relative to nonsmokers. In a case-control study by Slattery *et al.* (54) primarily among Mormons, ever-smokers were at elevated risk (RR, 1.7; 95% CI, 1.0–2.8), and a dose-response was observed. This study, although supportive, should be interpreted with some caution because in this population, smokers may differ from nonsmokers more so than in a general population, and thus confounding is difficult to exclude.

The study of male health professionals (17) that first established a 35–40-year induction period demonstrated about a 2-fold elevated risk in men who had accumulated at least 10 cigarette pack-years more than 35 years previously. The vast majority of ever-smokers were past smokers who had quit decades previously; the elevated risk remained decades after quitting in these men.

After the report in health professionals, Heineman *et al.* (55) examined additional data from the Veterans Administration study that initially were null between smoking and colorectal cancer (10, 11). In a period covering 1954 to 1980, there were 3812 colon cancer deaths and 1100 rectal cancer deaths. Men who had started smoking after age 25 years had only a 10% to 20% elevated risk of colorectal cancer, but risk increased with an earlier age of initiating smoking (about a 40% to 50% increase for those who began before the age of 15 years). The results were highly statistically significant, but the magnitude of the RR was slightly weaker than other studies supporting an association, possibly because this study encompassed cases occurring as early as 1954.

A study of Hawaiian-Japanese men (56) found a dose-response for cigarette pack-years and colorectal cancer risk. The results were not statistically significant up until 30 pack-years, but the RR = 1.48 (95% CI, 1.13–1.94) for colon cancer and RR = 1.92 (95% CI, 1.23–2.99) for rectal cancer for 30+ pack years. LeMarchand *et al.* (57), in a case-control study in Hawaii, found a statistically significant positive association between smoking and colorectal cancer risk and a generally increasing risk with time since smoking. Slattery *et al.* (58) found an increasing trend of colon cancer risk with greater cigarette pack-years (RR, 1.38; 95% CI, 1.11–1.71 with >35 pack-years) in a case-control study. Risk increased with the number of cigarettes/day, and risk remained elevated even in those who had quit for ≥15 years. In this study population, a subsequent analysis showed an association between initiation of smoking at a young age and smoking for 35 or more years with tumors categorized by microsatellite instability (63). Another study (64) also indicated that there was a higher risk of mismatch repair-deficient colorectal cancer in cigarette smokers.

An analysis by Hsing *et al.* (59) in the prospective Lutheran Brotherhood Study showed a linear dose-response between cigarettes/day in current smokers at baseline and colon cancer risk, although the number of cases was limited (n = 120). Relative to never-smokers, the RR (and 95% CI) for past smokers was 1.45 (95% CI, 0.8–2.7); current smokers (1–19 cigarettes/day), 1.1 (95% CI, 0.5–2.5); current smokers (20–29 cigarettes/day), 1.6 (95% CI, 0.7–3.4); current smokers (≥30 cigarettes/day), 2.3 (95% CI, 0.9–5.7).

In the Physicians' Health Study, smoking status was examined in 1982, and men were followed for more than 12 years (60). The RR of colorectal cancer in a multivariate model was elevated for current smokers (RR, 1.81; 95% CI, 1.28–2.55) and past smokers (RR, 1.49; 95% CI, 1.17–1.89). Smoking up to 20 years before baseline (P = 0.05) and smoking up to and including age 30 years (P = 0.01) were statistically significantly related to risk, even controlling for subsequent smoking history. The authors concluded that their results agree with the hypothesis that the amount smoked in the distant past is the main risk factor, but they also suggest a role of recent past smoking.

In the Cancer Prevention II study, a prospective study of mortality of 312,332 men and 469,019 women begun in 1982, smoking for ≥20 years after baseline was associated with an increased risk of colorectal cancer in men (61). Dose-response relations were observed for cigarettes/day, pack-years smoked, and earlier age started smoking for current and past smokers. In this study, risk was not elevated for those who quit smoking >20 years before baseline. Adjustment for multiple covariates, including diet, had little impact on the results.

Studies in United States Women. Because United States women began smoking in substantial numbers only during the late 1940s and 1950s (65), a rise in the incidence of colorectal cancer would not have been expected until approximately the late 1980s, assuming a 35–40 year induction period (17, 18). No positive studies of smoking and colorectal cancer risk among women in the United States were found in the literature up to around 1990. Since then, there have been seven reports of studies that have included women. The first to show an association was from the Nurses' Health Study (18), which found a 2-fold elevated RR among long-term smokers, including past smokers. An earlier analysis in this cohort, which included cases diagnosed from June 1976 to May 1984, found only a weak, statistically nonsignificant association between smoking history and colon cancer, although past smoking was significantly associated with risk of rectal carcinoma (66). In this earlier report of the Nurses' Health Study, very few women had begun smoking more than 35 to 40 years previously.

A case-control study by Newcomb *et al.* (67) found an elevated risk only among women who smoked for at least 31 years, and a dose-response relation with cigarettes/day was observed. Earlier age at initiation also was associated with an increased risk, and past smokers had a moderately increased risk. Another case-control study by Slattery *et al.* (58) found that >35 pack-years of smoking was associated with an elevated risk (RR, 1.38; 95% CI, 1.11–1.71) in women. Also, the usual number of cigarettes/day was associated with an elevated risk (≥20 cigarettes/day: RR, 1.45; 95% CI, 1.15–1.83). The risk was particularly strong for women with a high body mass index (RR, 1.98). The number of cigarettes/day appeared to be more important than the duration in this study. A study by Le Marchand *et al.* (Ref. 57; 1987–1991) also found an elevated

risk of colorectal cancer, and the risk was particularly strong for women who had smoked for >30–40 years in the past.

In a prospective study of Iowa women (68) followed from 1986 to 1990, no association was found among current smokers (RR, 1.09; 95% CI, 0.74–1.59) or former smokers (RR, 0.92; 95% CI, 0.64–1.32). However, this study did not report on smoking intensity and did not explicitly examine duration of smoking. Most studies show associations at relatively high levels of smoking (*e.g.*, 20+ cigarettes/day). Details on smoking patterns were not presented, but notably, alcohol consumption in this population was quite low (69).

The Cancer Prevention Study II (61) found in women, as for men, elevated risks of colorectal cancer mortality in both current smokers (RR, 1.41; 95% CI, 1.26–1.58) and past smokers (RR, 1.22; 95CI %, 1.09–1.37). Risks were significantly elevated only after 20–30 years of smoking duration before baseline, for both current and past smokers. Multivariate analysis yielded similar results to age-adjusted analyses.

Several United States studies reported results combined for men and women. One study by Freedman *et al.* (70) was designed to investigate the association between p53 overexpression (a marker of p53 mutations) in colorectal cancer and cigarette smoking. In that study, smoking status or total pack-years of smoking was not associated with cases that were positive for p53 mutations, but current and past smokers had a 2-fold risk of developing cancers without p53 overexpression (comprising about 55% of all of the tumors), and a dose-response relation was observed with cigarette pack-years ($P = 0.03$). These findings suggest that colorectal cancers related to smoking may proceed through a p53-independent pathway. Another case-control study (71) of United States blacks conducted from 1973 to 1976 found an elevated risk of colorectal cancer with 20+ years of smoking. A cohort study by Klatsky *et al.* (72) followed 106,203 men and women from 1978 to 1984. There were 203 total colon cancer cases and 66 rectal cancer cases. Results were essentially null, with only suggestive increases in risk of colon cancer for smokers of ≥1 cigarette packs (RR, 1.35; 95% CI, 0.78–2.35) and past smokers for rectal cancer (RR, 1.28; 95% CI, 0.72–2.28). However, the majority of cases were female, and because the follow-up period was from 1978 to 1984, it is unlikely that an appreciable number of women had smoked for greater than 35–40 years.

Recent Studies in Other Countries. Smoking became prevalent for men and women during varying times in the twentieth century in non-United States populations. A small Japanese study of 59 male and 34 female colorectal cancer cases conducted over the years 1981–1983 yielded null results (73), but smoking became prevalent in Japan only in the 1950s, so sufficient numbers had probably not accrued 40 or more years of smoking. A hospital-based case-control study in Nagoya, Japan (74) examined "habitual" smoking (both past and current) and risk of colon cancer ($n = 231$) and rectal cancer ($n = 201$) over the years 1988–1992. The study population consisted of both males (average age of cases, 60.6 years) and females (average age, 56.8 years). No relationship was observed for colon cancer, but "habitual" smoking increased risk for rectal cancer in both males (OR, 1.9; 95% CI, 1.1–3.2) and females (OR, 1.7; 95% CI, 1.0–3.1). A recent case-control study in Tokyo (75) of 129 colorectal carcinoma *in situ* cases, 66 colorectal cancers, and 390 controls from 1991 to 1993 found that cumulative exposure (pack-years) to cigarette smoking within the prior 20 years was significantly associated with risk for colorectal carcinoma *in situ* [RR, 3.7; 95% CI, 1.6–8.4 for ≥31 *versus* 0 pack-years; P (trend) = 0.0003], whereas smoking until 20 years before the diagnosis was associated with risk for colorectal cancer [RR, 5.0; 95% CI, 1.3–18.3; for ≥31 *versus* 0 pack-years; P(trend) = 0.005]. This finding was quite similar to that seen in United States health professionals and nurses (17, 18).

In a long-term follow-up study of British male doctors (76), smoking was strongly related to risk of rectal cancer ($n = 168$). Smokers of 25+ cigarettes/day had a 4.4-fold higher rate of rectal cancer ($P < 0.001$). For colon cancer ($n = 437$), there was only weak evidence of a positive, not statistically significant trend (RR, 1.44). This study had long-term follow-up (40 years), but included cases diagnosed throughout the follow-up. A recent population-based case-control study of men and women in Great Britain of 174 colorectal cancer cases (77) found smoking cigarettes within the last 5 years associated with an increased risk (OR, 1.77; 95% CI, 1.03–3.14). It is unknown for how long these persons had been smoking, but because the median age of cases was 69 years and the vast majority of smokers begin in adolescence or early adulthood, many were probably long-term smokers.

A cohort study (78) in Norway followed 68,825 men and women from 1972 to 1988. There were 51 colon cancer deaths and 40 fatal rectal cancers. Male past smokers had a moderately increased risk for fatal colon cancer (RR, 1.2) and fatal rectal cancer (RR, 1.4). Male current smokers were at elevated risk for death from colon cancer (RR, 1.5) and rectal cancer (RR, 1.8). Few women would have been expected to have smoked for 40+ years.

A recent prospective study (79) from Finland also examined smoking and risk of colorectal cancer, taking into account a long induction period. Among 56,973 men and women followed from baseline in 1966–72 to 1994, a weak nonstatistically significant overall association was observed, but for follow-up periods of between 11 and 20 years, a significant increase in risk was observed for smokers (RR, 1.57; 95% CI, 1.09–2.24). At baseline, smokers had smoked for 20 years on average, suggestive of an induction period of 31–40 years. This association was limited to men (RR, 1.94; 95% CI, 1.25–2.24), possibly because they smoked more. In addition, a comparison of risk of colorectal cancer in persons recorded as smokers in both of two baseline examinations revealed a significant increase in the persistent smokers (RR, 1.71; 95% CI, 1.09–2.68).

A cohort study (80) of 11,580 women and 11,366 men, which followed participants from 1968 to 1995, was conducted in Iceland. Over this period, there were 193 cases of colorectal cancer in men and 145 in women. In this cohort, the rate of current smoking at baseline was higher in women than in men (1–14 cigarettes/day, 11% of men and 20% of women; 15–24 cigarettes/day, 13% of men and 16% of women; 25+ cigarettes/day, 6% of men and 3% of women). Among women, a dose-response relation was observed with an increasing level of cigarette smoking (RRs, 1.37, 1.53, and 2.48) in a multivariate model. Results were not presented for men, presumably because they did not achieve statistical significance (80).

A hospital-based case-control study was conducted in Yugoslavia for colon and rectal cancers over the time period 1984–1986 (81, 82). The analysis showed a dose-response for cigarettes/day. Risk of colorectal cancer was not elevated among men and women who had smoked for 1–30 years (RR, 1.0), but risk was elevated for total colorectal cancer (RR, 2.0) and rectal cancer (RR, 2.7) among those who had smoked for more than 30 years.

A hospital case-control study of 955 cases of colon cancer and 629 cases of rectal cancer in northern Italy did not support an association between smoking and colorectal cancer risk (83).

No association was found with the number of cigarettes smoked, duration, time since starting, and time since stopping, and no trend was observed for increasing number of pack-years. Findings were null for both males and females.

Several studies conducted in Sweden do not support a relationship between smoking and colorectal cancer risk, even accounting for a long induction period. A random sample of 26,000 Swedish women were asked about their smoking status in the early 1960s and followed for 26 years (84). Given the smoking patterns for Swedish women, it is unlikely that much of the follow-up exceeded a 30–40-year induction period, because tobacco use rose largely in the 1950s and peaked in the 1960s. Over a 26-year follow-up, no overall association was observed, except for a slight suggestive increase in smokers of 16+ cigarettes/day at baseline (RR, 1.42; 95% CI, 0.77–2.60). A case-control study (45) of 352 colon cancer cases and 217 rectal cancer cases also did not find an elevated OR, even among long-term smokers (40+) years. A follow-up study of Swedish construction workers did not find any association among 713 men with colon cancer and only a weak association with 505 rectal cancer cases (85). Among smokers with more than 30 years of smoking at the start of follow-up, the RR was 1.03 (95% CI, 0.85–1.25) for colon cancer and 1.21 (95% CI, 0.96–1.53) for rectal cancer. However, a recent study (86) of tobacco smoking and colorectal cancer in a prospective cohort study of 17,118 Swedish twins found that long-term heavy smoking was associated with an increased risk of colorectal cancer (RR, 3.1; 95% CI, 1.4–7.1).

Generally, associations have been observed for both colon and rectal cancers. Interestingly, in several studies (8, 18, 66), an association was observed only with rectal cancer although there were more cases of colon cancer. In one of these studies (66), with additional follow-up (18), an association emerged for colon cancer as well. In some studies, the association has been appreciably stronger for rectal cancer (18, 55, 67, 76) or perhaps only present for rectal cancers (56, 74, 85). Yet, this pattern has not been universal, and some studies even suggest a stronger relationship for colon cancer (17, 56).

Summary of Evidence That Smoking Causally Increases Risk of Colorectal Cancer

The following lines of evidence presented in this review indicate that cigarette smoking is an important risk factor for colorectal cancer after accounting for a sufficiently long time lag of up to 35–40 years: (*a*) almost all of the studies conducted for adenomas, precursors of colorectal cancer, have yielded statistically significant positive associations with long-term smoking. In none of the studies did controlling for various potential confounders attenuate the association, and this relationship was observed in all of 12 studies that examined large adenomas (17, 18, 23, 25, 28, 30, 33–38); (*b*) essentially all of the major earlier studies (8–14, 47–51) of smoking and cancer, which covered mostly the 1950s and 1960s, showed no association between smoking and colorectal cancer even among heavy smokers. During this time period, few men and especially few women would have exceeded four decades of smoking; (*c*) in studies of United States men with a follow-up time exclusively after 1970, for which many smokers may have exceeded four decades of smoking, 10 of 10 published studies (17, 52, 54–61) report a positive association; (*d*) women in the United States began to smoke mostly in the late 1940s and 1950s, and thus four decades of smoking would only be achieved by around 1990. Although no positive studies of smoking were identified in United States women before 1990, five of five published studies (18, 57, 58, 61, 67) with a follow-up time in the 1990s report statistically significant positive associations; (*e*) in studies conducted outside of the United States, although there have been several null studies (45, 83–85), recent studies in Japan (74, 75), Finland (79), England (77), Norway (78), Iceland (80), Yugoslavia (81, 82), and Sweden (86) show long-term smokers to be at elevated risk.

Studies have assessed tobacco use in different ways, and dose-response relations with colorectal cancer have been reported for cigarette pack-years, smoking duration, smoking intensity, smoking history in the distant past, and younger age at initiation of smoking. Although it is clear that long-term heavy smokers are at higher risk of colorectal cancer, the relative importance of dose and duration remains somewhat in question because these are correlated. Nonetheless, the evidence as just summarized strongly indicates the importance of a significant time lag, so those who begin smoking at younger ages and at heavy doses will tend to experience the greatest lifetime risk. How much and how quickly risk drops after quitting remains somewhat in question and should be studied further, but most data suggest that at least some of the excess risk persists indefinitely in past smokers (17, 18, 52, 58, 60). Only one study (61) suggests that the excess risk approaches zero after greater than 20 years after smoking cessation, but this study did not show that these were not light smokers when they smoked.

The only plausible alternative explanation of the data is residual confounding attributable to unmeasured factors. This scenario appears unlikely given the consistency of the findings for men and women in diverse populations. Some studies have controlled for physical activity, diet, and alcohol, which would appear to be the most likely confounders, and the association between smoking and colorectal cancer persisted (17, 18, 56–58, 61, 67).

Some studies have attempted to estimate the population-attributable risk because of smoking in the United States. Estimates have been 21% of colorectal cancer in men (17), 16% of colon cancer and 22% of rectal cancer in men (55), 12% of colorectal cancer in men and women (61), and 11% of colon cancer and 17% of rectal cancer in women (67).

These data strongly indicate that colorectal cancer should be added to the list of tobacco-associated malignancies. In the United States, up to one in five cases of colorectal cancers may be potentially attributable to tobacco use (17, 55, 61, 67). These findings have obvious public health implications and possible clinical relevance regarding surveillance for colorectal neoplasia. In studies of polymorphic genes encoding xenobiotic-metabolizing enzymes, potential interactions with tobacco have been examined in a relatively small proportion of the studies (87). Further investigation in this area may help identify susceptible individuals. Whether tobacco use is linked primarily to specific subgroups of colorectal cancers, such as those with p53 mutations (70), or those categorized by microsatellite instability (63) requires further study.

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Cancer Epidemiol Biomarkers Prev 2001;10:725-731.