

Etiology of colorectal cancer (C18–20) in Central and South America

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How to cite:

Sierra MS, Forman D (2016). Etiology of colorectal cancer (C18-20) in Central and South America. In: Cancer in Central and South America. Lyon: International Agency for Research on Cancer. Available from: http://www-dep.iarc.fr/CSU_resources.htm, accessed [date].

Colorectal cancer is a heterogeneous disease that arises from multiple tumorigenic pathways [1–6]. Colon and rectal adenocarcinomas are the result of a stepwise progression from normal tissue to dysplastic epithelium to carcinoma – referred to as the adenoma–carcinoma sequence – which is accompanied by multiple genetic alterations including oncogenes, the activation and inactivation of tumour suppressor genes, and mismatch repair genes [6].

Most colorectal cancers are sporadic [7, 8] but can arise from inherited cancer syndromes, such as Lynch syndrome (the most common syndrome), and hamartomatous, hyperplastic, autosomal recessive MYH-associated, and familial juvenile polyposis; however, these only represent about 2–5% of all colon and rectal cancers [8, 9]. Inflammatory conditions, such as ulcerative colitis and Crohn disease, have been associated with an increased risk of colon and rectal cancers, but only account for 1–2% of all cases [7, 10, 11]. Because most of these cancers are sporadic and their incidence has been reported to be high in economically transitional countries, especially in those that have adopted lifestyles typical of industrialized countries (diets with a low intake of fruit and vegetables, increased consumption of red or processed meat, physical inactivity, tobacco smoking, and alcohol consumption) [12, 13], this section focuses on their relationship to modifiable lifestyle factors, such as obesity, diet (consumption of dietary fibre, fruit and vegetables, and meat), and physical activity, which are relevant to their prevention in the Central and South American region.

Increased body weight and physical inactivity

The International Agency for Research on Cancer (IARC) evaluated the available and concluded that there is sufficient evidence (a causal relationship) that overweight and physical inactivity increase the risk of colon cancer; for rectum cancer the relationship is less clear [14]. Obesity, especially abdominal obesity, and physical inactivity have been hypothesized to cause insulin resistance and chronic hyperinsulinaemia. Chronic hyperinsulinemia leads to reduced concentrations of insulin-like growth factor (IGF) binding proteins 1 and 2 and increased tissue levels of IGF-1 which plays a critical role in the development and progression of cancers [14–18]. The mechanisms by which increased physical activity may reduce the risk of colon and rectal cancer are: a reduction in gastrointestinal transit time, which decreases the time that carcinogens are in contact with colonic mucosal cells, immune function, insulin and IGFs, genetic mutations, and obesity [14, 19].

When body mass index (BMI) increases from 23 kg/m² to 30 kg/m², the risk of colon cancer increases linearly by approximately 50% in men and 25% in women, whereas an increase in the levels of physical activity (either in intensity, duration or frequency) is associated with an approximate 40% reduction in cancer risk. The association between overweight and physical inactivity with rectal cancer was less evident [14]. Of the colon and rectal cancers that occurred worldwide in 2012, 13% and 6% of those in men and approximately 8% and 4% of those in women were estimated to be attributable to high BMI (> 25 kg/m² vs < 25 kg/m²), respectively [20]. Results from recent meta-analyses revealed similar associations: a higher BMI was moderately associated with the development of both colon and rectal cancers in men [18, 21–23] and with that of colon cancer in women [18, 21, 22], and the associations with colon cancer were consistently stronger in men than in women. Evidence of a dose–response relationship between increased body mass and colon and rectal cancer was found in several studies [17, 18, 22]. For instance, an increase of 5 kg/m² in BMI was positively associated with colon cancer in men and women (relative risk [RR], 1.24; 95% confidence interval [CI] 1.21–1.28 in men; RR, 1.09; 95% CI, 1.05–1.14 in women) and with rectal cancer in men (RR, 1.09; 95% CI, 1.06–1.12) [17].

The association between physical activity and colon and rectal cancer was evaluated in two meta-analyses with inconsistent results [19, 24]. Recreational activities were associated with a lower risk of colon cancer in both men and women (RR, 0.78; 95% CI, 0.68–0.91 in men; RR, 0.71; 95% CI, 0.57–0.88 in women) whereas occupational activities were related to a lower risk of colon cancer in men (RR, 0.79; 95% CI, 0.72–0.87) but not in women [24]. Increased leisure-time physical activity was inversely related to the risk of colon cancer among both men (RR, 0.80; 95% CI, 0.67–0.96) and women (RR, 0.86; 95% CI, 0.76–0.98) [19]. Neither occupational or recreational activities, nor leisure-time physical activity were associated with a change in the risk of rectal cancer [19, 24].

Dietary factors

Vitamin D and calcium

Although a growing body of epidemiological evidence has linked vitamin D consumption with a lower risk of colon and rectal cancer [25–30], a lack of consistency has been found across study findings and randomized control trials in humans have yet to support conclusively a beneficial role for vitamin D in the development of these cancers [29].

Circulating levels of vitamin D in blood have been inversely associated with the risk of colon and rectal cancer in three separate meta-analyses [15, 26–28]. Patients with high levels of 25-hydroxyvitamin D (25(OH)D) had a lower risk of colorectal cancer (pooled odds ratio [OR], 0.66; 95% CI, 0.54–0.81 for the top vs the bottom quantiles of circulating 25(OH)D levels), after adjusting for relevant confounders; the association was stronger for rectal cancer than for colon cancer (for the top vs the bottom quantiles of circulating 25(OH)D levels: OR, 0.50; 95% CI, 0.28–0.88 for rectal cancer; OR, 0.77; 95% CI, 0.56–1.07 for colon cancer) [26]. A 10-ng/mL increase in serum 25(OH)D was also related to a lower risk of colorectal cancer (pooled OR, 0.85; 95% CI, 0.79–0.91) [28].

In a meta-analysis of 60 studies (26 cohort and 34 case-control), Huncharek et al. [25] found an inverse relationship between calcium intake and the risk of colorectal or colon cancer (cohort studies: pooled RR, 0.77; 95% CI, 0.71–0.81 for colorectal cancer; pooled RR, 0.76; 95% CI, 0.69–0.84 for colon cancer); similar protective effects were observed when calcium intake and the risk of either colon or rectal cancers alone was evaluated. High (vs low) consumption of milk (all types) or dairy products was inversely associated with the risk of colorectal or colon cancer (cohort studies: pooled RR, 0.90; 95% CI, 0.83–0.97 for colorectal cancer; pooled RR, 0.84; 95% CI, 0.75–0.95 for colon cancer). Milk intake was not related to the risk of rectal cancer. Protective effects were observed for the dietary intake of vitamin D and the risk of rectal cancers (5 cohort studies: pooled RR, 0.83; 95% CI, 0.70–1.04) and for the dietary intake of calcium supplement and the risk of colorectal cancer (cohort studies: pooled RR, 0.76; 95% CI, 0.65–0.89). Similar protective effects for colorectal cancer were reported for calcium, milk/dairy and vitamin D intake when all case-control studies were pooled.

Fibre

The evidence linking dietary fibre with the prevention of colon and rectum cancer remains contradictory [31–33]. Results from two meta-analyses [33, 34] and a large cohort study including 1.8 million person-years and 1596 cases of colorectal cancer [32] found weak to null inverse associations between dietary fibre consumption (i.e., intake of fibre, cereal fibre, vegetables, and fruit) and the risk of these cancers. Overall, these results do not support the association between fibre intake and colorectal cancer but reveal considerable confounding by other dietary and lifestyle factors.

Meat intake

Red meat consumption has been related to an increased risk of colorectal cancer [35, 36], and the polycyclic aromatic hydrocarbons formed during the cooking process may also be responsible for such an increased risk, although the underlying mechanisms are still unclear [31, 37–39]. Larsson et al. [35] reported a moderate increase in CRC risk with the highest versus the lowest intake categories of red meat and processed meat (13 studies: RR, 1.28; 95% CI, 1.15–1.42 for red meat; RR, 1.20; 95% CI, 1.11–1.31 for processed meat). Red meat was associated with an increased risk of colon (9 studies: RR, 1.21; 95% CI, 1.05–1.40) and rectal (7 studies: RR, 1.56; 95% CI, 1.25–1.95) cancers, but not with the risk of cancer of the proximal or distal colon. Processed meat was associated with an increased risk of colon cancer (10 studies: RR, 1.21; 95% CI, 1.09–1.34), distal colon cancer (3 studies: RR, 1.41; 95% CI, 1.09–1.94), and rectal cancer (8 studies: RR, 1.20; 95% CI, 0.98–1.46, with evidence of heterogeneity between studies), but not with the risk of proximal colon cancer.

In a case-control study conducted in Cordoba, Argentina, Navarro et al. [38] reported that the consumption of large amounts of cold cuts and sausages and bovine viscera was positively associated with an increased risk of colorectal cancer (third vs first tertile of consumption: OR, 1.47; 95% CI, 1.02–2.15 for cold cuts and sausages; OR, 1.73; 95% CI, 1.18–2.54 for bovine viscera) while lean beef was inversely associated with the risk of colorectal cancer (OR, 0.64; 95% CI, 0.43–0.94 for the second vs first tertile; OR, 0.67; 95% CI, 0.40–0.97 for the third vs first tertile). In a second analysis, Navarro et al. [39] showed that barbecuing bovine viscera, frying lean beef, and frying lean fish were positively associated with the risk of colorectal cancer (OR, 2.084; 95% CI, 1.31–3.32

for barbecuing bovine viscera; OR, 2.27; 95% CI, 1.38–3.73 for frying lean beef; OR, 2.36; 95% CI, 1.47–3.79 for frying lean fish) while iron-pan cooking of lean beef was inversely related with the risk of colorectal cancer (OR, 0.428; 95% CI, 0.224–0.817). When the temperature levels used to cook meats (red, white, or both), evaluated by the darkness of the surface, was considered, darkly browning was strongly related with an increased risk of colorectal cancer (OR, 1.42–4.57). These results indicated that the increased risk of colorectal cancer is related not only to the type of meat consumed but also to high cooking temperatures.

Dietary patterns

Evidence from a matched case–control study conducted in Montevideo, Uruguay, indicated that high consumption (compared with low consumption) of fruit and vegetables reduced the risk of colorectal cancer by 62% (OR, 0.38; 95% CI, 0.20–0.71 for the fourth vs first quartile) [40]. Having a ‘prudent diet’ pattern (high intakes of white meat, dairy foods, raw vegetables, and total fruit) was also shown to be protective against colon and rectal cancers in men and women (risk estimates, 0.51–0.61 for men and 0.45–0.66 for women) and having a traditional diet pattern (high intakes of desserts, cooked vegetables, all tubers, and legumes) was protective against colon and rectal cancers in men (OR, 0.49–0.76), whereas a diet pattern typical of industrialized countries (high intakes of red meat, processed meat, and total eggs) was associated with a 2.6-fold increase in the risk of colon cancer in men and a 1.95-fold increase in the risk in women [41]. In Brazil, Neves et al. [42] showed that mortality from colon and rectal cancers between 1980 and 1997 in 10 Brazilian capitals was positively correlated with previous (1974–75) high consumption of calories, cereals, eggs/milk/cheese, meat, and oil/fat.

Tobacco smoking

Cigarette smoking has been associated with an increased risk of adenomatous polyps in the large bowel which are precursor lesions of colorectal cancer [43]. IARC evaluated the data on smoking and cancer risk and concluded that there is sufficient evidence that smoking causes colon and rectal cancer [44]. Several mechanistic pathways by which compounds found in tobacco (i.e., the nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and *N*-nitrosonornicotine) and in tobacco smoke (arylamines, polycyclic aromatic hydrocarbons, and volatile organic compounds) cause cancer have been described. Heterocyclic amines found in tobacco smoke have been shown to cause intestinal cancer in rats and mutate the *adenomatous polyposis coli* gene in mice; this gene is also mutated and its expression is altered in human colon cancer [44]. Moreover, exposure to tobacco smoke has been related to mutational or epigenetic changes in *KRAS* and *BRAF*, which are also identified in the majority of cases of colon and rectal cancer [45].

In a meta-analysis of case–control and cohort studies conducted in Asia, Europe, and North America, Botteri et al. [46] found that, compared with never-smokers, ever-smokers and former smokers had a higher risk of colorectal cancer (pooled RR, 1.18; 95% CI, 1.11–1.25 in 25 studies; pooled RR, 1.17; 95% CI, 1.11–1.22 in 47 studies) but the associations for current smokers were weak or null. Smoking (ever, current, and former) was positively associated with cancers of the rectum. Ever having smoked and formerly having smoked were positively related to colon cancer and to proximal colon

cancers but not to distal colon cancers. A linear dose–response relationship has been described for smoking patterns (cigarettes per day, number of pack–years, and duration) and the risk of colon/rectal cancers compared with never smoking [46, 47].

The incidence of and the risk of dying from colon and rectal cancer have been shown to be higher among smokers than never-smokers [46, 47]. In a stratified analysis of 19 cohort studies, the incidence of colon and rectal cancers was 65.5 per 100 000 for smokers and 54.7 per 100 000 for non-smokers (a risk difference of 10.8 per 100 000 person–years) [46]. In a meta-analysis of 20 studies (16 for incidence and 4 for mortality), Liang et al. [47] found that the risk of developing or dying from colon and rectal cancer was higher in current (RR, 1.17; 95% CI, 0.97–1.40 for colon cancer; RR, 1.40; 95% CI, 1.06–1.84 for rectal cancer) and former (RR, 1.25; 95% CI, 1.04–1.51 for colon cancer; RR, 1.15; 95% CI, 0.90–1.48 for rectal cancer) smokers than in never-smokers. Smoking has also been related to a poorer prognosis for colorectal cancer compared with never smoking [48].

Alcohol consumption

IARC concluded that there was sufficient evidence to support the conclusion that consumption of alcoholic beverages is causally related to colon and rectal cancer. Also, the evaluation revealed that the risk may only be increased at relatively high levels of intake (i.e., > 30 g per day). The evidence indicates that all alcoholic beverages have the same effect. Alcohol consumption results in exposure to acetaldehyde (a metabolite of ethanol) which has genotoxic effects and has also been classified as carcinogenic to humans [49]. Heavy alcohol consumption leads to folate deficiency (by reducing the absorption of folate or by the inhibition of enzymes that are important for DNA synthesis and methylation) and other nutritional deficiencies, such as vitamins A, B12, B6, and others (by impairing intestinal absorption and by changing metabolic pathways). Alcohol consumption may also alter the immune surveillance of the immune system, thus favouring the development of cancer [50].

Three meta-analyses have also shown the strong association between alcohol consumption and an increase in the risk of colon and rectal cancer in case–control and cohort studies [51–53]. Light drinking (up to one drink per day), however, has not been associated with the risk of colorectal cancer (RR, 0.99; 95% CI, 0.95–1.04 in 54 studies) [54]. A dose–response meta-analysis indicated that every 100 g increase in alcohol intake per week resulted in a 19% increase in the risk of colorectal and a 15% increase in the risk of colon or rectal cancers [51]. A recent meta-analysis of four studies showed that the risk of colorectal cancer increased with increasing daily alcohol consumption (P for trend < 0.01) and was similar for both men and women [53].

Other factors

Family history

It has been shown that having a first-degree relative with colon or rectal cancer, familial adenomatous polyposis or hereditary non-polyposis increases the risk of colorectal cancer, perhaps due to a combination of hereditary factors and shared environment factors [55]. In a meta-analysis of 13 cohort and 34 case–control studies, Butterworth et al. [55] showed that having one or more affected first-degree relative (parent, sibling, or

child) increased the risk of colorectal cancer 2-fold compared with those with no family history (RR, 2.24; 95% CI, 2.06–2.43 in 47 studies) and the risk increased dramatically as the number of first-degree relatives increased (RR, 3.97; 95% CI, 2.60–6.06 for at least two affected relatives in 10 studies). The risk was even greater if the relative was diagnosed at a young age (RR, 3.17; 95% CI, 2.37–4.25 for < 50 years; RR, 1.90; 95% CI, 1.59–2.28 for ≥ 50 years).

Oral contraceptives and postmenopausal hormonal therapy

IARC reviewed the available experimental and epidemiological evidence on estrogen–progestogen oral contraceptives, estrogen–progestogen menopausal therapy, and estrogen-only menopausal therapy on the risk of colon and rectal cancer and concluded that the evidence suggested a lack of carcinogenicity. In fact, the evidence revealed that oral contraceptives and estrogen-only menopausal therapy may reduce the risk of colon and rectal cancer [56]. Several biological mechanisms have been proposed for the effect of oral contraceptives and postmenopausal hormone therapy on these cancers and include a decrease in the production of secondary bile acids, a decrease in the production of IGF-1 and IGF binding protein-3, and microsomal instability, all of which are linked with an increased risk of colon/rectal cancers, and a direct effect in epithelial cells because estrogens inhibit colon carcinogenesis in animal models [57, 58]. Oral contraception has been shown to reduce the number of colon/rectal adenomas in familial adenomatosis polyposis (as cited in [57]).

Grodstein et al. [59] found that postmenopausal hormone therapy was associated with a 20% reduction in the risk of colon and rectal cancer compared with never use (in 10 cohort and eight case–control studies), and the reduction was stronger among current users (RR, 0.66; 95% CI, 0.59–0.74 in 7 cohort and 3 case–control studies). Bosetti et al. [57] showed that ever-users of oral contraceptives had a 19% (95% CI, 0.72–0.92) lower risk of colon and rectal cancers (7 cohort and 11 case–control studies) and a 15% (95% CI, 0.75–0.93) lower risk of colon cancer (5 cohort and 10 case–control studies) than never-users.

Although the use of these medications appears to lower the risk of colon and rectal cancer, which preparations of estrogen-alone or estrogen–progestogen are optimal remains unclear [56]. Moreover, as postmenopausal hormones increase the risk of breast cancer and cardiovascular events, the risk may outweigh the benefit [58].

Aspirin and non-steroidal anti-inflammatory drugs

Epidemiological evidence suggests that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) reduce the risk of colorectal cancer [60–63]. Evidence from four randomized trials showed that aspirin use (any dose) reduced the risk of any adenoma in the large bowel by 17% (pooled RR, 0.83; 95% CI, 0.72–0.96) and that of advanced adenomas by 28% (pooled RR, 0.72; 95% CI, 0.57–0.90) compared with a placebo, with an absolute risk reduction of 7.5% (95% CI, 3.2–10.2%). Aspirin use (any dose) also reduced the risk of advanced lesions by 28% [62]. A recent pooled analysis of four randomized trials evaluating the long-term effect of aspirin use on the incidence of and mortality from colon and rectal cancer showed a 24% (95% CI, 0.60–0.96) reduction in the incidence of and a 35% (95% CI, 0.48–0.88) reduction in mortality from colon cancer compared with the control group. However, no decline in the incidence of

or mortality from rectal cancers was detected. Aspirin use reduced the incidence of and mortality from proximal colon cancer (RR, 0.45; 95% CI, 0.28–0.74 for incidence; RR, 0.34; 95% CI, 0.18–0.66 for mortality) but not those of distal colon cancer (RR, 1.10; 95% CI, 0.73–1.64 for incidence; RR, 1.21; 95% CI, 0.66–2.24 for mortality) compared with the control group. Aspirin (75–1200 mg) use for ≥ 5 years reduced the risk of proximal colon cancer and rectal cancer [60]. Randomized trials with a ≥ 5 -year scheduled duration of daily aspirin use reduced the risk of death from colon and rectal cancer by 21% at 0–10 years, 41% at 10–20 years, and 40% at 0–20 years of follow-up compared with the control group [63].

In spite of these results, there is a concern about haemorrhagic stroke and gastrointestinal bleeding among aspirin and NSAID users, especially with long-term use. Therefore, these risks may outweigh the benefits of aspirin and NSAIDs use for the primary prevention of colorectal cancer in asymptomatic adults who are at an average risk of colon and rectal cancers. The United States Preventive Services Task Force and an international consensus panel have called for further investigation to evaluate the effects of using aspirin and NSAIDs on other organs and cancers, and to determine the optimal lowest dose, duration, age at initiation, and frequency, particularly among high-risk populations for which benefits might outweigh side effects [58, 64].

Acknowledgements

This work was undertaken during the tenure of a Postdoctoral Fellowship by Dr Mónica S. Sierra from the International Agency for Research on Cancer, partially supported by the European Commission FP7 Marie Curie Actions – People – Co-funding of regional, national and international programmes (COFUND). The authors wish to thank Drs Isabel Izarzugaza and Joannie Lortet-Tieulent for their valuable comments.

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