Current hypotheses on the etiology of colorectal cancer Critical review of the epidemiological evidence

E. Riboli, A. J. Sasco
Unit of Analytical Epidemiology, Division of Epidemiology and Biostatistics, International Agency for Research on Cancer, 150 cours Albert Thomas, F-69372 Lyon Cédex 08.

The task of reviewing the epidemiological evidence supporting major etiological hypotheses on cancer of the colon and rectum may seem daunting. Several hundreds of papers have been published on this topic in recent years, but only a few report results from analytical epidemiology studies, the others being the formulation of hypotheses, discussions, recommendations or reviews of the literature. More words than hard data are available on this topic. The limited number of epidemiological studies available today should be kept in mind when considering the great uncertainty still existing concerning the etiology of colorectal cancer. Factors possibly involved in the etiology of colorectal cancer, of exogenous or endogenous origin, are reviewed below.

1. Diet

Diet is the most obvious factor involved in the etiology of colorectal cancer, but what is still not clearly evident is which particular dietary pattern could be incriminated. One of the most authoritative statements on this matter is the conclusion reached by the Committee on Diet, Nutrition and Cancer of the National Research Council of the USA, which stated in 1982 "Three hypotheses appear to be supported by data ... from epidemiological studies of both colon and rectal cancer: 1) causal association with total (saturated?) fat, 2) protective effect of dietary fibre, 3) protective effect of cruciferous vegetables."

The degree of evidence on which these conclusions are based has to be considered separately for each item:

a) *Fat:* The risk for high consumption of saturated and total fat has been evaluated in eight case-control studies [4, 7, 8, 10, 12–14, 16] and, in all but one [16], increased risk was found. The evidence for a risk associated with a high-fat diet is fairly strong and very well supported by experimental studies on animals.

b) *Meat:* Meat consumption was considered in ten case-control studies [2–4, 6–9, 13, 15, 16] and one cohort study [11]. Five case-control studies found an increased risk [2–4, 8, 15], four case-control studies found no effect [6, 9, 13, 16], and one cohort study found a protective effect [11]. The results appear contradictory. It is possible that the association of meat with the risk of colorectal cancer varies with the type of local diet and is only indirectly related to the disease. It is also possible that the effect is weak and therefore difficult to uncover and quantify.

c) *Fish:* Only four studies [2–4, 6] considered the role of fish in the etiology of colorectal cancer. One study [2] found a high consumption of fish to be protective, whereas two other studies considered it to be a risk factor [4, 6].

d) *Vegetables:* In six [2, 4, 6, 9, 15, 16] out of eight case-control studies [2–4, 6, 9, 13, 15, 16] and in one cohort study [11], a decreased risk was found for high consumption of vegetables. Two studies [6, 15] indicate that the protective effect might be stronger for the consumption of cruciferous vegetables.

e) *Fibre:* The evidence for a protective effect of fibre partially overlaps that for vegetables, which are an important source of fibre. There are actually two case-control studies [2, 5] and a cohort study [11] which indicate a reduced risk for high fibre intake. Two studies found no effect [10, 16], while in one case-control study in Puerto-Rico [8] and in one descriptive epidemiology study in Hong Kong [17] an increased risk was observed. In this last study, colon cancer risk was in fact associated with the highest social class, whose members consume more foods (of any type) than those of lower income groups. The same uncertainty applies to the results of experimental studies in animals, which are inconsistent and particularly difficult to extrapolate to humans.

f) *Rice:* Two studies found a slightly increased risk associated with a high consumption of rice [3, 9], whereas a negative association was found in two other studies [1, 11].

g) *Fruits:* The risk associated with the consumption of fruits was estimated in three case-control studies [1, 2, 16] with contrasting results. Wynder et al. found an increased risk for high consumption [1], Bjelke a reduced risk [2], while in the study by Macquart et al. [16] a slightly reduced risk was found but it disappeared when vegetable intake was controlled for in multivariate analyses.

h) Vitamins A and C: Two studies [10, 16] found no association of risk of colorectal cancer with estimated intake of vitamins C or A. In only one study some reduction of risk was found for high intake of vitamin A [2].

2. Alcohol

The association between colorectal cancer and consumption of alcohol has been investigated after a positive geographical correlation was found between colorectal cancer mortality and beer drinking [19, 20]. The results were inconsistent. A significantly increased risk of death from cancer of the rectum was found in workers at a Dublin brewery [21], but not in workers at a Danish brewery [22] nor among US veterans [23]. Similarly, no association was found in a case-control

Author(s)	Reference	Reference in text	Exposure under study							
			Diet							
			Fat	Meat	Fish	Vege-tables	Fibre	Rice	Fruits	Vit. A and C
Wynder et al.	1969, Cancer 23:1210–20	1						–	+	
Bjelke	1971, ICS Year Book Med. Publ.	2		+	–	–	–		–	–
Haenszel et al.	1973, JNCI 51:1765–79	3		+	(–)	–		–		
Phillips	1975, Cancer Res. 35:3513–22	4	+	+	+	–			(+)	
Modan et al.	1975, JNCI 55:15–8	5					–			
Graham et al.	1978, JNCI 61:709–14	6		N.E.	+ (colon)	–				
Dales et al.	1979, Am. J. Epidemiol. 109:132–44	7	(+)	(+)	(+)		(–)			
Martinez et al.	1979, Adv. Med. Oncol. 3:45–52	8	+	+			+			
Haenszel et al.	1980, JNCI 64:17–22	9		N.E.		–		+		
Jain et al.	1980, Int. J. Cancer 26:757–68	10	+				N.E.			
Hirayama	1981, Banbury Report 7:409–26	11		–		–	–	–		
Potter et al.	1982, Proc. Nutr. Soc. Austr. Ann. Conf. 7:123–6	12	+							
Miller et al.	1983, Int. J. Cancer 32:155–61	13	+	N.E.		N.E.				
Lyon	1983, Food & Nutrition Press	14	+							
Manousos et al.	1983, Int. J. Cancer 32:1–5	15		+		–				
Macquart et al.	1985, Int. J. Cancer (in press)	16	N.E.	N.E.		–	N.E.		(–)	N.E.
Hill et al. (correlation study)	1979, Lancet 436	17	+	+	+	+	+	+	+	
			Alcohol							
Bjelke	1971, ICS Year Book Med. Publ.	2	No effect							
Bjelke	1973, Univ. Minnesota Thesis	18	+							
Breslow & Enström	1974, JNCI 53:631–9	19	Beer: + (rectum)							
Enström	1977, Br. J. Cancer 35:674–83	20	Beer: +							
Dean et al.	1979, Br. J. Cancer 40:581–9	21	Beer: + (rectum)							
Jensen	1979, Int. J. Cancer 23:454–63	22	Beer: no effect							
Schmidt & Popham	1981, Cancer 47:1031–41	23	No effect							
			Occupation and physical activity							
Hammond et al.	1965, Ann. NY Acad. Sci. 132:519–25	24	Insulation workers (asbestos): +							
Berg & Howell	1975, J. Toxicol. Env. Hlth 1:75–89	25	Professionals: + (colon)							
Decoufle	1978, JNCI 61:1025–30	26	Cutting oils: + (colon)							
Huseman et al.	1980, Onkol. 41:168–71	27	Sedentary work: +							
Robinson et al.	1980, Am. J. Ind. Med. 1:159–65	28	Pattern and model workers: + (colon)							
Swanson et al.	1982, JOM 24:315–9	29	Wood workers in automotive industry: +							
Garabrant et al.	1984, Am. J. Epidemiol. 119:1005–14	30	Sedentary job: + (colon); no effect (rectum)							
Vena et al.	1985, Am. J. Epidemiol. 122:357–65	31	Sedentary job: + (colon); no effect (rectum)							
			Sex-related and metabolic factors							
McMichael & Potter	1985, JNCI (in press)	32	Women: calorie-associated risk greatest in young age groups; diet-associated risks maximal in right colon Men: calorie-associated risk greatest in older age groups; diet-associated risks maximal in left colon							
Weiss et al.	1981, JNCI 67:57–60	33	Parity: – (colon); no effect (rectum)							
Byers et al.	1982, JNCI 69:1059–62	34	Parity: no effect							
Potter & McMichael	1983, JNCI 71:703–9	35	Parity: –; late age at first live birth: +							
Papadimitriou et al.	1984, Int. J. Epidemiol. 13:155–9	36	Parity: no effect; late age at first pregnancy: no effect							
Vernick & Kuller	1981, Lancet 381–3	37	Cholecystectomy: + (right colon)							
McMichael & Potter	1985, JNCI 75:185–91	38	Cholecystectomy: + (right colon) greater in women Low serum cholesterol: +; nulliparity: + Hormonal treatment in males: +							

+	indicates a risk factor
–	indicates a protective effect
(–) or (+)	not statistically significant at 0.05 level
N.E.	no effect

Summary table of risks associated with colorectal cancer. Evidence from selected epidemiological studies.

study by Bjelke [2] whereas the same investigator found an increased risk in a cohort study [18].

3. Occupation and Physical Activity

Risk of digestive tract cancer has been found for some specific occupations such as insulation workers [24], workers exposed to cutting oils [25], pattern and model workers [28], and wood cutters in the automotive industry [29]. In addition, professionals and subjects with only light physical job activity are at a higher risk of colon cancer, but not of rectal cancer [25, 30, 31]. An evaluation of physical activity outside the job would be of interest for a better understanding of the relation between colon cancer and exercise.

4. Hormonal and Metabolic Aspects of Colorectal Cancer

The reasons for the apparent inconsistencies of published analyses have been reviewed by McMichael and Potter [32] who discussed the degree of specificity of the dietary etiology of colon cancer and advocated the need for independent analyses of risk or protective factors according to sex, age and anatomical subsite. Descriptive epidemiology in Western populations indicates that the incidence rate of colon cancer in women is greater than in men below the age of 55 for all sites, whereas the incidence rate for right colon cancer exceeds that in men at all ages. Analytical epidemiology shows that in women the colon cancer risk tends to be inversely related to parity [33] and positively related to age at first live birth [33, 35], although two studies failed to find such associations [34, 36]. Part of this risk could be mediated through hormonal influences, endogenous or exogenous, on bile metabolism, and its resulting action within the gut. The hypothesis is supported by an increase in proximal colon cancer risk following cholecystectomy [37], with a greater effect for women than for men [38]. Metabolic epidemiology indicates that, relative to men, women tend to have slower bowel transit, lower faecal weight, higher faecal pH and a high secondary/primary bile acids ratio. All these factors could play a role in colon carcinogenesis.

Summary

The epidemiological evidence supporting hypotheses concerning colorectal carcinogenesis presents conflicting findings. Even the detrimental role of high fat intake and the protective effect of fibre have to be qualified. In order to improve knowledge on the etiopathogenesis of colorectal cancer, more attention should be directed to the modifiers of the action of carcinogenic or anti-carcinogenic substances. Sex, age, hormonal and metabolic status should be precisely accounted for, as should the exact anatomical subsite of the cancer.