Epidemiology of colorectal cancer

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Colorectal cancer is a important public health problem: there are nearly one million new cases of colorectal cancer diagnosed world-wide each year and half a million deaths. Recent reports show that, in the US, it was the most frequent form of cancer among persons aged 75 years and older. Given that the majority of cancers occur in elder people and with the ageing of the population in mind, this observation gives further impetus to investigating prevention and treatment strategies among this subgroup of the population. Screening research, recommendations and implementation is an obvious priority.

While there are many questions to be resolved, it is apparent that many facets of colorectal cancer are becoming increasingly understood and prospects for prevention are becoming apparent. Achieving colorectal cancer control is the immediate challenge.

In 2000, there was an estimated total of 944,717 incident cases of colorectal cancer diagnosed world-wide: 498,754 new cases diagnosed in men and 445,963 new cases in women[1]. Global, age standardized rates of colorectal cancer (ICD 153 and 154 combined) incidence are higher in men than in women (19.1 and 14.4 per 100,000, respectively)[1]. Over one-third (329,529 cases [36%]) of new cases of colorectal cancer occur outside industrialised countries: the standard myth of colorectal cancer being a disease restricted to western countries needs to be dispelled. In the US, colorectal cancer is the most frequent form of cancer among persons aged 75 and older[2]. The rapidly ageing population of non-industrialised countries will increase the numbers of colorectal cancers diagnosed there in years to come.

The incidence of this malignancy shows considerable variation among racially or ethnically defined populations in multiracial/ethnic countries. The diseases of colon and rectal cancer appear to be distinct but, unfortunately, there are recognised difficulties in distinguishing colon and rectal cancer in mortality statistics for a variety of reasons[3]. Wherever possible, the distinction between colon and rectum will be preserved.

In men, 8 of the 10 highest incidence age standardized rates of colon cancer are recorded in population groups in the US with Canada, Japan and New Zealand completing the group (Table 1). It is of potentially considerable significance that these high rates are to be found in a

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variety of population groups including Blacks in Detroit (34.9 per 100,000), Los Angeles (34.8), San Francisco (33.8), Atlanta (32.4) and New Orleans (31.4), Japanese and Whites in Hawaii (34.4 and 32.7, respectively) and non-Maori in New Zealand (31.2). More recent data from the US on colorectal incidence and mortality rates from 1992 to 1998, age-adjusted to the 1970 US standard population, confirm the racial/ethnic gradient of this disease. In detail, incidence rates (per 100,000) reported for Blacks, Whites, Asian/Pacific Islanders, American Indian/Alaskan and Hispanics are 50.1, 42.9, 38.2, 28.6 and 28.4 respectively[5]. World-wide, in men the lowest incidence rates are found in a variety of population groups in the non-industrialised countries with the lowest rate reported in Setif, Algeria (0.4 per 100,000). In women, the group of highest incidence rates includes population groups in New Zealand and North America with the lowest rates recorded in Algeria and India (Tables 1–3). In each sex, a number of low rate regions are found in India[4].

Ethnic and racial differences in colon cancer as well as studies on migrants suggest that environmental factors play a major role in the

Table 1 Ten highest and ten lowest average, annual, all ages, age-standardised, incidence rates per 100,000 population for colon cancer in men and women world-wide around the early 1990s

Colon, male ICD9 153 Registry	Cases	Rate	Colon, female ICD9 153 Registry	Cases	Rate
US, Detroit: Black	806	34.9	New Zealand: non-Maori	3650	29.6
US, Los Angeles: Black	771	34.8	Canada, Newfoundland	503	28.1
US, Hawaii: Japanese	462	34.4	US, San Francisco: Black	408	27.9
US, San Francisco: Black	353	33.8	US, Detroit: Black	899	27.9
US, Hawaii: White	293	32.7	US, San Francisco: Japanese	57	27.0
US, Atlanta: Black	300	32.4	US, Los Angeles: Black	860	26.5
Japan, Hiroshima	939	31.6	US, Atlanta: Black	400	26.1
Canada, Newfoundland	504	31.4	US, New Orleans: Black	314	25.8
US, New Orleans: Black	247	31.4	Canada, Nova Scotia	1028	25.2
New Zealand: non-Maori	3045	31.2	US, Connecticut: Black	188	25.2
Thailand, Chiang Mai	139	4.1	Viet Nam, Hanoi	81	2.9
Ecuador, Quito	64	3.9	Kuwait: non-Kuwaitis	13	2.2
Kuwait (Kuwaitis)	22	3.5	India, Bangalore	128	2.0
Uganda, Kyadondo	16	3.1	China, Qidong	79	2.0
Mali, Bamako	22	3.1	Mali, Bamako	13	1.4
China, Qidong	64	2.1	India, Madras	84	1.3
India, Madras	122	1.8	India, Karunagappally	5	1.3
India, Karunagappally	5	1.4	India, Trivandrum	8	1.0
India, Barshi, Paranda	6	0.7	Algeria, Setif	7	0.6
Algeria, Setif	4	0.4	India, Barshi, Paranda	4	0.4

Data are abstracted from Parkin *et al*[4].

aetiology of the disease. In Israel, male Jews born in Europe or America are at higher risk for colon cancer than those born in Africa or Asia and a change in risk in the offspring of Japanese having migrated to the US (heralded by Haenszel and Kurihara[6]) has taken place, the incidence rates approaching or surpassing those in whites in the same population and being three or four times higher than among Japanese in Japan.

Colorectal mortality rate is decreasing in the US. Disease detected at earlier stages due to screening practices and the availability of more efficient treatment regimens, appear to have driven this reduction in cancer death. Still, average annual colorectal cancer death rates in the US have shown higher rates in Blacks for both sexes (27.2 and 19.5 in Black male and females and 20.1 and 13.7 in White male and female)[5]. In other parts of the world, increasing rates are observed in the Nordic countries while, in England and Wales, mortality rates are declining in all age groups in both sexes. Mortality rates from colorectal cancer in men and women have remained fairly constant throughout the century in Ireland[8]. However, there are rapid changes being experienced in many countries previously considered to be low-risk. For example, mortality

Table 2 Ten highest and ten lowest average, annual, all ages, age-standardised, incidence rates per 100,000 population for rectal cancer in men and women world-wide around the early-1990s

Rectum, male ICD9 154 Registry	Cases	Rate	Rectum, female ICD9 154 Registry	Cases	Rate
Canada, Yukon	25	33.7	Canada, Yukon	12	14.4
Czech Republic	7970	24.2	Israel: Jews born Europe	1053	12.8
Zimbabwe, Harare: European	23	22.4	Czech Republic	5602	11.6
France, Haut-Rhin	446	21.5	South Australia	673	11.4
Slovakia	2984	20.6	Israel: all Jews	1533	11.4
New Zealand: non-Maori	1955	20.1	France, Haut-Rhin	343	11.2
Japan, Hiroshima	576	19.4	New Zealand: non-Maori	1362	11.2
US, San Francisco: Japanese	28	19.3	Australia, Victoria	1876	11.0
Australia, Victoria	2610	19.2	Australian Capital Territory	74	11.0
US, Hawaii: Japanese	235	19.0	Germany, Saarland	691	10.9
India, Bangalore	212	3.1	Viet Nam, Hanoi	70	2.4
Israel: non-Jews	31	3.1	Algeria, Setif	27	2.3
Thailand, Chiang Mai	101	3.1	India, Trivandrum	18	2.3
India, Trivandrum	21	3.0	Kuwait: non-Kuwaitis	13	2.3
Thailand, Khon Kaen	63	3.0	Thailand, Khon Kaen	48	1.9
Mali, Bamako	26	2.9	Kuwait: Kuwaitis	11	1.9
Brazil, Belem	30	2.8	Uganda, Kyadondo	11	1.8
Algeria, Setif	24	2.6	India, Barshi, Paranda, Bhum	10	1.1
India, Barshi, Paranda, Bhum	23	2.6	Mali, Bamako	8	0.7
India, Karunagappally	6	1.6	India, Karunagappally	1	0.3

Data are abstracted from Parkin *et al*[4].

Table 3 Ten highest and ten lowest average, annual, all ages, age-standardised, incidence rates per 100,000 population for colon and rectum cancer combined in men and women world-wide around early 1990s

Colorectum, male ICD9 153–154 Registry	Cases	Rate	Colorectum, female ICD9 153–154 Registry	Cases	Rate
US, Hawaii: Japanese	697	53.5	New Zealand: non-Maori	5012	40.8
New Zealand: non-Maori	5000	51.3	Canada, Newfoundland	678	38.3
Japan, Hiroshima	1515	51.0	US, Detroit: Black	1172	36.6
France, Haut-Rhin	1041	49.9	US, Los Angeles: Black	1182	36.5
Italy, Trieste	547	49.4	US, San Francisco: Black	527	36.4
France, Bas-Rhin	1445	49.2	Israel, Jews born Amer/Eur	3034	35.8
Canada, Yucon	39	49.0	US, San Francisco: Japanese	76	35.4
US, Detroit: Black	1100	48.3	US, Atlanta: Black	529	35.0
Czech Republic	15,906	48.2	Canada, Nova Scotia	1400	35.0
US, Los Angeles: Black	1061	47.9	South Australia	2047	34.2
Brazil, Belem	73	7.3	Thailand, Khon Kaen	129	5.2
Ecuador, Quito	123	7.2	Uganda, Kyadondo	26	5.1
Thailand, Chiang Mai	240	7.2	India, Bangalore	300	4.8
Mali, Bamako	48	6.0	Kuwait: non-Kuwaitis	26	4.5
India, Madras	367	5.6	India, Madras	258	4.1
India, Bangalore	374	5.5	India, Trivandrum	26	3.3
India, Trivandrum	38	5.4	Algeria, Setif	34	2.9
India, Barshi, Paranda, Bhum	29	3.3	Mali, Bamako	21	2.1
Algeria, Setif	28	3.1	India, Karunagappally	6	1.6
India, Karunagappally	11	3.1	India, Barshi, Paranda, Bhum	14	1.5

Data are abstracted from Parkin *et al*[4].

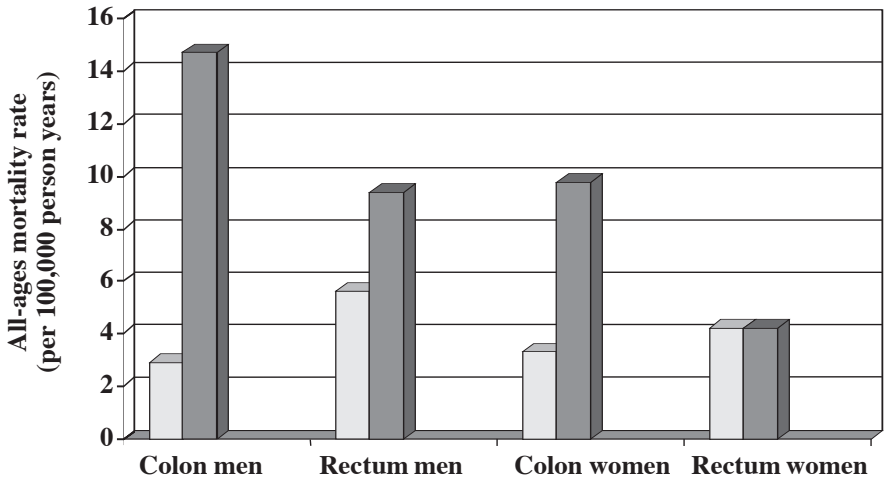

Fig. 1 Age-standardised, all ages mortality rate (per 100,000 person-years) from colon and rectal cancer in Japan, 1950 and 1999. Data kindly supplied by Yoshitaka Tsubono (Migayi, Japan).

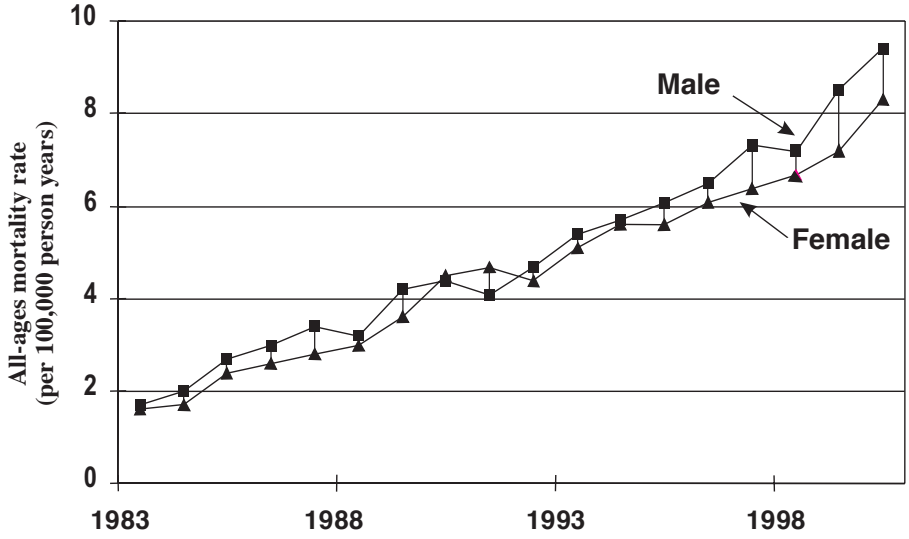

Fig. 2 Age-standardised, all ages mortality rate (per 100,000 person-years) from colorectal cancer in Korea, 1983–2000. Data kindly supplied by Won Chul Lee (Seoul, Korea).

rates in Japan have increased 5-fold since 1950 (Fig. 1) and 4-fold in Korea since 1983 (Fig. 2).

Colorectal cancer is not uniformly fatal although there are large differences in survival according to stage of disease. In advanced colorectal cancer in which curative resection is possible, 5-year survival in Dukes' B is 45% which drops to 30% in Dukes' C[9]. Five year survival in resected Dukes' A is around 80% and survival following simple resection of an adenomatous pedunculated polyp containing carcinoma *in situ* (or severe dysplasia) or intramucosal carcinoma is generally close to 100%. It is estimated that there are, however, still nearly half-a-million deaths from colorectal cancer annually[1].

Clearly colorectal cancer is an important public health problem, not only of western lifestyle countries but increasingly in other parts of the world. The ageing population world-wide will have an obvious impact of the global burden of colorectal cancer unless effective control action is taken.

Analytical epidemiology

Most colorectal cancers, at least two-thirds and perhaps as much as 90%, arise from benign, adenomatous polyps lining the wall of the bowel with those which grow to a large size and have a villous

appearance or contain dysplastic cells being most likely to progress to cancer[10]. The development of colorectal cancer is a multi-step process involving genetic mutations in mucosal cells, the activation of tumour promoting genes and the loss of genes which suppress tumour formation[11]. The natural history and the role of several risk factors in the aetiology of colorectal cancer are becoming more clearly understood[12,13] and the genetic events involved in colorectal cancer susceptibility are being uncovered with increasing frequency[14,15]: progress in understanding of the genetics of colorectal cancer is impressive[16,17]. Few specific risk factors of a non-dietary origin have been established for colorectal cancer; inflammatory bowel diseases and familial polyposis syndromes produce a high risk of colorectal cancer in affected individuals but account for only a small proportion of the overall incidence of colorectal cancer[18,19].

Physical activity, body mass index and energy intake

Men with high occupational or recreational physical activity appear to be at a lower risk of colon cancer[20]. Such evidence comes from follow-up studies of cohorts who are physically active or who have physically demanding jobs as well as case-control studies that have assessed physical activity – for example, by measurement of resting heart rate, or by questionnaire. The association remains even after control for potential confounding factors such as diet and body mass index and its effect, although not exactly clearly understood, may well be working through multiple biological mechanisms that influence the carcinogenic process[21].

In a key publication, the risk of colorectal cancer and self-reported occupational and recreational physical activity was investigated in a population-based cohort in Norway[22]. Physical activity at a level equivalent to walking 4 h per week was associated with a decreased risk of colon cancer among women when compared to the (referent) sedentary group (RR, 0.62; 95% CI, 0.40, 0.97): this was particularly marked in the proximal colon (RR, 0.51; 95% CI 0.28, 0.93). The trend in reducing risk with increased physical activity was similar in women and in men aged over 45 years[22].

The Nurses' Health Study quantified time spent on physical activity during leisure time as well as the energy equivalent spent during such activity (metabolic equivalents, MET)[23]. Women with more than 21 MET-hours per week on leisure time physical activity had a relative risk of colon cancer which was almost half that of women who spent less than 2 MET-hours per week (RR, 0.54; 95% CI, 0.33, 0.90)[23]. Women who had a body mass index greater than 29 kg/m^2 had a relative risk of colon cancer which was increased by about one-half (RR, 1.45; 95% CI, 1.02, 2.07) compared with women who had a body mass index less than

21 kg/m^2. The trend in risk showed an increasing trend with increasing waist-to-hip ratio (RR, 1.48; 95% CI, 0.88–2.49) for comparison of the highest quintile ratio (> 0.833) to the lowest (< 0.728)). The significant inverse association between leisure-time physical activity and the risk of colon cancer in women resembles the association previously described in men. Increasing physical activity and maintaining lean body weight should be regarded as preventive practices to reduce the risk of developing colon cancer.

It has been a fairly consistent finding in studies which have examined the issue that energy intake is higher in cases of colorectal cancer than in the comparison group: the mechanism is, however, complex[24]. Physically active individuals are likely to consume more energy but recent studies suggest that physical activity reduces colorectal cancer risk[25–27]. There has been some recent attention given to the study of such factors in the development of adenomas, the benign lesion from which the majority of colorectal cancers develop. A case-control study was conducted among patients seen at three colonoscopy practices in New York City: all patients had a history of adenomas[28]. Men in the upper quarter of the body mass index (BMI) range were found to have an increased risk of recurrent adenomas: the odds ratios were found to be 2.2, 1.9 and 1.9, respectively, in the second, third and fourth quarter of BMI compared to the lowest quarter. However, no effect was found in women. This either detracts from the findings given the lack of internal consistency or indicates that there is a true biological interaction: in any event, this issue deserves further study.

A case-control study of new adenoma cases and adenoma-free controls demonstrated that physical activity in leisure protected women against colorectal adenomas. There was no evidence of a protective effect of work activity among either women or men, although men who participated in no sport were at an increased risk for adenomas (OR, 1.68; 95% CI, 0.93, 3.20)[29].

Giovannucci *et al*[30] examined the influence of physical activity, BMI and the pattern of adipose distribution on the risk of colorectal adenomas. Within the Nurses' Health Study, 13,057 female nurses, aged 40–65 years in 1986, had an endoscopy between 1986 and 1992. During this period, 439 were newly diagnosed with adenomas of the distal colorectum. After controlling for age, prior endoscopy, parental history of colorectal cancer, smoking, aspirin use and dietary intakes, physical activity was associated inversely with the risk of large adenomas (greater or equal to 1 cm) in the distal colon (RR, 0.57; 95% CI, 0.30, 1.08), comparing high and low quintiles of average weekly energy expenditure from leisure activities. Much of this benefit came from activities of moderate intensity such as brisk walking.

Additionally, BMI was associated directly with risk of large adenomas in the distal colon (RR, 2.21; 95% CI, 1.18, 4.16), for BMI 29 kg/m^2 or

over compared to BMI values less than 21 kg/m^2. The relationships between BMI or physical activity were considerably weaker for rectal adenomas[30]. This study indicates that the association between physical activity and occurrence of adenomas is similar in many respects to that for colorectal cancer. Exercise appears to protect against adenomas and colorectal cancer as does increasing BMI serve to increase the risk of both.

The reason for such an association has not been identified, but has been variously postulated as being due to the effect of exercise on bowel transit time[31], the immune system[32] or serum cholesterol and bile acid metabolism[33]. The same consistent results have not been reported until recently on studies in women, but one possible explanation is the lesser variation in, for example, occupational activity among women may make such an association more difficult to detect. Also, infrequent bowel movement, directly related to bowel transit time, has not been associated with an increased risk of colorectal cancer in women[34], whether or not physical activity affects transit time.

It is very difficult to interpret in a straightforward manner associations between obesity and colorectal cancer risk since analysis and interpretation of this factor is difficult in retrospective studies where weight loss may be a sign of the disease. The evidence, including that with adenoma, is strongly suggestive of an association although this positive effect of energy does not appear to be merely the result of overeating, therefore, and may reflect differences in metabolic efficiency. (If the possibility that the association with energy intake is a methodological artefact is excluded, as it seems unlikely that such a consistent finding would emerge from such a variety of study designs in a diversity of population groups, it would imply that individuals who utilise energy more efficiently may be at a lower risk of colorectal cancer).

Dietary and nutritional practices

A decade ago, the dietary aetiology of colorectal cancer seemed to be clearly understood: risk was increased by increasing consumption of dietary fat, particularly animal fat, and meat and was reduced by consumption of vegetables and fruits. Today the situation could be best characterised as an 'era of recent retreats in nutritional epidemiology'.

For many years, a diet rich in vegetables and fruit has been associated with a reduced risk of colorectal cancer in many, but not all, observational studies[35]. The association between fruit and vegetable consumption and the incidence of colon and rectal cancers has been studied in two cohorts: the Nurses' Health Study (88,764 women) and the Health Professionals' Follow-up Study (47,325 men)[36]. Assessment of the diet was completed during different calendar years in women and

men, during which a total of 1,743,645 person-years of follow-up were accrued and 937 cases of colon cancer were identified. No association was found between colon cancer incidence and fruit and vegetable consumption. For women and men combined, a difference in fruit and vegetable consumption of one additional serving per day was associated with a co-variate-adjusted RR of greater magnitude but lacking statistical significance (1.02; 95% CI, 0.98–1.05)[35].

This lack of association between consumption of vegetables and fruits and colorectal cancer risk contradicts a widely accepted relationship between nutritional practices and chronic disease risk. Another association under scrutiny is that between fat intake and colorectal cancer risk. Hitherto, there appeared to be consistent evidence from epidemiological studies that intake of dietary fat and meat is positively related to colorectal cancer risk: this evidence is obtained from ecological studies, animal experiments, case-control and cohort studies. Many of these studies have failed to demonstrate that the association observed with fat intake is independent of energy intake.

Willett *et al*[37] published the results obtained from the United States Nurses Health study involving follow-up of 88,751 women aged 34–59 years who were without cancer or inflammatory bowel diseases at recruitment. After adjustment for total energy intake, consumption of animal fat was found to be associated with increased colon cancer risk. The trend in risk was highly significant ($P = 0.01$) with the relative risk in the highest quintile, compared to the lowest, being 1.89 (95% CI, 1.13, 3.15). No association was found with vegetable fat. The relative risk of colon cancer in women who ate beef, pork or lamb as a main dish every day was 2.49 (95% CI, 1.24, 5.03) as compared with those women reporting consumption less than once per month. The authors interpreted their data as providing evidence for the hypothesis that a high intake of animal fat increases the risk of colon cancer, and they supported existing recommendations to substitute fish and chicken for meats high in fat[37]. However, with an increasing amount of information becoming available from prospective studies as observation time increases, there is only weak evidence of an association between fat intake and colorectal cancer risk[38]. In addition, a meta-analysis of 13 case-control studies has aggregated 5287 cases and 10,470 controls. Positive associations with energy intake were observed in 11 of 13 studies. There was little evidence of an energy independent effect of total fat (ORs in quintiles were 1.0, 1.08, 1.06, 1.21 and 1.06 [P trend 0.67]) or saturated fat (ORs in quintiles 1, 1.08, .06, 1.21 and 1.06 [P trend 0.39])[39]. Nevertheless, there is still evidence of a positive association coming out from retrospective studies such as that from Italy[40] and Vaud, Switzerland[41]. Clearly, there is some further work required on this particular topic.

The report by Willett *et al*[37] provided the best epidemiological evidence to date identifying increased meat consumption as a risk factor for colon cancer independently of its contribution to fat intake and total caloric intake. A recently published meta-analysis of 13 prospective studies looking at meat consumption and colorectal cancer risk has reported an increased risk (12–17%) with a daily increase of 100 g of all meat or red meat. The risk was higher (49%) with a daily increase of 25 g of processed meat[42]. Again, in a second study published in parallel, high intake of carcinogenic compounds produced when meat is well-cooked at high temperatures has been associated with an increased risk of colorectal adenomas[43].

Among protective dietary factors, the original hypothesis of the effect of dietary fibre was based on a clinical/pathological observation and a hypothesised mechanism whereby increasing intake of dietary fibre increases faecal bulk and reduces transit time. The term 'fibre' encompasses many components each of which has specific physiological functions. The commonest classification is into the insoluble, non-degradable constituents (mainly present in cereal fibre) and into soluble, degradable constituents like pectin and plant gums which are mainly present in fruits and vegetables. Epidemiological studies have reported differences in the effect of these components. For example, Tuyns *et al*[44] and Kune *et al*[45] found a protective effect for total dietary fibre intake in case-control studies and the same was found in one prospective study[46]. However, a large number of studies could find no such protective effect (see Willett[24] for review). The large majority of studies in humans found no protective effect of fibre from cereals but consistently found a protective effect of fibre from vegetable and, perhaps, fruit sources[24,35] and dietary diversity has been shown to be an important element in this protection[47]. This could conceivably reflect an association with other components of fruits and vegetables, with 'fibre' intake acting merely as an indicator of consumption.

Two randomized studies, conducted in the US, looking at dietary interventions and the risk of recurrent adenomatous polyps have revealed no protective effect on the recurrence rate of colorectal polyps. The dietary interventions in question were, for the Polyp Prevention Trial[48], to have either intensive counselling to follow a low-fat, high-fibre, fruit and vegetable diet or to be given a brochure on healthy eating, and, for the Wheat Bran Fiber Study[49], to have a high wheat bran fibre cereal supplement (13.5 g of fibre in 2/3 cup cereal per day) or low wheat bran fibre cereal supplement (2 g of fibre in 2/3 cup cereal per day). The latter study reports that increasing dietary fibre will not reduce the risk of developing colorectal cancer, however, praising the benefits of high fibre diets for the prevention of other chronic conditions. Possible explanations for the observed negative results in

both studies may be a short follow-up period precluding the detection of cancerous lesions that require of longer time before emerging.

A potential pathway for this protective association has been investigated in a novel epidemiological study design[50]. Cruciferous vegetable intake exhibited a significant inverse association with colorectal cancer risk (OR, 0.59; 95% CI, 0.34, 1.02). When tumours were characterised by p53 over-expression (p53 positive) aetiological heterogeneity was suggested for family history of colorectal cancer (OR, 0.39; 95% CI, 0.16, 0.93), intake of cruciferous vegetables (test for trend, $P = 0.12$) and beef consumption (test for trend, $P = 0.08$). Cruciferous vegetable consumption exhibited a significant association when p53 positive cases were compared with controls (OR, 0.37; 95% CI, 0.17, 0.82). When p53 negative cases were compared with controls, a significant increase in risk was observed for family history of cancer (OR, 4.46; 95% CI, 2.36, 8.43) and beef consumption (OR, 3.17; 95% CI, 1.83, 11.28). The p53 (positive) dependent pathway was characterised by an inverse association with cruciferous vegetable intake and p53 independent tumours were characterised by family history and beef consumption[50].

Insulin-like growth factor-1 (IGF-1) levels have been reported to correlate with risk of cancer in several sites (prostate and colorectal cancer in men, breast in pre-menopausal women, and lung in men and women). Prediagnostic plasma levels of IGF-1 and IGFBP-3 (which posses an opposing effect) have been assessed in association with the risk of colorectal cancer and adenoma in women in the Nurses' Health Study[51]. The study indicates that high levels of circulating IGF-1 and particularly low levels of IGFBP-3 are associated independently with an elevated risk of large or tubulovillous/villous colorectal adenoma and cancer[51]. Insulin and insulin-like growth factors can stimulate proliferation of colorectal cells and a high intake of refined carbohydrates and markers of insulin resistance are associated with colorectal cancer. A case-control study on colorectal cancer conducted in Italy was employed to test the insulin/colon cancer hypothesis by determining whether the dietary glycaemic index and the glycaemic load are associated with colorectal cancer risk[51a]. Average daily dietary glycaemic index and glycaemic load were calculated, and fibre intake was estimated from a validated food frequency questionnaire. Direct associations with colorectal cancer risk emerged for glycaemic index (OR in highest *versus* lowest quintile, 1.7; 95% CI, 1.4–2.0) and glycaemic load (OR, 1.8; 95% CI, 1.5–2.2), after allowance for sociodemographic factors, physical activity, number of daily meals, and intakes of fibre, alcohol and energy. ORs were more elevated for cancer of the colon than rectum. Overweight and low intake of fibre from vegetables and fruit appeared to amplify the adverse consequences of high glycaemic load[40]. An attractive hypothesis has been developed to explain this[52] and this is clearly an important area of research which should be urgently pursued.

The role of a variety of various micronutrients in colorectal cancer risk has been examined as well. Calcium has been proposed on theoretical grounds as potentially having a modifying role in colorectal carcinogenesis[53], but little supporting evidence was immediately forthcoming from epidemiological studies[54], although these early studies in humans are of limited value because of questionable study design or the inadequacy of the estimation of diet.

To investigate this hypothesis, an intervention trial of colorectal adenoma recurrence was established in North America[55,56]. This trial involved 930 subjects (mean age, 61 years; 72% men) with a recent history of colorectal adenomas randomly assigned to receive either calcium carbonate (3 g [1200 mg of elemental calcium] daily) or placebo, with follow-up colonoscopies one and four years after the qualifying examination. Subjects in the calcium group had a lower risk of recurrent adenomas detected at 1-year or 4-year colonoscopy. Among the 913 subjects who underwent at least one study colonoscopy, the adjusted risk ratio for any recurrence of adenoma on the calcium supplementation group as compared with placebo was 0.85 (95% CI, 0.74, 0.98). The main analysis was based on the 832 subjects (409 in the calcium group and 423 in the placebo group) who completed both follow-up examinations. At least one adenoma was diagnosed between the first and second follow-up endoscopies in 127 subjects in the calcium group (31%) and 159 subjects in the placebo group (38%); there was a reduction in risk of recurrent adenoma of about one fifth associated with calcium supplementation (OR, 0.81; 95% CI, 0.67, 0.99). The adjusted ratio of the average number of adenomas in the calcium group to that in the placebo group was 0.76 (95% CI, 0.60, 0.96). The effect of calcium was independent of initial dietary fat and calcium intake.

In another study conducted in Europe, 665 patients with a history of colorectal adenomas were randomly assigned to three treatment groups, one of which used calcium but in a different form to that employed in North America (calcium gluconolactate and carbonate [2 g elemental calcium daily])[57]. Participants had a colonoscopy after 3 years of follow-up. Among the 552 participants who completed the follow-up examination, 94 had stopped treatment early. At least one adenoma developed in 28 (15.9%) of 176 patients in the calcium group, 58 (29.3%) of 198 in the fibre group, and 36 (20.2%) of 178 in the placebo group. The adjusted odds ratio for recurrence was reduced by one-third for calcium treatment (OR, 0.66; 95% CI, 0.38–1.17) and was increased (OR, 1.67; 95% CI, 1.01–2.76) for patients in the group allocated to fibre. The odds ratio associated with the fibre treatment was significantly higher in participants with baseline dietary calcium intake above the median than in those with intake below the median. The findings suggested to the authors that supplementation with fibre (in the form of ispaghula

husk) may have adverse effects on colorectal adenoma recurrence, especially in patients with high dietary calcium intake. However, once again calcium supplementation was associated with a modest, although in this case non-significant reduction in the risk of adenoma recurrence. This hypothesis is worth further study on a larger scale despite the clear problems in investigating such dietary hypotheses[58].

The potential association between calcium intake and colon cancer risk was examined in two prospective cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS)[59]. The study population included 87,998 women in NHS and 47,344 men in HPFS who, at baseline (1980 for NHS and 1986 for HPFS), completed a food frequency questionnaire and provided information on medical history and life-style factors. Dietary information was updated at least every 4 years. During the follow-up period (1980 to 31 May 1996 for the NHS cohort; 1986 to 31 January 1996 for the HPFS cohort), 626 and 399 colon cancer cases were identified in women and men, respectively. In women and men considered together, an inverse association was found between higher total calcium intake (> 1250 mg/day *versus* ≤ 500 mg/day) and distal colon cancer (women: multivariate RR, 0.73; 95% CI, 0.41–1.27; men: RR, 0.58; 95% CI, 0.32–1.05; pooled RR, 0.65; 95% CI, 0.43–0.98). No such association was found for proximal colon cancer (women: RR, 1.28; 95% CI, 0.75–2.16; men: RR, 0.92; 95% CI, 0.45–1.87; pooled RR, 1.14; 95% CI, 0.72–1.81). The incremental benefit of additional calcium intake beyond approximately 700 mg/day appeared to be minimal and the observed risk pattern was consistent with a threshold effect, suggesting that calcium intake beyond moderate levels may not be associated with a further risk reduction[59].

Both body iron stores and dietary iron intake have been reported to increase risk of colorectal neoplasms. The potential association between serum ferritin concentration and recurrence of colorectal adenomas was assessed among 733 individuals with baseline determinations of ferritin as part of a multicentre clinical trial of antioxidant supplements for adenoma prevention[60]. This study demonstrated no statistically significant linear association between log ferritin concentration and adenoma recurrence (P = 0.33). Dietary intake of iron and red meat was inversely associated with adenoma recurrence among participants with replete iron stores but not consistently associated among those with non-replete stores[60]. These findings suggest that any role of iron stores and dietary iron in influencing risk of colorectal adenoma recurrence is likely to be complex and difficult to disentangle.

One of the major reasons why such trials and studies can be difficult to interpret relates to off-study use of vitamins and minerals, which are probably becoming more common and certainly vary from country to country. During the course of a colorectal neoplasia chemoprevention trial

using aspirin in a group of colorectal carcinoma survivor in the US, Sandler et al[61] obtained information on the use of vitamins, minerals, and supplements at baseline and every 6 months. One or more supplements were used at some time by 55% of subjects. Among those who took supplements, 66% took more than 1 and 13% took 5 or more. The mean number of supplements taken was 2.6 (1.7 standard deviation). Vitamins were the most commonly used (49%), followed by minerals (22%), botanicals (13%), and others (5%). Calcium (16%) was the most frequent mineral. Among users, there were no differences in supplement use by age or gender. However, it is clear that this is a major factor which needs to be taken into account in the design (e.g. assessing sample size correctly) and interpretation phase of such intervention studies.

A number of studies have reported positive associations with alcohol consumption and colorectal cancer risk[62] but it remains to be proven whether the putative association is with alcohol per se and not with the calorie contribution of alcohol or due to influences in the components of diet in alcohol drinkers. There is some experimental evidence that vitamin E and selenium may be protective against colon tumours[63] and there is support for the hypothesis that β-carotene protects also[24]. Lactobacilli, found in some dairy products, may have a favourable effect on the intestine[64]. Twelve case-control studies of sufficient quality addressed the issue of coffee consumption and the risk of colorectal cancer and 11 of these have indicated inverse (protective) associations[65] and subsequently confirmed[66]. No association has been found with tea drinking or caffeine intake from all sources considered.

Tobacco smoking and colorectal cancer risk

The large bowel has not historically been considered as a site where the risk of cancer is linked to cigarette smoking[67] although it has been suggested that it may be an independent risk factor which may be specifically associated with the early stages of colorectal epidemiology[68,69]. A more recent review of all epidemiological evidence has indicated the strength and consistency of this finding[70]. Giovannucci[70] concluded that 21 out of 22 studies found that long-term, heavy cigarette smokers have a 2–3-fold elevated risk of colorectal adenoma. The risk of large adenomas, those who present a high risk of colorectal cancer within a relatively short time frame, was elevated in smokers in all 12 studies which examined this association.

The studies of smoking and colorectal cancer risk conducted earlier in the 1950s through 1970s, did not show consistently any association and led review groups to consider that based on the available evidence that there was no association demonstrated (e.g. IARC[67]). However, 27

studies in various countries, including the large majority of those that have been conducted in the past two decades, show a consistent association between tobacco use (essentially cigarette smoking) and colorectal cancer. In the US, 15 of 16 studies conducted after 1970 in middle-age men and elderly men and, in the 1990s, in women demonstrate such an association. Giovannucci[70] considered that this temporal pattern is consistent with an induction period of three to four decades between exposure and the development of clinical colorectal cancer. Overall, accumulating evidence, much within the past decade, strongly supports the addition of colorectal cancer to the list of tobacco-associated malignancies. Such an association has biological plausibility since carcinogens from tobacco could reach the colorectal mucosa through either the alimentary tract or the circulatory system and then damage or alter expression of cancer-related genes. It appears likely that up to one in five colorectal cancers in the US may be associated with such exposure.

Hormone replacement therapy (HRT)

There is increasing evidence supporting an (originally unexpected) association between HRT use and a reduced risk of colorectal cancer. A Medline search was used to identify observational studies published between January 1974 and December 1993 for a meta-analysis[71]. The overall risk for colorectal cancer and oestrogen replacement therapy was 0.92 (95% CI, 0.74, 1.5). There was neither a separate effect when colon and rectal cancer were considered as separate entities[71]. Subsequent to this report there have been further studies published.

A case-control study from Seattle (US) among 193 women aged 30–62 years with colon cancer and an equal number of controls was conducted to examine the relationship between colon cancer and female hormone use[72]. Use of non-contraceptive hormones after age 40 years was associated with a reduced risk of colon cancer (OR, 0.60; 95% CI, 0.35, 1.01). The risk among women with five or more years of use was 0.47 (95% CI, 0.24, 0.91)[72].

Colorectal cancer mortality was examined in some detail in the American Cancer Society Prospective Study[73]. With the risk set to 1.0 among women who reported to be never users of HRT (the referent group), the risk associated with ever use was 0.69 (95% CI, 0.60, 0.79). Relative to the risk in never users, the risk associated with less than 1 year of use was 0.81 (95% CI, 0.63, 1.03), with between 2 and 5 years of use was 0.76 (95% CI, 0.61, 0.95), for between 6 and 10 years of use was 0.55 (95% CI, 0.39, 0.77) and was 0.54 (95% CI, 0.39, 0.76) for 11 or more years of use of HRT[73].

Of 19 published studies of HRT and colorectal cancer risk, 10 support an inverse association and the remaining five show a significant reduction in risk. The risk seems lowest among long-term users. Although there is still some contradictions in the available literature, it appears likely that use of hormone replacement therapy reduces the risk of colorectal cancer in women. The risk appears to half with 5–10 years of such use. The role of unopposed as compared to combination HRT is an open issue for colorectal cancer.

More recently published studies add evidence of a protective effect of HRT use and risk of colon cancer or mortality from colon cancer. Use of HRT, present or past, has been associated with an increased short-term survival after diagnosis with colon cancer in post-menopausal women[74], a 50% reduction in the risk of colon cancer[75], and protection against microsatellite instability-positive tumours[76]. A meta-analysis of HRT use and colon cancer has found that there is a protective effect and such effect is stronger in current or recent users, and among users of more than 5 years' duration[77].

To assess the major health benefits and risks of the most commonly used combined hormone preparation in the US, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16,608 postmenopausal women aged 50–79 years with an intact uterus at baseline were recruited by 40 US clinical centres in 1993–1998. Participants received conjugated equine oestrogens, 0.625 mg/day, plus medroxyprogesterone acetate, 2.5 mg/day, in 1 tablet (n = 8506) or placebo (n = 8102)[78]. Overall health risks exceeded benefits from use of combined oestrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD. Colorectal cancer rates were reduced by 37% (10 *versus* 16 per 10,000 person-years), also reaching nominal statistical significance[78].

Despite these encouraging findings, it is important to emphasize that women using HRT tend to adopt life-styles choices that confer protection from colon cancer or other chronic conditions such that confounding can not be excluded with certainty from studies assessing HRT as a protective factor in colon cancer. For example, the practice of exercise involving increased physical activity, increased consumption of fruits and vegetables and reduced fat intake and/or past screening (colonoscopy, sigmoidoscopy or occult blood test) tend to be emulated more often by women who are HRT ever-users than by never-users[75]. Beral and colleagues[79] in their review of the use of HRT and the subsequent risk of cancer advocate caution in over-interpreting the suggested protective effect in colon cancer.

Prospects for chemoprevention

Current candidates as chemopreventive agents for colorectal cancer include vitamin A or β-carotene, vitamin C, vitamin D, vitamin E, calcium supplements, folate and anti-inflammatory drugs and H2 antagonists[80]. Relatively novel chemical entities such as protease inhibitors are at an earlier stage of development making prolonged treatment too speculative a possibility. Taken overall, there are suggestions of benefit for all of the above compounds, some stronger than others, in reducing the risk of developing colorectal cancer, and/or in preventing polyp occurrence. The largest body of evidence supports the possibility that NSAIDs and COX-2 inhibitors may be potentially most useful in this regard.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) have recently been implicated as potential protective agents against colorectal cancer and adenomatous polyps. Initial anecdotal reports noting regression of adenomas in patients with familial adenomatous polyps have been followed by substantial epidemiological studies. There is a general level of agreement in the finding of a protective effect from such studies. There are randomised trials of familial adenomatous polyps demonstrating the regression of adenomas by NSAIDs. For example, complete regression of rectal polyps in 6 of 9 patients taking sulindac and partial regression in 3 others: in the placebo group, polyps increased in 5, remained unchanged in 2 and decreased in the remaining 2[81]. In laboratory rodents, piroxicam, sulindac and aspirin all have been shown to reduce the frequency of development of colorectal neoplasia[82].

There is abundant evidence that use of NSAIDs is associated with reduced risks of colorectal cancer and adenomatous polyps[83–87]. Effects have been demonstrated consistently, though not completely uniformly, are evident in case-control and cohort studies, and appear to be dose and duration of treatment related[80]. Effects are biologically plausible because NSAID use appears to prevent or reduce the frequency of carcinogen-induced animal colonic tumours because NSAIDs appear to reduce growth rates in colon cancer cell lines and because polyp formation in familial adenomatous polyposis coli appears to be retarded.

The mechanism of any effect remains obscure as does the dose required, and it is disappointing that the randomised intervention trial of low-dose aspirin in the United States Physicians Health Study was null although this may represent a situation where the dose given was too low or the period of use too short to achieve the protective effect[88].

However, there is a very good case for a controlled trial of NSAIDs, probably using aspirin, in the prevention of colorectal cancer[89].

NSAIDs have class adverse effects on the kidney (interstitial nephritis), skin (rash and photosensitivity), lung (predispose to asthma) and liver (hepatitis – particularly with diclofenac). However, none of these, individually or collectively, is as frequent as gastrointestinal bleeding from peptic ulcers and, to a lesser extent, from the colon. Risks vary up to 20-fold between agents and by up to 10-fold by dose[90]. Risks can almost certainly be reduced by using the enteric coated drug, but available evidence has generally been obtained with standard preparations. Whether it would be wise to alter deliberately the delivery pattern in treating large intestinal disease is unclear. Enteric coated preparations are probably completely absorbed in the small bowel – and the non-enteric in the stomach and small bowel, so differences may be immaterial. Since in the United States Physicians Health Study, low dose aspirin (325 mg on alternate days) appeared relatively ineffective in preventing colon cancer, doses of at least 325 mg daily may be required. It is unclear, however, whether in that study follow-up was sufficiently prolonged.

COX-2 inhibitors

Considerations of chemopreventive strategies need to remain focused on the condition being dealt with. As Sporn[91] pointed out, the disease is 'carcinogenesis' and not cancer and nowhere is this process better understood than in the case of colorectal cancer. Although the mode of action of the NSAIDs in reducing the incidence of colon cancer is not entirely understood there are some strong clues including a body of clinical evidence and recent experimental evidence demonstrating the effect of NSAIDs on colorectal carcinogenesis. NSAIDs have demonstrated effects on the modulation of several putative biomarkers of colorectal cancer in rats treated with azoxymethane including the formation of aberrant crypt foci (ACF) and oncogene (myc, ras, p53) expression. NSAIDs also inhibit the production of prostaglandins, and other eicosanoids from arachidonic acid by the cyclo-oxygenase (COX) component of prostaglandin synthase. There is considerable evidence that PGE_2 induces cellular proliferation and may also suppress immune surveillance and killing of malignant cells. High levels of PGE_2 can also cause down-regulation of the signal transduction mechanisms responsible for maintaining the differentiated state of the cell. Two isoforms of COX exist. The COX-1 isoform is expressed constitutively throughout normal human tissues, including the kidney and gastric mucosa, where the prostaglandins produced are thought to play a protective role. The COX-2 isoform is an inducible form of cyclo-

oxygenase found in very low levels in normal tissues and in greatly increased levels in inflamed tissues.

NSAIDs reduce the incidence of colorectal cancer in humans and in animal models and COX-2 expression is increased in animal models of colorectal cancer and FAP (AOM rat and MIN mouse). COX-2 inhibitors are chemopreventive in animal models of colorectal cancer in AOM-induced ACF and tumour model and in knockout mice[80]. In addition, NSAIDs reduce mucosal prostaglandins and cause ulcers which can result in bleeding, perforation or outlet obstruction; and exogenous prostaglandins reduce both endoscopic ulcers and ulcer complications by ~50% over 6 months.

Screening

Encouragement to establish screening programmes for colorectal cancer comes from a variety of sources, principally the observation that outcome is significantly improved when the disease is treated in an early stage and through the demonstrated efficacy of screening tests. Colorectal cancer is not uniformly fatal although there are large differences in survival according to stage of disease. In advanced colorectal cancer in which curative resection is possible, 5-year survival in Dukes' B is 45% which drops to 30% in Dukes' C. Five year survival in resected Dukes' A is around 80% and survival following simple resection of an adenomatous pedunculated polyp containing carcinoma *in situ* (or severe dysplasia) or intramucosal carcinoma is generally close to 100%. Despite this knowledge, there are still 394,000 deaths from colorectal cancer world-wide annually[92].

The large differences in survival between early and late stage disease clearly indicate the advantage in detecting colorectal cancer early. The simplest advice is to ensure that any change in bowel habits or unexpected presence of blood in the stool should be investigated. Faecal occult blood testing (FOBT) is aimed at the detection of early asymptomatic cancer and is based on the assumption that such cancers will bleed and that small quantities of blood lost in the stool may be detected chemically or immunologically. A significant reduction in colorectal cancer mortality with haemocult testing has been reported[93–96]. A meta-analysis of all four studies produces a relative risk of colorectal cancer death of 0.84 (95% CI, 0.77–0.93)[97]. The results are of considerable importance but it is difficult to ignore the observation that in Minnesota[93], 38% of those screened annually and 28% of those screened biennially underwent at least one colonoscopy during the study.

These findings are important confirmation that haemocult screening may be effective in the prevention of death from colorectal cancer[99]. An

important development has been the demonstration that after 18 years there is a significant reduction in the incidence of colorectal cancer in subjects randomised to the haemocult arm of the Minnesota study[98].

There is a good deal of evidence supporting infrequent sigmoidoscopy as a potentially effective screening modality for colorectal cancer although randomised trials have not yet been reported. Impressive reductions in rectal cancer and cancer of the proximal colon have been reported from demonstration studies[100–103]. Although the initial examination may be expensive, there is an advantage that polyps may be removed at the time of the initial procedure and no follow-up visits will be required. Use of a 65 cm flexible sigmoidoscope appears to be the most effective proposition at the present time since this avoids the more complicated colonoscopy and yet still covers a large part of the large bowel. Colonoscopy itself, with the clearance of polyps, is also strongly supported from observational studies although randomised trial data are not available. Both sigmoidoscopy and colonoscopy offer the possibility of reducing the incidence of colorectal cancer both by a greater magnitude and considerably quicker than haemocult.

Summary and conclusions

Colorectal cancer is a important public health problem: there are nearly one million new cases of colorectal cancer diagnosed world-wide each year and half a million deaths. Edwards *et al*[2] recently reported that in the US, colorectal cancer was the most frequent form of cancer among persons aged 75 years and older. Given that the majority of cancers occur in elder people and with the ageing of the population in mind, this observation gives further impetus to investigating prevention and treatment strategies among this subgroup of the population.

The disease is not uniformly fatal although there are large differences in survival according to stage of disease. Five year survival in resected Dukes' A is around 80% and survival following simple resection of an adenomatous pedunculated polyp containing carcinoma *in situ* (or severe dysplasia) or intramucosal carcinoma is generally close to 100%. Screening research, recommendations and implementation is an obvious priority.

The classical concept of risk of colorectal cancer being increased by increasing consumption of fat, protein and meat and to be reduced by increased consumption of fruits and vegetables[35] is currently being challenged as more epidemiological data become available. It has been hypothesised that alterations to serum triglycerides and/or plasma glucose could be one possible vehicle for the effects of various aetiological factors[104]. Thus there are prospects for primary prevention although it is difficult to know how to successfully bring about such

large-scale alterations to the diets of large proportions of populations. The large bowel has not been traditionally considered as a site where the risk of cancer is linked to cigarette smoking[67] although more recent evidence strongly points to the existence of such an association between cigarette smoking and an increased risk of both adenomatous polyps and colorectal cancer[70]. There is also interesting evidence suggesting that specific chemopreventive strategies could prove useful in the prevention of colorectal cancer[80].

While there are many questions to be resolved, it is apparent that many facets of colorectal cancer are becoming increasingly understood and prospects for prevention are becoming apparent. Making colorectal cancer a form of cancer for which a large proportion of deaths may be preventable[105] is a success for epidemiology. Achieving colorectal cancer control is the immediate challenge.

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