Curr Nutr Rep (2012) 1:44–54
DOI 10.1007/s13668-011-0006-7

CANCER (MF LEITZMANN, SECTION EDITOR)

Recent Evidence for Colorectal Cancer Prevention Through Healthy Food, Nutrition, and Physical Activity: Implications for Recommendations

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Published online: 10 January 2012

Abstract The aim of this paper is to present results from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Continuous Update Project on colorectal cancer and food, nutrition, and physical activity, an updated systematic literature review on evidence forming part of the 2007 WCRF/AICR Second Expert Report. Convincing evidence indicates that physical activity protects against colon cancer and that foods containing dietary fiber protect against colorectal cancer. Consumption of red meat and processed meat, ethanol from alcoholic drinks (by men and probably by women), as well as body fatness and abdominal fatness and the factors that lead to greater adult-attained height or its consequences are convincing causes of colorectal cancer. Consumption of garlic, milk, and calcium probably protects against this cancer. The updated evidence shows that food, nutrition, and physical activity have an important role in the causation and prevention of colorectal cancer.

Keywords Colorectal cancer · Prevention · Bowel cancer · Food · Nutrition · Physical activity · Cancer prevention · Recommendations · Systematic reviews · Meta-analysis · Evidence · Continuous Update Project · Garlic · Milk · Calcium

Introduction

Colorectal cancer is the third most common type of cancer worldwide, with more than 1 million new cases diagnosed in 2008, accounting for 9.7% of all incident cancers [1]. Men accounted for 664,000 new cases and women 571,000 new cases. Incidence is highest in high-income countries such as those in North America and Western Europe but also in Asian countries that have experienced nutrition transition such as Japan, Singapore, and North Korea [1]. It remains relatively uncommon in Africa and much of Asia and is somewhat more common in men than in women. Nevertheless, although it can be successfully treated at early stages, it is fatal in just under one half of all cases and is the fourth most common cause of death from cancer.

Environmental and in particular diet and lifestyle factors are likely to be the main determinants of colorectal cancer risk, which is indicated by the rapid increase in colorectal cancer incidence in parallel with economic development and adoption of a Western lifestyle [2]. In the United Kingdom, one third of the most common cancers (mouth, pharynx, larynx, esophagus, lung, stomach, pancreas, gallbladder, liver, colorectum, breast, endometrium, prostate, and kidney) are estimated to be preventable through a healthy diet, being physically active, and maintaining a healthy weight. For colorectal cancer, the proportion of preventable cases is about 43% [3••].

Second Expert Report and Recommendations

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) published its Second Expert Report, *Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective* [4], in 2007, a comprehensive and systematic analysis of the evidence on the links between food, nutrition, physical activity, and risk of cancer, including colorectal cancer. This report of an independent panel of international experts shows the important role that food, nutrition, and physical activity have in

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the prevention and causation of colorectal cancer. It includes recommendations for cancer prevention:

1. Be as lean as possible without becoming underweight.
2. Be physically active for at least 30 min every day.
3. Avoid sugary drinks and limit consumption of energy-dense foods (particularly processed foods high in added sugar, low in fiber, or high in fat).
4. Eat more of a variety of vegetables, fruits, whole grains, and pulses.
5. Limit consumption of red meats and avoid processed meats.
6. If consumed at all, limit alcoholic drinks to 2/d for men and 1/d for women.
7. Limit consumption of salty foods and foods processed with salt (sodium).
8. Do not use supplements to protect against cancer.
9. It is best for mothers to breastfeed exclusively for up to 6 months and then add other liquids and foods.
10. After treatment, cancer survivors should follow the Recommendations for Cancer Prevention.

The Continuous Update Project

Since the Second Expert Report, WCRF/AICR have initiated the Continuous Update Project (CUP) in collaboration with a team at Imperial College London in order to keep the evidence updated into the future. An independent panel of experts comprising leading scientists in the fields of diet, physical activity, obesity, and cancer reviews the findings and draws conclusions based on the body of scientific evidence and when necessary will revise the 2007 WCRF/AICR recommendations.

The CUP follows the same robust process as the Second Expert Report. The database of published journal articles is updated on a rolling basis from which at any point in time, the most current review of scientific data (including meta-analyses where appropriate) can be performed. All 17 cancer sites reviewed in the original Second Expert Report will be updated in the CUP database by 2015. From 2015 to 2017, the panel will formally review the recommendations from the Second Expert Report.

The goals of the CUP are as follows:

- Provide the scientific community with comprehensive and up-to-date evidence related to food, nutrition, physical activity, body weight, and cancer.
- Become a trusted source used by scientists, health professionals, and policy makers.
- Ensure WCRF/AICR education resources for health professionals and the general public are based on the most up-to-date evidence.

Herein we present the systematically reviewed evidence for colorectal cancer in relation to food, nutrition, and physical activity, updated with studies published since 2006, and the implications for the WCRF/AICR Cancer Prevention Recommendations.

Methodology

For the Second Expert Report, a series of specially commissioned systematic literature reviews (SLRs) covering 17 cancer sites, the determinants of obesity, and recommendations made by other authoritative reports also related to the prevention and control of other diseases formed the basis for the panel's judgements on the causal relationships between food, nutrition and physical activity, and cancer. The SLRs included evidence published up to the end of 2005 and principally included a combination of different types of epidemiologic evidence, mechanistic data, and (where available) randomized controlled trials.

The evidence in both the Second Expert Report and the CUP was graded based on the approach by Hill [5] to identify exposures (environment, including lifestyle factors) associated with disease that demonstrate evidence of causality that is strong enough to warrant action to address them. Recommendations were only made when the panel judged that there was sufficient evidence of causality (ie, that a factor either directly decreases or increases the risk of cancer) to justify making recommendations.

Based on the experience of conducting the SLRs for the Second Expert Report, some modifications to the methodology were made. The literature search was restricted to Medline. Retrospective case–control studies were only included in the reviews when insufficient data were available from prospective studies. The 2010 CUP-updated analysis for colorectal cancer included studies published up to December 2009 for all exposures, and for fruits, vegetables, red and processed meat, vitamin D, alcohol, and height papers published up to May/June 2010 [6••]. Where possible, studies were included in meta-analyses (Table 1). A summary of the conclusions is available [7••].

Summary of Recent Evidence

The updated evidence on colorectal cancer for exposures deemed convincing or probable is summarized in this section (Table 2 and Table 3), with a brief summary for exposures where evidence was more limited. A total of 516 papers are now included in the CUP database for colorectum

Table 1 What is a meta-analysis?

- Study-level meta-analysis provides single estimates of effect using information from multiple studies of the same design. These summary estimates can provide evidence regarding the presence or absence of an association and examine possible dose–response relationships.
- Meta-analysis, often displayed graphically on a forest plot (Fig. 1), can also identify heterogeneity between studies. This heterogeneity can be quantified using a measure called I^2, which ranges from 0%–100% and indicates the percentage of total variation across studies that is not due to chance. In general, an I^2 of ≤25% indicates low heterogeneity, ~50% indicates moderate heterogeneity, and ≥75% indicates high heterogeneity. The confidence interval (CI) is an indication of how much random error underlies the point estimate; it does not take into account confounding and other forms of systematic bias. A confidence level of 95% indicates a 95% probability that the true value falls within the CI.
- Random effects models are used to generate the forest plots. This type of model does not assume that the links between exposure and outcome are the same in different studies.

(253 from the Second Expert Report and 263 from the CUP); these form the basis of this report.

Table 2 Convincing and probable conclusions from the WCRF/AICR CUP on colorectal cancer

Food, nutrition, physical activity, and cancers of the colon and rectum		
	Decreases risk	Increases risk
Convincing	Physical activity[ab]	Red meat[d]
	Foods containing dietary fiber[c]	Processed meat[e]
		Alcoholic drinks (men)[f]
		Body fatness
		Abdominal fatness
		Adult-attained height[g]
Probable	Garlic	Alcoholic drinks (women)[f]
	Milk[h]	
	Calcium[i]	

[a] Physical activity of all types: occupational, household, transport, and recreational

[b] The panel judges that the evidence for colon cancer is convincing; no conclusion was drawn for rectal cancer

[c] Includes foods naturally containing the constituent and foods that have the constituent added; dietary fiber is contained in plant foods

[d] The term *red meat* refers to beef, pork, lamb, and goat from domesticated animals

[e] The term *processed meat* refers to meats preserved by smoking, curing, salting, or addition of chemical preservatives

[f] The judgements for men and women are different because fewer data are available for women; for colorectal and colon cancers, the effect appears stronger in men than in women

[g] Adult-attained height is unlikely to modify the risk of cancer directly; it is a marker for genetic, environmental, hormonal, and nutritional factors affecting growth during the period from preconception to completion of linear growth

[h] Milk from cows (most data are from high-income populations, in which calcium can be taken to be a marker for milk/dairy consumption); the panel judges that a higher intake of dietary calcium is one way in which milk could have a protective effect

[i] The evidence is derived from studies using supplements at a dose of 1,200 mg/d

CUP, Continuous Update Project; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research

Overweight and Obesity

Excess energy from food and beverages is stored in the body as fat in adipose tissue. Since the 1980s, typical body compositions have changed, with a worldwide increase in average body fatness and in overweight and obesity. This change is most notable in high-income countries and in industrial and urban environments in many countries. In several low-income countries, high levels of body fatness exist alongside undernutrition in the same communities.

Body mass index (BMI) is most commonly used as an indirect marker for body fatness. The mechanisms through which body fatness could plausibly influence cancer risk are outlined in Table 4.

Body Fatness

The majority of the 29 studies for colorectal cancer showed increased risk with increased body fatness. Meta-analyses (per kg/m^2 increment) showed increased risks of 2%, 3%, and 1% for colorectal, colon, and rectal cancers, respectively. They also showed a larger effect in men than women (4% vs 2% for colon cancer) (Table 5).

Two other published dose–response meta-analyses (per 5 kg/m^2) with a large number of cases (>20,000 for colon cancer for both men and women separately) showed a 24% increased risk for men and 9% increased risk for women (20,975 cases from 19 studies) for colon cancer and 9% increased risk for men (14,894 cases from 18 studies) and nonsignificant increased risk for women (9,052 cases from 14 studies) for rectal cancer [8, 9].

Abdominal Fatness

All studies showed increased risk with increased waist circumference (five studies) or increased waist-to-hip ratio (nine studies) and colorectal cancer. Similar results were shown for colon and rectal cancers.

Meta-analyses for waist circumference (per 2.54 cm) for studies that did not adjust for BMI showed increased risks of 3%, 5%, and 3% for colorectal, colon, and rectal cancers

Table 3 Conclusions for convincing and probable exposures from the recent evidence on colorectal cancer

Exposure	Conclusions
Body fatness	•There is abundant and consistent epidemiologic evidence of a clear dose–response relationship, and evidence for plausible mechanisms that operate in humans.
	•The evidence that greater body fatness is a cause of colorectal cancer is convincing
Abdominal fatness	•There is ample consistent evidence from cohort studies of a clear dose–response relationship and robust evidence for mechanisms that operate in humans.
	•The evidence that abdominal fatness is a cause of colorectal cancer is convincing.
Physical activity	•There is abundant epidemiologic evidence from prospective studies showing a lower risk of colorectal cancer with higher overall levels of physical activity, and there is evidence of a dose–response effect.
	•The effect is strong for colon cancer; however, there is no evidence of an effect for rectal cancer. The effect is strong and consistent in men but less strong in women. There is plausible evidence for mechanisms operating in humans.
	•The evidence that higher levels of physical activity, within the range studied, protect against colon cancer is convincing.
Foods containing dietary fiber	•There is substantial consistent evidence from cohort studies, together with a clear dose–response relationship, supported by evidence for plausible mechanisms. The effect is apparent in men and women.
	•Since the publication of the Second Export Report, the recent evidence has strengthened; foods containing dietary fiber convincingly decrease colorectal cancer risk.
Garlic	•The evidence, though not copious and mostly from case–control studies, is consistent with a dose–response relationship. There is evidence for plausible mechanisms.
	•Garlic probably protects against colorectal cancer.
Red meat	•A substantial amount of data from cohort studies showed a dose–response relationship, supported by evidence for plausible mechanisms operating in humans.
	•Consumption of red meat is a convincing cause of colorectal cancer.
Processed meat	•There is a substantial amount of evidence, with a dose–response relationship apparent from cohort studies. There is strong evidence for plausible mechanisms operating in humans.
	•Consumption of processed meat is a convincing cause of colorectal cancer.
Milk	•The evidence on milk from cohort studies is reasonably consistent, supported by stronger evidence from dietary calcium as a marker. There is evidence for plausible mechanisms.
	•Milk probably protects against colorectal cancer.
Alcoholic drinks (ethanol)	•There is ample and generally consistent evidence from cohort studies. A dose–response relationship is apparent. There is evidence for plausible mechanisms. For colorectal and colon cancer, the effect appears stronger in men than in women.
	•Ethanol from alcoholic drinks is a convincing cause of colorectal cancer in men and probably a cause in women.
Dietary supplements	•There is generally consistent evidence on dietary calcium, total calcium (dietary and supplemental), and calcium supplements from cohort studies. The effect was apparent in men and women. There is evidence for plausible mechanisms.
	•Calcium probably protects against colorectal cancer.
Adult-attained height	•There is ample epidemiologic evidence from cohort studies, which is consistent, and there is a clear dose–response relationship, with evidence for plausible mechanisms operating in humans.
	•The evidence that the factors that lead to greater adult-attained height or its consequences are a cause of colorectal cancer is convincing. The causal factor is unlikely to be tallness itself, but rather factors that promote linear growth in childhood.

(Table 5), respectively, that were only slightly attenuated when adjusted for BMI. For colon cancer specifically, there was a 6% increased risk in men and a 3% increased risk in women (Table 5). Meta-analyses for waist-to-hip ratio (per 0.1 increment) showed a 17%, 27%, and 20% increased risk for colorectal, colon, and rectal cancers, respectively (Table 5).

Physical Activity

The review included total physical activity as well as different types of activity, such as recreational and occupational. Eight of 10 studies on colon cancer reported a lower risk with increased total physical activity. Many studies were

Table 4 Mechanisms for body fatness influencing cancer risk

- Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factor-1, and estrogens, creating an environment that encourages carcinogenesis and discourages apoptosis.
- Insulin resistance is increased, in particular by abdominal fatness, and the pancreas compensates by increasing insulin production. This hyperinsulinemia increases the risk of cancers of the colon and endometrium, and possibly of the pancreas and kidney [24]. Adipose tissue is the main site of estrogen synthesis in men and postmenopausal women, and increased body fatness results in increased estradiol in men and women and may also result in higher testosterone levels in women (extreme obesity can lead to polycystic ovary disease) [24]. Increased levels of sex steroids are strongly associated with risk of endometrial and postmenopausal breast cancers [25, 26] and may impact on colon and other cancers.
- Obesity is characterized by a low-grade chronic inflammatory state. The adipocyte (fat cell) produces proinflammatory factors, and obese individuals have elevated concentrations of circulating tumor necrosis factor-α [24], interleukin-6, and C-reactive protein compared with lean people [27], as well as of leptin, which also functions as an inflammatory cytokine [28]. Such chronic inflammation can promote cancer development.

Table 5 Summary estimates for convincing and probable exposures for colorectal, colon, and rectal cancers

Exposure	Summary relative risk estimates (95% CI)		
	Colorectal cancer	Colon cancer	Rectal cancer
Body fatness, *BMI* (per kg/m^2)	1.02 (1.02–1.03); I^2=60% (*n*=23)	1.03 (1.03–1.04); I^2=68% (*n*=29)	1.01 (1.01–1.02); I^2=14% (*n*=22)
	M: 1.03 (1.03–1.04); I^2=0% (*n*=12)	M: 1.04 (1.03–1.05); I^2=50% (*n*=22)	M: 1.02 (1.01–1.02); I^2=0% (*n*=18)
	W: 1.02 (1.01–1.03); I^2=67% (*n*=16)	W: 1.02 (1.01–1.03); I^2=53% (*n*=24)	W: 1.01 (1.00–1.02); I^2=32% (*n*=18)
Abdominal fatness/waist circumference (per 2.54 cm)	1.03 (1.02–1.04); I^2=0% (*n*=3)	1.05 (1.03–1.06); I^2=63% (*n*=6)	1.03 (1.01–1.04); I^2=0% (*n*=3)
		M: 1.06 (1.04–1.08); I^2=53% (*n*=6)	
		W: 1.03 (1.02–1.04); I^2=49% (*n*=6)	
Waist-to-hip ratio (per 0.1 increment)	1.17 (1.09–1.25); I^2=0% (*n*=3)	1.27 (1.15–1.41); I^2=0% (*n*=5)	1.20 (1.07–1.34); I^2=0% (*n*=3)
Total physical activity (for an increase of 5 MET h/d)	0.97 (0.94–0.99); I^2=0% (*n*=3)	0.92 (0.86–0.99); I^2=80% (*n*=5)	1.02 (0.95–1.10); I^2=34% (*n*=3)
Recreational activity (for an increase of 5 MET hour/week)	0.97 (0.94–1.00); I^2=66% (*n*=3)	0.98 (0.96–1.00); I^2=52% (*n*=5)	1.00 (0.97–1.03); I^2=45% (*n*=5)
Foods containing dietary fiber (per 10 g dietary fiber/d)	0.90 (0.86–0.94); I^2=4% (*n*=15)	0.89 (0.81–0.97); I^2=35% (*n*=12)	0.91 (0.81–1.03); I^2=15% (*n*=10)
	M: 0.88 (0.78–0.99); I^2=35% (*n*=5)	M: 0.86 (0.76–0.96). I^2=20% (*n*=7)	M: 0.90 (0.69–1.19); I^2=43% (*n*=5)
	W: 0.92 (0.87–0.98); I^2=0% (*n*=10)	W: 0.94 (0.82–1.08); I^2=30% (*n*=8)	W: 0.91 (0.76–1.08); I^2=0% (*n*=6)
Red and processed meat (per 100 g/d)	1.16 (1.04–1.30); I^2=47% (*n*=9)	1.21 (1.06–1.39); I^2=56% (*n*=7)	1.31 (1.13–1.52); I^2=18% (*n*=5)
	M: 1.08 (0.84–1.39); I^2=0% (*n*=2)	M: 1.41 (0.98–2.03); I^2=71% (*n*=2)	
	W: 1.02 (0.77–1.34); I^2=61% (*n*=4)	W: 1.05 (0.78–1.40); I^2=57% (*n*=4)	
Red meat (per 100 g/d)	1.17 (1.05–1.31); I^2=0% (*n*=8)	1.12 (0.97–1.29); I^2=0% (*n*=9)	1.18 (0.98–1.42); I^2=0% (*n*=7)
	M: 1.28 (0.49–3.35); I^2=64% (*n*=2)	M: 1.06 (0.75–1.50); I^2=0% (*n*=2)	
	W: 1.05 (0.78–1.42); I^2=22% (*n*=3)	W: 1.00 (0.72–1.38); I^2=0% (*n*=4)	
Processed meat (per 50 g/d)	1.18 (1.10–1.28); I^2=12% (*n*=9)	1.24 (1.13–1.36); I^2=0% (*n*=9)	1.12 (0.99–1.28); I^2=0% (*n*=8)
	M: 1.11 (0.86–1.44); I^2=35% (*n*=2)	M: 1.64 (0.94–2.84); I^2=72% (*n*=3)	
	W: 1.09 (0.88–1.33); I^2=0% (*n*=4)	W: 1.38 (1.06–1.78); I^2=0% (*n*=4)	
Milk (per 200 g/d)	0.91 (0.86–0.97); I^2=0% (*n*=7)	0.91 (0.83–1.00); I^2=25% (*n*=5)	0.98 (0.82–1.17); I^2=0% (*n*=3)
	M: 0.89 (0.82–0.98); I^2=0% (*n*=2)	M: 0.92 (0.83–1.02); I^2=26% (*n*=3)	
	W: 0.94 (0.85–1.04); I^2=10% (*n*=5)	W: 1.01 (0.87–1.17); I^2=0% (*n*=2)	
Dietary calcium (per 200 mg/d)[a]	0.94 (0.93–0.96); I^2=0% (*n*=13)	0.93 (0.89–0.97); I^2=10% (*n*=10)	0.94 (0.86–1.02); I^2=35% (*n*=8)
	M: 0.93 (0.88–0.99); I^2=52% (*n*=3)		
	W: 0.93 (0.91–0.95); I^2=0% (*n*=9)		
Ethanol in alcoholic drinks (per 10 g ethanol/d)	1.10 (1.06–1.13); I^2=51% (*n*=8)	1.08 (1.04–1.13); I^2=60% (*n*=12)	1.10 (1.07–1.12); I^2=0% (*n*=11)
	M: 1.11 (1.08–1.15); I^2=21% (*n*=7)	M: 1.10 (1.06–1.14); I^2=62% (*n*=10)	M: 1.10 (1.07–1.13); I^2=6% (*n*=9)
	W: 1.07 (0.98–1.17); I^2=0% (*n*=2)	W: 1.03 (0.96–1.10); I^2=34% (*n*=8)	W: 1.09 (1.03–1.16); I^2=0% (*n*=7)
Adult-attained height (per 5 cm)	1.05 (1.03–1.08); I^2=11% (*n*=8)	1.09 (1.05–1.12); I^2=42% (*n*=9)	1.03 (0.99–1.07); I^2=25% (*n*=8)
	M: 1.04 (1.03–1.06); I^2=0% (*n*=6)	M: 1.08 (1.03–1.13); I^2=56% (*n*=7)	M: 1.05 (1.01–1.08); I^2=0% (*n*=7)
	W: 1.06 (1.04–1.09); I^2=16% (*n*=5)	W: 1.09 (1.06–1.13); I^2=0% (*n*=7)	W: 1.00 (0.95–1.06); I^2=20% (*n*=6)

[a] Meta-analyses were not conducted for garlic and calcium supplements

BMI, body mass index; CI, confidence interval; M, men; MET, metabolic equivalent task; W, women

unsuitable for meta-analysis due to the disparate measures used to assess physical activity.

Meta-analyses for total physical activity (for an increase of 5 metabolic equivalent tasks [MET] h/d) showed a 3% decreased risk of colorectal cancer and an 8% decreased risk of colon cancer (Table 5). For recreational activity (for an increase of 5 MET hour/week), summary estimates from meta-analyses were in the direction of decreased risk of colorectal and colon cancers but did not reach statistical significance (Table 5), whereas meta-analyses per 30 min/d showed an 11% decreased risk of colorectal and a 12% decreased risk of colon cancer. The data also suggested that the effect was less for rectal cancer [6••].

A published meta-analysis of highest versus lowest comparisons of leisure time physical activity and colon cancer showed a 20% decreased risk in men (10 studies) and 14% decreased risk in women (9 studies) for colon cancer. A nonsignificant increased risk was found for rectal cancer [10].

Sustained moderate physical activity raises the metabolic rate and increases maximal oxygen uptake. In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity (the amount of work that it can perform) and thus have a beneficial effect on body fatness. In addition, physical activity may protect against colon cancer by decreasing inflammation and reducing insulin levels and insulin resistance [4].

Patterns of Diet

The evidence is reviewed under the headings of plant foods, animal foods, alcoholic drinks, and dietary supplements.

Plant Foods

Foods Containing Dietary Fiber Dietary fiber is the residue of plant foods that is undigested in the small bowel and reaches the large bowel, where it is fermented by the colonic flora. It is characterized principally by its content of non-starch polysaccharides and is found in vegetables, fruits, pulses (legumes), whole grain cereals, roots, tubers, and plantains. Thirteen of 18 studies for colorectal cancer showed decreased risk with increased intake of total dietary fiber.

Meta-analyses (per 10 g/d) showed a 10% lower risk for colorectal cancer and an 11% lower risk for colon cancer (Table 5 and Fig. 1). The summary estimates for rectal cancer were in the direction of decreased risk but did not reach conventional levels of statistical significance (Table 5) [6••].

Meta-analyses (per 10 g/d) showed a 12% decreased risk for men and an 8% decreased risk for women for colorectal cancer (Table 5). Adjustment for folate intake had little effect on the summary estimates.

Meta-analyses for sources of fiber and colorectal cancer showed a 10% decreased risk for cereal fiber; summary estimates for other sources of fiber were in the direction of

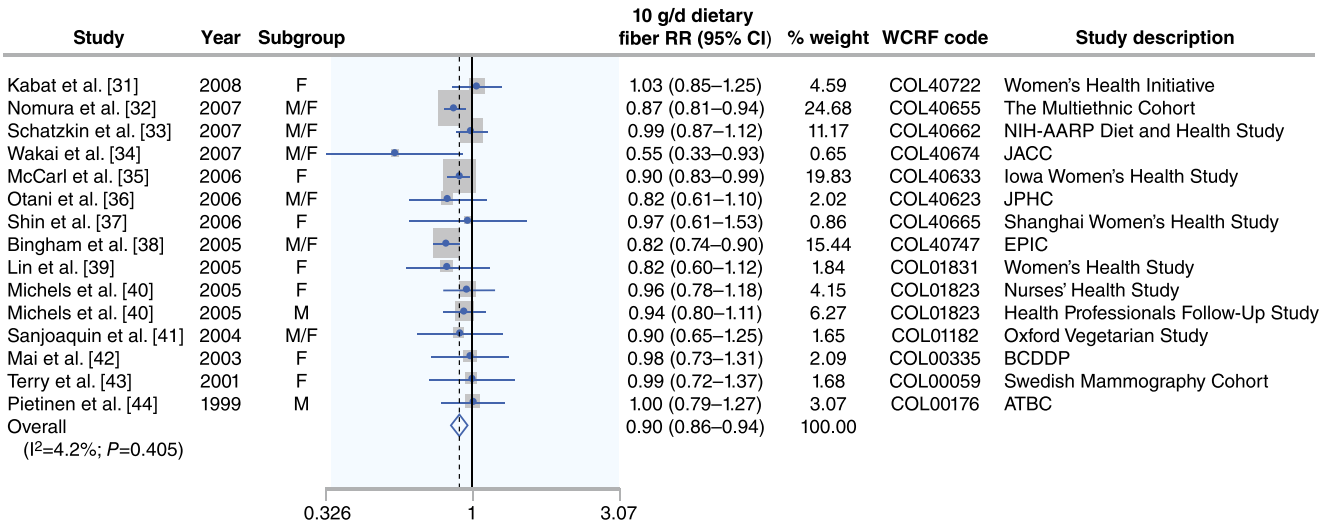

Fig. 1 Dose–response meta-analysis of dietary fiber and colorectal cancer per 10 g/d. This figure presents the results of the dose–response meta-analysis of dietary fiber and colorectal cancer of 15 included studies. Most of the studies' point estimates are to the left of the "no-effect-on-risk" line. The confidence interval (CI) for studies crossing the "no-effect-on-risk" line indicates that the estimates are not statistically significant. The study giving the most weighting (influence) is Nomura et al. [32] (24.68%), shown by the size of the square around the point estimate. Of all the studies presented, four are significant, suggesting a protective effect of fiber on colorectal cancer (that is, it has a relative risk [RR] <1.00). F, female; M, male; WCRF, World Cancer Research Fund

decreased risk but did not reach statistical significance [6••]. For whole grains, there was a 21% decreased risk per 3 servings/d for colorectal cancer and a 16% decreased risk for colon cancer [6••]. A published pooled analysis of 8,100 colorectal cancer cases among 730,000 participants, followed up for 6 to 20 years, showed a nonsignificant decreased risk for the groups that consumed the most dietary fiber [11].

Fiber exerts several effects in the gastrointestinal tract, but the precise mechanisms for its probable protective role are still not clearly understood. Fiber dilutes fecal content, decreases transit time, and increases stool weight. The gut flora produce fermentation products, especially short-chain fatty acids, from a wide range of dietary carbohydrates and mucins that reach the colon. Short-chain fatty acids such as butyrate induce apoptosis, cell cycle arrest, and differentiation in experimental studies. Fiber intake is also strongly correlated with intake of folate, though adjusting for this often does not affect the risk reduction attributed to fiber [4].

Garlic No new cohort studies were identified as part of the CUP. Two cohort studies and six case–control studies identified as part of the Second Expert Report investigated garlic. All studies reported decreased risk with increased intake, with none reporting contrary results. Most studies did not reach statistical significance, and meta-analysis was not possible.

Considerable preclinical evidence with model carcinogens and transplantable tumors supports an anticancer effect of garlic and some of its allyl sulfur components. Animal studies demonstrate that allyl sulfides effectively inhibit colon tumor formation and also can inhibit cell growth in laboratory experiments [12–15].

Animal Foods

Red and Processed Meat Red meat includes beef, lamb, and pork, and processed meat includes red meat that has been preserved by smoking, curing, salting, or adding other chemical preservatives. Nine of 10 studies on colorectal cancer showed increased risk with higher intake. Meta-analyses (per 100 g/d) for colorectal, colon, and rectal cancers showed 16%, 21%, and 31% increased risks, respectively (Table 5).

A published meta-analysis of highest versus lowest intakes of red and processed meat of 13,407 cases from 33 risk estimates showed a significant increased risk (21% for colorectal cancer) [16]. A published dose–response meta-analysis of 7,367 cases from 14 studies showed a 28% increased risk per 120-g/d increase in red and processed meat [17].

Red meat. Nine of 12 studies for colorectal cancer showed increased risk with higher intake. Meta-analysis (per 100 g/d) showed a 17% increased risk for colorectal cancer (Table 5). Summary estimates were in the direction of increased risk of colon and rectal cancers but did not reach statistical significance (Table 5).

There are several potential underlying mechanisms for a positive association of red meat consumption with colorectal cancer. Red meat contains haem, which promotes the formation of potentially carcinogenic *N*-nitroso compounds, as well as cytotoxic alkenals from fat peroxidation. Red meat cooked at high temperatures results in the production of heterocyclic amines and polycyclic aromatic hydrocarbons that can cause colon cancer in individuals with a genetic predisposition [4].

Processed meat. Ten of 13 studies for colorectal cancer showed increased risk with higher intake. Meta-analysis (per 50 g/d) showed an 18% increased risk for colorectal cancer and a 24% increased risk for colon cancer (Table 5). The summary estimate for rectal cancer was in the direction of increased risk but did not reach statistical significance (Table 5). Meta-analyses (per 50 g/d) showed a 38% increased risk for women and a 64% increased risk for men for colon cancer, though the results for men did not reach statistical significance (Table 5).

Heterogeneity was low and explained by the disparity in category definitions between studies as well as by improved adjustment for confounders in recent studies. A published meta-analysis of highest versus lowest intakes of processed meat of 13,471 cases from 30 risk estimates showed a 19% increased risk for colorectal cancer [16]. A published dose–response meta-analysis of 10 studies showed a 10% increased risk of colorectal cancer for each 30 g/d of processed meat consumed. The same study showed an increased risk of 16% for 20 studies in a meta-analysis of highest versus lowest intakes of processed meat [18].

Milk Eight of 10 cohort studies for colorectal cancer showed decreased risk with increased milk intake. Summary estimates for meta-analyses (per 200 g/d) showed a 9% decreased risk for colorectal cancer and were in the direction of decreased risk for colon and rectal cancers but did not reach statistical significance (Table 5). These findings that milk consumption is associated with a reduction in colorectal cancer risk were recently published [19•].

A published meta-analysis of highest versus lowest comparison of milk intake for 2,813 cases from 14 cohort studies showed a 10% decreased risk for colorectal/colon cancer and a nonsignificant decreased risk for rectal cancer [20]. A published pooled analysis of 4,992 cases among 534,536 participants, followed up for 6 to 16 years, showed a 15% decreased risk for the groups that drank the most milk, and a 14% decreased risk for the groups with the highest dietary calcium intake [21].

Sixteen of 17 cohort studies reported decreased risk of colorectal cancer with increasing dietary calcium intake. Meta-analyses for dietary calcium (per 200 mg/d) showed decreased risks of 6% and 7% for colorectal and colon cancers, respectively (Table 5). The summary estimate for rectal cancer was in the direction of decreased risk for rectal cancer but did not reach statistical significance. Meta-analyses (per 200 mg/d) for colorectal cancer showed a 7% decreased risk for both men and women when analyzed separately (Table 5).

Most of the evidence comes from Western countries, in which dietary calcium intake can be taken as a marker for dairy consumption. Any effect of milk in reducing colorectal cancer risk is likely to be mediated at least in part by calcium, which restrains cellular proliferation and promotes differentiation and apoptosis in healthy and tumor colorectal cells [22]. Milk includes many other bioactive constituents that may also play a role. The Second Expert Report also found that diets high in calcium probably increase the risk of prostate cancer, and for this reason, no recommendations were made for dairy foods.

Alcoholic Drinks (Ethanol)

All studies investigating alcohol as ethanol showed increased risk with increased intake for colorectal (8 studies) and colon cancers (12 studies). Meta-analyses (per 10 g ethanol/d) showed a 10% increased risk of colorectal and rectal cancers and an 8% increased risk of colon cancer (Table 5). Meta-analyses showed a greater effect in men than women for colorectal and colon cancers, with the results for colorectal cancer showing an 11% increased risk in men, compared with 7% for women (Table 5). A published pooled analysis of more than 4,600 colorectal cancer cases among more than 475,000 participants, followed up for 6 to 16 years, showed a 41% increased risk for the groups that drank the most alcohol [23].

There was some suggestion of a greater effect in men than in women, possibly because of the generally higher consumption of alcohol among men. Also, men and women may prefer different types of alcoholic drinks; there may be hormone-related differences in alcohol metabolism or in susceptibility to alcohol. Data also suggested a J-shaped dose–response relationship, with low intake being associated with lower risk compared with no intake [4].

Some metabolites of alcohol, such as acetaldehyde, are carcinogenic. There is also an interaction with smoking. Tobacco may induce specific mutations in DNA that are less efficiently repaired in the presence of alcohol. Alcohol may also function as a solvent, enhancing penetration of other carcinogenic molecules into mucosal cells. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation, and the generation of free radical oxygen species. Lastly, high consumers of alcohol may have diets low in essential nutrients, making tissues susceptible to carcinogenesis [4].

Dietary Supplements

The Second Expert Report found that in trials of high-dose nutrient supplements, cancer incidence was variously increased or decreased in selected populations. Such studies do not relate to widespread use among the general population, in whom the balance of risks and benefits cannot be predicted confidently, and a general recommendation to consume supplements for cancer prevention might have unexpected adverse effects. Increasing consumption of the relevant nutrients through the usual diet is preferred.

Calcium Six of the seven studies for colorectal cancer reported decreased risk with calcium supplementation, and no meta-analyses were conducted. A published meta-analysis showed a 24% decreased risk with use of calcium supplements for colorectal/colon cancer [20]. A pooled analysis of 4,992 cases among 534,536 participants, followed up for 6 to 16 years, showed a 22% decreased risk for the groups with the highest calcium intakes (dietary and supplemental sources) [21]. In addition, two randomized controlled trials and four cohort studies investigated calcium supplements and the risk of adenomas. Both trials and most of the cohort studies showed decreased risk with supplementation.

Calcium from diet is an important nutrient; intracellular calcium is a pervasive second messenger acting on many cellular functions, including cell growth. Calcium restrains cellular proliferation and promotes differentiation and apoptosis in healthy and tumor colorectal cells [22].

Life Course: Adult-Attained Height

Six of the eight cohort studies for colorectal cancer showed increased risk with increased height. Meta-analyses (per 5 cm) showed a 5% and 9% increased risk for colorectal and colon cancers, respectively (Table 5). The summary estimate for rectal cancer was in the direction of increased risk but did not reach statistical significance (Table 5). For both colorectal and colon cancers, the increased risk was observed in both men and women; however, for rectal cancer, it was only statistically significant in men (Table 5).

The general mechanisms through which the factors that lead to greater adult attained height or its consequences could plausibly influence cancer risk are outlined in the Second Expert Report [4]. Many of these, such as early-

Table 6 Foods containing vitamin D

- Two recent papers have now been included in the Continuous Update Project (CUP) database looking at dietary vitamin D. This includes one from the European Prospective Investigation into Cancer and Nutrition (EPIC) and one from the Japan Public Health Center–based Prospective Study on Cancer and Cardiovascular Diseases [29, 30].
- The evidence suggesting that vitamin D or foods containing it protect against colorectal cancer is limited, but it is important to highlight that the effects of vitamin D and calcium are strongly interrelated. This is because both are growth restraining and both induce differentiation and apoptosis in intestinal cells, and calcium-mediated effects are strongly dependent on vitamin D levels.
- Data from observational studies are probably hampered by the fact that total levels of the biologically active form are not only dependent on diet but also on supplements and UV exposure of the skin. Serum/plasma 25-hydroxyvitamin D status is therefore considered a more accurate measure of vitamin D status than vitamin D intake.
- It is important to be aware of the mechanistic effects of vitamin D polymorphism, as evidence shows that this could have an effect on susceptibility to colorectal cancer risk. The recent EPIC study included a meta-analysis looking at various polymorphisms, although no significant associations were noted [29].

life nutrition, altered hormone profiles, and the rate of sexual maturation, could plausibly increase cancer risk.

Other Exposures

The evidence that nonstarchy vegetables, fruits, and foods containing vitamin D protect against colorectal cancer and that cheese or foods containing iron, animal fats, or sugars are causes of this cancer is too limited to make recommendations. Evidence for foods containing folate, fish, and selenium is more limited, and no conclusion could be drawn. For more information on foods containing vitamin D, nonstarchy vegetables, and fruits, see Tables 6 and 7.

Conclusions

In total, 263 new papers were identified between 2006 and 2010. The strongest evidence, corresponding to judgements of "convincing" and "probable," shows that physical activity protects against colon cancer and foods containing dietary fiber protect against colorectal cancer. The evidence also shows that consumption of red meat and of processed meat, ethanol from alcoholic drinks (by men and probably by women), as well as body fatness and abdominal fatness and the factors that lead to greater adult-attained height or its consequences are convincing causes. Consumption of garlic, milk, and calcium are probably protective. The evidence that nonstarchy vegetables, fruits, and foods containing vitamin D protect against colorectal cancer and that cheese or foods containing iron, animal fats, or sugars are causes of this cancer is too limited to make recommendations. Evidence for foods containing folate, fish, and selenium is more limited, and no conclusion could be drawn.

The recent evidence presented here shows that food, nutrition, and physical activity have an important role in the prevention and causation of colorectal cancer, supporting WCRF/AICR Recommendations for Cancer Prevention. Health professionals have a direct and obvious influence on people's health. Clinicians in particular are trusted by the public and are expected to give advice and guidance on good health and well-being and the prevention of disease, as well as diagnosis and treatment of disorders and diseases. In their daily interactions with people, health professionals have unrivaled opportunities to provide information and encouragement in support of healthy ways of life [3••].

The aim for health professionals should be to conduct professional practice to realize the potential for promoting health, including cancer prevention. The Second Expert Report outlines public health goals designed to be used by health professionals as well recommendations for individuals. The WCRF/AICR 2009 Policy Report makes the following recommendations for health professionals [3••]:

Table 7 Nonstarchy vegetables and fruits

- There is a substantial amount of evidence for nonstarchy vegetables and fruits, but it is too inconsistent and limited to show that they protect against colorectal cancer.
- Although this is the case, it must be noted that this is a wide and disparate food category, and many different plant food constituents could feasibly contribute to a protective effect of nonstarchy vegetables and fruits. It is difficult to unravel the relative importance of each constituent and it is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis. These include dietary fiber, folate, selenium, allyl sulfides, glucosinolates, dithiolethiones, indoles, coumarins, ascorbate, chlorophyll, and antioxidants (including flavonoids, carotenoids, phenols, and phytoestrogens).
- There is also evidence that nonstarchy vegetables and fruit are probably protective against other cancers (nonstarchy vegetables: mouth, pharynx, larynx, esophagus, and stomach; fruits: mouth, pharynx, larynx, esophagus, lung, and stomach).

- Prioritize public health, including cancer prevention, quality food, nutrition, and physical activity, in core training, practice, and professional development.
- Take a lead in educating and working with colleagues, other professionals, and other actors to improve public health, including cancer prevention.
- Involve people as family and community members and take account of their personal characteristics in all types of professional practice.

Acknowledgments The authors wish to acknowledge the research team at Imperial College London (United Kingdom) who prepared the 2010 CUP Colorectal Cancer Report [6••] and are responsible for updating the CUP database, and the CUP Expert Panel for reviewing the evidence (for more information, please visit http://www.wcrf.org/cancer_research/cup/index.php).

Disclosure No potential conflicts of interest relevant to this article were reported.

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