



Concept of chemoprevention in colorectal cancer

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide leading to significant mortality and morbidity^[1]. Colorectal cancer incidence rates both among men and women are nearly fourfold higher in more-developed as compared with less-developed regions of the world^[1]. The reasons for this variability in CRC prevalence in different geographical areas are not fully known. This however has been studied extensively and the role of various carcinogenic factors has been the target of clinical, experimental, and epidemiological studies. Most studies favour an aetiological role of dietary, lifestyle, and genetic factors in CRC, however, some studies have demonstrated equivocal or even negative results. These observations have been analysed in detail in a recent review^[2].

Colorectal screening programmes are an excellent opportunity to educate the public regarding the carcinogenic potential of dietary and lifestyle factors. Current emphasis of most CRC screening programmes is to detect cancer at an early, or preferably at a precancerous-stage of colonic polyps. This approach maximises survival outcomes. Modifications of carcinogenic factors coupled with chemoprevention are important targets for the future approach to CRC prevention. We will focus on the role of chemoprevention in this review, while giving brief description of lifestyle and dietary factors.

CHEMOPREVENTION IN COLORECTAL CANCER

Observations from earlier experimental studies suggested a protective effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on the development of tumour growth^[3,4]. Such experimental data was supported from epidemiological studies which showed significant

Abstract

Colorectal cancer remains a significant cause of morbidity and mortality throughout the world. The incidence of colorectal cancer is nearly four-fold higher in more-developed as compared with less-developed regions of the world. At present an early detection of colorectal cancer remains a crucial step in determining the therapeutic outcomes. Screening programmes have been introduced in an effort to detect colorectal cancer at an early stage or at a precancerous colonic polyp stage. These programmes should be used by the health professionals as an opportunity to educate the public regarding the use of chemoprevention in colorectal cancer, which is the main focus of this review and an attractive concept needing further evaluation.

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Key words: Colorectal cancer; Chemoprevention; Geographical variations; Dietary carcinogens

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Table 1 Use of aspirin in average risk subjects and colonic neoplasia risk reduction

Study	n	Aspirin dose (mg/AD)	Study duration (yr)	Relative risk reduction (95% CI)
Thun <i>et al</i> ^[13]	622424	100 mg ²	≥ 1	0.58 (0.36-0.93) ¹ 0.61 (0.38-0.97) ²
Gann <i>et al</i> ^[14]	22071	325	5	1.15 (0.80-1.65) ¹
Cook <i>et al</i> ^[15]	39876	100	10	0.97 (0.77-1.24) ²
Stürmer <i>et al</i> ^[16]	22071	325	12	1.03 (0.83-1.28)
Giovannucci <i>et al</i> ^[17]	47900	325	4	0.54 (0.34-0.84) ¹
Paganini-Hill <i>et al</i> ^[18]	13979	325	7-10	1.38 (NR) ¹
Chan <i>et al</i> ^[19]	89446	100	10	0.62 (0.44-0.86) ²
Friis <i>et al</i> ^[20]	29470	325	6	0.9 (0.70-1.10) ¹
García-Rodríguez <i>et al</i> ^[21]	12005	325	> 2	0.9 (0.8-1.1)
Reeves <i>et al</i> ^[22]	845	100	> 5	0.79 (0.46-1.36) ²
Juarranz <i>et al</i> ^[23]	502	325	NR	0.32 (0.09-1.10)
La Vecchia <i>et al</i> ^[24]	3248	325	5	0.7 (0.50-1.00)
Kune <i>et al</i> ^[25]	1442	325	NR	0.57 (0.41-0.79)
Suh <i>et al</i> ^[26]	2704	325	6	0.33 (0.15-0.72)
Slattery <i>et al</i> ^[27]	3051	325	> 5	0.7 (0.6-0.8)

¹Males; ²Females; ³Daily; AD: Alternate day dosage; CI: Confidence interval; NR: Not reported.

Table 2 Role of aspirin in colorectal neoplasia risk among patients with past tumour

Trials	n	Aspirin dose	Duration (yr)	Relative risk (95% CI)
Baron <i>et al</i> ^[28]	1121	81/325 mg	1	0.96 (0.81-1.13)
Benamouzig <i>et al</i> ^[29]	272	160/300 mg	1	0.82 (0.7-0.95)
Greenberg <i>et al</i> ^[30]	864		4	0.52 (0.31-0.89)
PPSG ^[31]	1905	< 325 mg	4	0.82 (0.65-1.02)
		> 325 mg		0.54 (0.3-0.96)
Sandler <i>et al</i> ^[32]	492	> 15 tab/month	5	0.84 (0.5-1.43)
Breuer-Katschinski <i>et al</i> ^[33]	442	> 4 tab/week	< 5	0.91 (0.32-2.64)
			> 5	0.09 (0.01-0.82)

CI: Confidence interval; PPSG: Polyp prevention study group.

nonspecific tumour risk reduction of between 20%-50% among NSAID users^[5-7]. A consistent beneficial effect of aspirin and NSAIDs in reducing formation of colonic polyps was also reported in a systemic review^[8].

Cancer chemopreventive mechanisms for NSAIDs

It is suggested that colorectal carcinoma risk reduction from NSAIDs is mainly related with inhibition of cyclooxygenase (COX), particularly COX-2, which is raised in colorectal neoplasia^[9]. Other effects of aspirin on the oncogenic Wnt/ β -catenin pathway activity in colorectal cancer cell lines have been studied. For example a dose-dependent decreased activity of this pathway, as judged by TCF-driven luciferase activity, reduced Wnt target gene expression and increased phosphorylation of β -catenin by immunoblotting^[10] has been demonstrated. In this study, ubiquitination and cytoplasmic levels of β -catenin were assessed by immunoblotting, and the localization of β -catenin was shown by green fluorescent protein-tagged β -catenin and time-lapse fluorescent imaging. Interestingly, aspirin treatment caused increased phosphorylation of protein phosphatase 2A (PP2A), an event associated with inhibition of PP2A enzymatic activity. This was confirmed by a reduction in enzymatic PP2A activity. Moreover, this inhibition of PP2A enzymatic activity appeared essential for the effects of aspirin on the Wnt/ β -catenin

pathway as shown by transient transfection with PP2A constructs. The findings in this trial provided a molecular explanation for the efficacy of aspirin in chemoprevention of colorectal cancer and showed biochemical evidence that PP2A had an important regulatory effect on Wnt/ β -catenin pathway activity in these cells.

Chemopreventive agents and outcomes

In various trials where aspirin and NSAIDs were used as chemoprotective agents, a higher dose had favourable results, however findings were inconsistent^[5,11,12]. In general the regular use of aspirin appears to reduce the incidence of colorectal adenoma with relative risk reductions on the order of 13% to 28% in average-risk individuals as shown in Table 1^[13-27]. On the basis of a limited number of studies, the relative risk reductions for individuals with a history of colonic adenoma are probably higher than for those at average risk. Furthermore, it appears that longer duration of aspirin use, as well as higher doses, are associated with greater relative risk reductions than smaller doses and shorter duration as shown in Table 2^[28-33]. A randomised, placebo-controlled trial included 2586 patients with a recent history of adenoma^[34]. These patients were assigned to receive either placebo or selective COX-2 inhibitor (rofecoxib 25 mg/d) with results showing

significant reduction in adenoma recurrence ($P < 0.0001$) in experimental group. However, in the rofecoxib group a significantly higher rate of upper gastrointestinal and thrombotic cardiovascular event were observed. With this initial and subsequent reporting of significant cardiovascular events, use of COX-2 inhibitors as a chemopreventive agent has largely been discontinued^[34,35].

5-aminosalicylates (ASA) in colorectal cancer prevention

Chemopreventive role of 5-ASA in colorectal carcinoma has been proposed in patients with inflammatory bowel disease. The effect of 5-ASA on the Wnt/ β -catenin pathway has been studied in colorectal cancer cell lines to find a molecular basis underlying its chemopreventive features^[36]. 5-ASA targets the Wnt/ β -catenin pathway in adenomatous polyposis coli mutated cells with intact β -catenin, judged by luciferase reporter assays. In addition, 5-ASA treatment leads to reduced expression of nuclear β -catenin and Wnt/ β -catenin target genes, and increased β -catenin phosphorylation. Such effects on the Wnt/ β -catenin pathway are mediated *via* protein phosphatase 2A (PP2A) and increased phosphorylation of PP2A after 5-ASA treatment coincides with decreased PP2A enzymatic activity. The inhibition of PP2A enzymatic activity by 5-ASA appears to be essential for its effect on the Wnt/ β -catenin pathway, as shown by transient transfection with siPP2A and mutant PP2A. These effects of 5-ASA are observed in similar doses as used in the treatment of inflammatory bowel disease.

LIFESTYLE AND DIETARY FACTORS

Lifestyle and dietary constituents including fibre content and its source, protein and fat types and their origin, and their consumption patterns vary enormously in different geographical areas and had been linked to CRC aetiology. The potential role of various dietary factors in CRC carcinogenesis and possible preventive strategies are given in Table 3.

The cancer protective role of fibre has been attributed to its bulking effect, faecal dilution factor, shortening of faecal transit time and fermentation properties. Fibre fermentation products have been studied extensively and among the various products, butyrate a naturally occurring fatty acid was found to be most relevant. Butyrate has a potential to inhibit cell proliferation, induce apoptosis and differentiation, and increase phase II enzyme activities in tumour cells, whereas little information is available on its protective effect in less-transformed colon cells^[37,38]. Butyrate from wheat bran leads to higher concentrations in distal large bowel and is more protective compared to butyrate from guar gum and oat bran^[39].

The role of fat components depends on the fatty acid composition of food. Thus docosahexaenoic acid which is rich in certain fish may have a role through inhibition of the arachidonic acid cascade involved in carcinogenesis and cell proliferation^[40]. The higher prevalence of colon cancer in South Africans whites (17:100 000) was investigated by estimating epithelial

Table 3 Colorectal cancer and the potential carcinogenic role of various factors

CRC category (% diagnosed with CRC)	Intervention strategies
Sporadic CRC (75%)	Screening Programmes Detection and removal of polyps (age > 50 yr) Role of chemoprevention NSAIDs/Aspirin 5-aminosalicylate Dietary and lifestyle factors Good: low protein, high fibre, low fat, micronutrients, exercise Bad: alcohol, tobacco, obesity
Familial syndromes + miscellaneous (25%)	Screening colonoscopy Other: Aspirin and NSAIDs, 5-ASA

CRC: Colorectal cancer; NSAIDs: Non steroidal anti-inflammatory drugs; 5-ASA: 5-aminosalicylates; IBD: Inflammatory bowel disease.

proliferation differences in the black Africans (cancer prevalence 1:100 000) based on dietary differences^[41]. The lower prevalence of CRC in Mediterranean countries may be related to the use of extra virgin olive oil.

Pinoresinol-rich extra virgin olive oil extracts have potent chemopreventive properties and specifically upregulate the ATM-p53 cascade^[42].

Data in relation to the use of red meat and a higher risk of colorectal cancer is relatively consistent, although controversies do exist^[43-45]. The proposed mechanisms involved in CRC carcinogenesis and meat consumption relate to intake of a higher quantity of red meat (> 120 g/d), formation of heterocyclic amines, polycyclic aromatic hydrocarbons (dependent on cooking methods) and nitrates, N-Nitroso compound formation, and heme component^[46-52].

A higher risk of CRC was suggested from a review of ecological studies which analysed meat consumption patterns among the included populations^[53]. Three meta-analyses which included 15 prospective studies on red meat, 14 prospective studies on processed meat, 18 case-control studies and 19 cohorts showed colorectal cancer risk with meat consumption^[54-56].

Certain lifestyle factors have been implicated in CRC carcinogenesis, including smoking, alcohol consumption, exercise lack, obesity, and genetics. Factors involved in DNA methylation, synthesis, and repair and factors with antioxidant properties may be involved in colorectal cancer risk which in turn may be influenced by other factors. In a large European cohort, both lifetime and baseline alcohol consumption showed increased colon and rectal cancer risk, with apparent risk being higher for alcohol intake greater than 30 g/d^[56]. In another large prospective European multicenter study 368 277 subjects were evaluated using various anthropometric measurements, which found body weight and body mass index to be associated with a significantly higher risk of colon cancer^[57]. An Austrian population-based study found an inverse association of weight loss to colorectal carcinoma while adjusting for smoking, occupational group, blood glucose, and body mass index at baseline in

over 65 000 subjects^[58]. Consumption of micronutrients including vitamin B6, folate, calcium, selenium, caffeine has also been studied in CRC carcinogenesis with mainly controversial results^[59,60].

CONCLUSION

Colorectal cancer is an important health issue particularly in the affluent countries. Chemoprevention is an attractive concept in colorectal cancer prevention. This however should be coupled with modification of other lifestyle and dietary factors which have important carcinogenic potential as evident from the current clinical, experimental, and epidemiological studies. We recommend that health professionals should promote public awareness regarding the aetiological role of the modifiable factors alongside the primary prevention using CRC screening programmes. Chemoprevention in the form of NSAIDs and 5-aminosalicylates has a significant role in individuals particularly those with genetic and other CRC predispositions.

REFERENCES

- 1 **Kamangar F**, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006; **24**: 2137-2150
- 2 **Martínez ME**, Marshall JR, Giovannucci E. Diet and cancer prevention: the roles of observation and experimentation. *Nat Rev Cancer* 2008; **8**: 694-703
- 3 **Taketo MM**. Cyclooxygenase-2 inhibitors in tumorigenesis (part I). *J Natl Cancer Inst* 1998; **90**: 1529-1536
- 4 **Taketo MM**. Cyclooxygenase-2 inhibitors in tumorigenesis (Part II). *J Natl Cancer Inst* 1998; **90**: 1609-1620
- 5 **González-Pérez A**, García Rodríguez LA, López-Ridaura R. Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis. *BMC Cancer* 2003; **3**: 28
- 6 **Khuder SA**, Mutgi AB. Breast cancer and NSAID use: a meta-analysis. *Br J Cancer* 2001; **84**: 1188-1192
- 7 **Grau MV**, Sandler RS, McKeown-Eyssen G, Bresalier RS, Haile RW, Barry EL, Ahnen DJ, Gui J, Summers RW, Baron JA. Nonsteroidal anti-inflammatory drug use after 3 years of aspirin use and colorectal adenoma risk: observational follow-up of a randomized study. *J Natl Cancer Inst* 2009; **101**: 267-276
- 8 **Asano TK**, McLeod RS. Nonsteroidal anti-inflammatory drugs and aspirin for the prevention of colorectal adenomas and cancer: a systematic review. *Dis Colon Rectum* 2004; **47**: 665-673
- 9 **Thun MJ**. Beyond willow bark: aspirin in the prevention of chronic disease. *Epidemiology* 2000; **11**: 371-374
- 10 **Bos CL**, Kodach LL, van den Brink GR, Diks SH, van Santen MM, Richel DJ, Peppelenbosch MP, Hardwick JC. Effect of aspirin on the Wnt/beta-catenin pathway is mediated via protein phosphatase 2A. *Oncogene* 2006; **25**: 6447-6456
- 11 **Chan AT**, Giovannucci EL, Schernhammer ES, Colditz GA, Hunter DJ, Willett WC, Fuchs CS. A prospective study of aspirin use and the risk for colorectal adenoma. *Ann Intern Med* 2004; **140**: 157-166
- 12 **Chan AT**, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Wu K, Fuchs CS. Aspirin dose and duration of use and risk of colorectal cancer in men. *Gastroenterology* 2008; **134**: 21-28
- 13 **Thun MJ**, Namboodiri MM, Heath CW Jr. Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med* 1991; **325**: 1593-1596
- 14 **Gann PH**, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. *J Natl Cancer Inst* 1993; **85**: 1220-1224
- 15 **Cook NR**, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005; **294**: 47-55
- 16 **Stürmer T**, Glynn RJ, Lee IM, Manson JE, Buring JE, Hennekens CH. Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study. *Ann Intern Med* 1998; **128**: 713-720
- 17 **Giovannucci E**, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. *Ann Intern Med* 1994; **121**: 241-246
- 18 **Paganini-Hill A**. Aspirin and colorectal cancer: the Leisure World cohort revisited. *Prev Med* 1995; **24**: 113-115
- 19 **Chan AT**, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA* 2005; **294**: 914-923
- 20 **Friis S**, Sørensen HT, McLaughlin JK, Johnsen SP, Blot WJ, Olsen JH. A population-based cohort study of the risk of colorectal and other cancers among users of low-dose aspirin. *Br J Cancer* 2003; **88**: 684-688
- 21 **García-Rodríguez LA**, Huerta-Alvarez C. Reduced risk of colorectal cancer among long-term users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs. *Epidemiology* 2001; **12**: 88-93
- 22 **Reeves MJ**, Newcomb PA, Trentham-Dietz A, Storer BE, Remington PL. Nonsteroidal anti-inflammatory drug use and protection against colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev* 1996; **5**: 955-960
- 23 **Juarranz M**, Calle-Purón ME, González-Navarro A, Regidor-Poyatos E, Soriano T, Martínez-Hernández D, Rojas VD, Guinee VF. Physical exercise, use of *Plantago ovata* and aspirin, and reduced risk of colon cancer. *Eur J Cancer Prev* 2002; **11**: 465-472
- 24 **La Vecchia C**, Negri E, Franceschi S, Conti E, Montella M, Giacosa A, Falcini A, Decarli A. Aspirin and colorectal cancer. *Br J Cancer* 1997; **76**: 675-677
- 25 **Kune GA**, Kune S, Watson LF. Colorectal cancer risk, chronic illnesses, operations, and medications: case control results from the Melbourne Colorectal Cancer Study. *Cancer Res* 1988; **48**: 4399-4404
- 26 **Suh O**, Mettlin C, Petrelli NJ. Aspirin use, cancer, and polyps of the large bowel. *Cancer* 1993; **72**: 1171-1177
- 27 **Slattery ML**, Samowitz W, Hoffman M, Ma KN, Levin TR, Neuhausen S. Aspirin, NSAIDs, and colorectal cancer: possible involvement in an insulin-related pathway. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 538-545
- 28 **Baron JA**, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, McKeown-Eyssen G, Summers RW, Rothstein R, Burke CA, Snover DC, Church TR, Allen JI, Beach M, Beck GJ, Bond JH, Byers T, Greenberg ER, Mandel JS, Marcon N, Mott LA, Pearson L, Saibil F, van Stolk RU. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003; **348**: 891-899
- 29 **Benamouzig R**, Deyra J, Martin A, Girard B, Jullian E, Piednoir B, Couturier D, Coste T, Little J, Chaussade S. Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. *Gastroenterology* 2003; **125**: 328-336
- 30 **Greenberg ER**, Baron JA, Freeman DH Jr, Mandel JS, Haile R. Reduced risk of large-bowel adenomas among aspirin users. The Polyp Prevention Study Group. *J Natl Cancer Inst* 1993; **85**: 912-916
- 31 **Tangrea JA**, Albert PS, Lanza E, Woodson K, Corle D, Hasson M, Burt R, Caan B, Paskett E, Iber F, Kikendall JW, Lance P, Shike M, Weissfeld J, Schatzkin A. Non-steroidal

- anti-inflammatory drug use is associated with reduction in recurrence of advanced and non-advanced colorectal adenomas (United States). *Cancer Causes Control* 2003; **14**: 403-411
- 32 **Sandler RS**, Galanko JC, Murray SC, Helm JF, Woosley JT. Aspirin and nonsteroidal anti-inflammatory agents and risk for colorectal adenomas. *Gastroenterology* 1998; **114**: 441-447
 - 33 **Breuer-Katschinski B**, Nemes K, Rump B, Leiendecker B, Marr A, Breuer N, Goebell H. Long-term use of nonsteroidal antiinflammatory drugs and the risk of colorectal adenomas. The Colorectal Adenoma Study Group. *Digestion* 2000; **61**: 129-134
 - 34 **Bresalier RS**, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; **352**: 1092-1102
 - 35 **Kerr DJ**, Dunn JA, Langman MJ, Smith JL, Midgley RS, Stanley A, Stokes JC, Julier P, Iveson C, Duvvuri R, McConkey CC. Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. *N Engl J Med* 2007; **357**: 360-369
 - 36 **Bos CL**, Diks SH, Hardwick JC, Walburg KV, Peppelenbosch MP, Richel DJ. Protein phosphatase 2A is required for mesalazine-dependent inhibition of Wnt/beta-catenin pathway activity. *Carcinogenesis* 2006; **27**: 2371-2382
 - 37 **Ebert MN**, Beyer-Sehlmeyer G, Liegibel UM, Kautenburger T, Becker TW, Pool-Zobel BL. Butyrate induces glutathione S-transferase in human colon cells and protects from genetic damage by 4-hydroxy-2-nonenal. *Nutr Cancer* 2001; **41**: 156-164
 - 38 **Crim KC**, Sanders LM, Hong MY, Taddeo SS, Turner ND, Chapkin RS, Lupton JR. Upregulation of p21Waf1/Cip1 expression in vivo by butyrate administration can be chemoprotective or chemopromotive depending on the lipid component of the diet. *Carcinogenesis* 2008; **29**: 1415-1420
 - 39 **McIntyre A**, Gibson PR, Young GP. Butyrate production from dietary fibre and protection against large bowel cancer in a rat model. *Gut* 1993; **34**: 386-391
 - 40 **Kuriki K**, Wakai K, Hirose K, Matsuo K, Ito H, Suzuki T, Saito T, Kanemitsu Y, Hirai T, Kato T, Tatematsu M, Tajima K. Risk of colorectal cancer is linked to erythrocyte compositions of fatty acids as biomarkers for dietary intakes of fish, fat, and fatty acids. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 1791-1798
 - 41 **O'Keefe SJ**, Kidd M, Espitalier-Noel G, Owira P. Rarity of colon cancer in Africans is associated with low animal product consumption, not fiber. *Am J Gastroenterol* 1999; **94**: 1373-1380
 - 42 **Fini L**, Hotchkiss E, Fogliano V, Graziani G, Romano M, De Vol EB, Qin H, Selgrad M, Boland CR, Ricciardiello L. Chemopreventive properties of pinoretinol-rich olive oil involve a selective activation of the ATM-p53 cascade in colon cancer cell lines. *Carcinogenesis* 2008; **29**: 139-146
 - 43 **Cross AJ**, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R. A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med* 2007; **4**: e325
 - 44 **Santarelli RL**, Pierre F, Corpet DE. Processed meat and colorectal cancer: a review of epidemiologic and experimental evidence. *Nutr Cancer* 2008; **60**: 131-144
 - 45 **Chao A**, Thun MJ, Connell CJ, McCullough ML, Jacobs EJ, Flanders WD, Rodriguez C, Sinha R, Calle EE. Meat consumption and risk of colorectal cancer. *JAMA* 2005; **293**: 172-182
 - 46 **Norat T**, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: dose-response meta-analysis of epidemiological studies. *Int J Cancer* 2002; **98**: 241-256
 - 47 **Sandhu MS**, White IR, McPherson K. Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 439-446
 - 48 **Larsson SC**, Wolk A. Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *Int J Cancer* 2006; **119**: 2657-2664
 - 49 **Gerhardsson de Verdier M**, Hagman U, Peters RK, Steineck G, Overvik E. Meat, cooking methods and colorectal cancer: a case-referent study in Stockholm. *Int J Cancer* 1991; **49**: 520-525
 - 50 **Bingham SA**, Pignatelli B, Pollock JR, Ellul A, Malaveille C, Gross G, Runswick S, Cummings JH, O'Neill IK. Does increased endogenous formation of N-nitroso compounds in the human colon explain the association between red meat and colon cancer? *Carcinogenesis* 1996; **17**: 515-523
 - 51 **Bingham S**, Riboli E. Diet and cancer--the European Prospective Investigation into Cancer and Nutrition. *Nat Rev Cancer* 2004; **4**: 206-215
 - 52 **Lee DH**, Anderson KE, Harnack LJ, Folsom AR, Jacobs DR Jr. Heme iron, zinc, alcohol consumption, and colon cancer: Iowa Women's Health Study. *J Natl Cancer Inst* 2004; **96**: 403-407
 - 53 **Larsson SC**, Rafter J, Holmberg L, Bergkvist L, Wolk A. Red meat consumption and risk of cancers of the proximal colon, distal colon and rectum: the Swedish Mammography Cohort. *Int J Cancer* 2005; **113**: 829-834
 - 54 **Flood A**, Rastogi T, Wirfalt E, Mitrou PN, Reedy J, Subar AF, Kipnis V, Mouw T, Hollenbeck AR, Leitzmann M, Schatzkin A. Dietary patterns as identified by factor analysis and colorectal cancer among middle-aged Americans. *Am J Clin Nutr* 2008; **88**: 176-184
 - 55 **Campbell PT**, Curtin K, Ulrich CM, Samowitz WS, Bigler J, Velicer CM, Caan B, Potter JD, Slattery ML. Mismatch repair polymorphisms and risk of colon cancer, tumour microsatellite instability and interactions with lifestyle factors. *Gut* 2009; **58**: 661-667
 - 56 **Ferrari P**, Jenab M, Norat T, Moskal A, Slimani N, Olsen A, Tjønneland A, Overvad K, Jensen MK, Boutron-Ruault MC, Clavel-Chapelon F, Morois S, Rohrmann S, Linseisen J, Boeing H, Bergmann M, Kontopoulou D, Trichopoulou A, Kassapa C, Masala G, Krogh V, Vineis P, Panico S, Tumino R, van Gils CH, Peeters P, Bueno-de-Mesquita HB, Ocké MC, Skeie G, Lund E, Agudo A, Ardanaz E, López DC, Sanchez MJ, Quirós JR, Amiano P, Berglund G, Manjer J, Palmqvist R, Van Guelpen B, Allen N, Key T, Bingham S, Mazuir M, Boffetta P, Kaaks R, Riboli E. Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer* 2007; **121**: 2065-2072
 - 57 **Pischon T**, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjønneland A, Halkjaer J, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Guernec G, Bergmann MM, Linseisen J, Becker N, Trichopoulou A, Trichopoulos D, Sieri S, Palli D, Tumino R, Vineis P, Panico S, Peeters PH, Bueno-de-Mesquita HB, Boshuizen HC, Van Guelpen B, Palmqvist R, Berglund G, Gonzalez CA, Dorronsoro M, Barricarte A, Navarro C, Martinez C, Quirós JR, Roddam A, Allen N, Bingham S, Khaw KT, Ferrari P, Kaaks R, Slimani N, Riboli E. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2006; **98**: 920-931
 - 58 **Rapp K**, Klenk J, Ulmer H, Concin H, Diem G, Oberaigner W, Schroeder J. Weight change and cancer risk in a cohort of more than 65,000 adults in Austria. *Ann Oncol* 2008; **19**: 641-648
 - 59 **Larsson SC**, Giovannucci E, Wolk A. Vitamin B6 intake, alcohol consumption, and colorectal cancer: a longitudinal population-based cohort of women. *Gastroenterology* 2005; **128**: 1830-1837
 - 60 **Kune G**, Watson L. Colorectal cancer protective effects and the dietary micronutrients folate, methionine, vitamins B6, B12, C, E, selenium, and lycopene. *Nutr Cancer* 2006; **56**: 11-21

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