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Dietary Risk Factors for Colorectal Adenomatous Polyps: A Mini Review

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ABSTRACT

At least 6 million deaths occurred worldwide are due to cancer and this figure is expected to rise to 15 millions by the year 2020. Colorectal cancer is among the most commonly occurring cancers both globally and in Malaysia. Numerous studies have shown significant relationships between various dietary components and the risks for colorectal cancer. Meanwhile, several theories have been suggested as etiological explanations, one of which is the influence of dietary factors on the cell proliferation rate. A higher cell proliferation rate is statistically associated with increased risk of colorectal cancer. However, evidence of a significant relationship between diet and colorectal adenomas, a potential precursor for colorectal cancer, remains insufficient. Colorectal adenomas or polyps are vital in their relationship with colorectal cancers as almost 70% of all colorectal cancers are developed from these polyps. Studying the modifiable risk factors related to polyps will provide an opportunity for the prevention of colorectal cancer even before it develops. This paper reviews the available evidence linking dietary factors with the risk for colorectal adenomas. As the numbers of published studies are limited, of which most are concentrated in Western countries, there is a need for epidemiological studies in Malaysia to strengthen the evidence of a relationship between diet and colorectal adenomas.

Keywords: Colorectal adenomas, risk factors, diet

INTRODUCTION

Cancer is becoming an increasingly important contributor to the global burden of disease. Based on the Globocan 2002 database, Ma and Yu (2006) reported that for the year 2002, there were 10,862,496 new cancer cases (excluding skin cancer) worldwide. Of these, 5,801,839 (53.4 percent) were males and 5,060,657 (46.6 percent) were females. Nearly 45 percent of the new cases were diagnosed in Asia. The World Health Organization (2003) estimated that the number of new cases annually will escalate from ten million in the year 2000 to 15 million by the year 2020.

On a global basis, the number of deaths caused by cancer in 2002 was 6,723,887, among which 3,795,991 were males and 2,927,896 were females (Ma and Yu, 2006). Some 60% of these cases occurred in the less developed parts of the world. Yet, with the existing knowledge, at least one-third of cancer cases, such as lung, colorectal and breast cancers, could be prevented through lifestyle changes (World Cancer Research Fund, 2007).

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Worldwide, colorectal cancer (CRC) was estimated to be the third most common cancer among men and fourth in women in the year 2002 (International Association for Cancer Registries, 2002). Among Malaysians, colon cancer ranked the third among all cancers reported in 2003 accounting for 7.6% and 6.0% in males and females, respectively (National Cancer Registry [NCR], 2004). The incidence of colon cancer was highest among Chinese, and the cumulative lifetime risk for Chinese males was 1 in 36, and 1 in 42 for Chinese females. Cancer of the rectum ranked fifth among the cancers reported in males (6.6%) and females (4.1%), respectively. Once again, the Chinese had the highest incidence of rectal cancer, and this was followed by Indians and Malays. The cumulative lifetime risk for developing rectal cancer for Chinese males was 1 in 48, while it was 1 in 71 for Indian males, and 1 in 91 for Malay males (NCR, 2004). A recent report on cancer incidences between 2003 and 2005 in Peninsular Malaysia (NCR, 2008) showed that colorectal cancer, which included cancer of the colon and rectum, was the most frequent cancer among men, accounting for 14.5% of all cancers. In women, CRC accounted for 9.9% of all cancers.

Having a risk factor for a certain cancer contributes to a higher chance of getting cancer, but it does not always lead to that particular cancer. On the other hand, the absence of any risk factor or having a protective factor does not necessarily protect any individual against cancer. It is important to note that different types of cancer have different risk factors. Factors that may lead to cancer can be classified into external factors, which include environmental toxins, viruses, radiation and chemicals, and internal factors such as hormones, immune setting and inherited mutations and behavioural factors such as diet and lifestyle (Chace and Keane, 1996; American Cancer Society, 2004).

Colorectal Adenomas or Polyps

Colon polyps are vital in their relationship with CRC. Polyps are benign growths involving the lining of the bowel (American Society for Gastrointestinal Endoscopy, 2006). They appear as small bumps that protrude from the lining of the bowel into the lumen. Polyps may vary in size, and can be 1 mm or more in diameter. The two common types of polyps are hyperplastic polyps and adenomas. Hyperplastic polyps do not pose risk for CRC and therefore, are not significant. However, adenomatous polyps are considered to be precursor lesions and may be markers for populations at high risk of CRC (Kahn *et al.,* 1998).

Adenomatous polyps can be sporadic polyps (Calvert and Frucht, 2002). More than 70% of CRC are developed from sporadic adenomatous polyps, and a review of some post-mortem studies have found the incidence of sporadic adenomas to be 30 – 40% in the Western population (Hardy *et al.,* 2000). In a large cohort of Japanese patients, the incidence rate of colorectal adenomas (CRA) in patients with no initial neoplasm (n=4028) was 7.2% per year, whereas the recurrence rates in those with small and advanced lesions (n=1818) were 19.3% and 22.9%, respectively (Yamaji *et al*., 2004). For advanced colorectal lesions (n=323), the incidence rate was 0.21% per year, whereas the recurrence rates in those with small adenomas and advanced lesions were 0.64% and 1.88% per year, respectively. In general, colorectal neoplasms are more likely to develop in males and older subjects. In Malaysia, the prevalence of colorectal adenomas in a multi-ethnic sample of 311 patients who underwent colonoscopy in a private medical centre was about 11%, based on the only published report (Rajendra, Ho and Arokiasamy, 2005). Meanwhile, the prevalence was highest among the Chinese (62%), followed by the Indians (22%) and Malays (16%). Using logistic regression analysis, only family history ($P = 0.05$) and age ≥ 50 years ($P = 0.011$) were found to be significantly associated with adenomas in this particular sample.

CRA can also develop as a result of DNA mutation. Familial adenomatous polyposis syndrome (FAP) is a genetic condition which affects one in 10,000 people and is caused by a mutation in the

APC gene (Olshwang, 2002). People with FAP develop hundreds of polyps and will almost certainly develop CRC, unless the colon is removed. FAP, which is also known as familial multiple syndrome (FMS) or familial polyposis of the colon (FPC), accounts for only about 1% of all CRCs.

Likewise, hereditary non-polyposis CRC (HNPCC) syndrome is an inherited genetic condition that can also cause CRC even though multiple polyps are not present. It is caused by mutations in mismatch repair genes located on chromosomes two, three, or seven (Burt, 2000). HNPCC mainly affects the right colon compared to the other areas of the gastrointestinal system (Hardy *et al*., 2000). If a person suffers from this condition, he or she has 80% lifetime risk for developing CRC compared to merely six percent in the general population (Pergament, 2003).

It is important to prevent recurrence of CRA as sufficient evidence links them to incidence of CRC in later life. Identification of dietary risk factors may play an important role in preventing adenomas and their recurrence.

METHODOLOGY

Articles eligible for inclusion met the following criteria: 1) they discussed at least one dietary factor associated with CRA, and/or 2) they studied dietary biomarkers associated with CRA. Since the focus of this review is on the dietary risk factors of CRA, the following factors were excluded: lifestyle factors such as alcohol consumption, tobacco smoking, obesity and non-behavioural risk factors for CRA, such as HPNCC and FAP. CRA outcomes comprised incidence of CRA and/or recurrence of CRA.

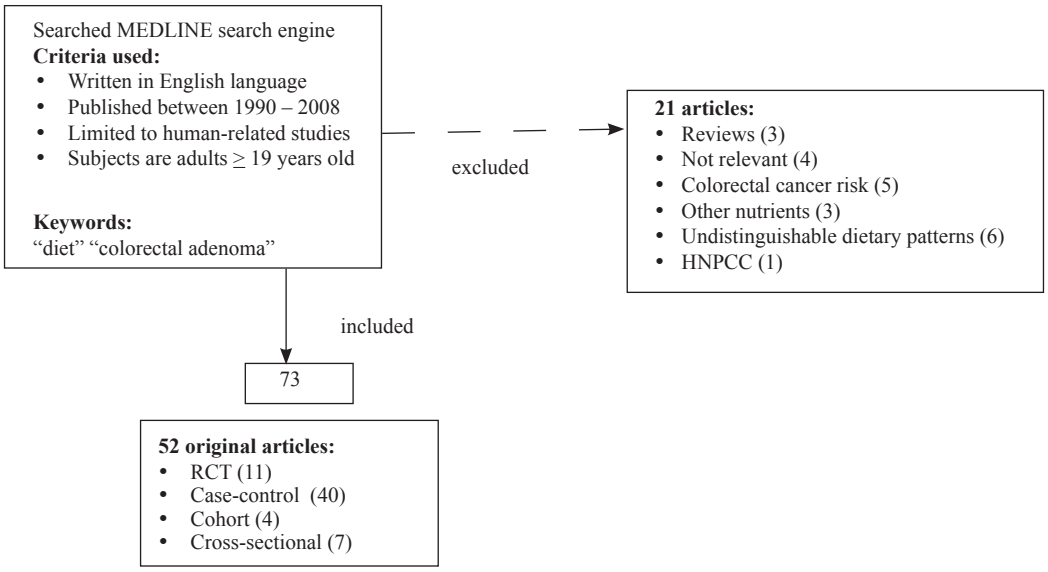

Fig. 1: Flow chart showing article selection process

Fig. 1 shows the flow chart of the article selection. For this purpose, the research papers, written in the English language and published from 1990 to 2008, were reviewed. Meanwhile, studies were initially identified through the search engine Medline by using the keywords ''diet'' and ''colorectal adenomas''. After excluding irrelevant articles, a total of 52 original articles were

selected for this review. Subsequently, the articles were grouped according to the particular dietary component that was studied. A summary of all the selected articles is presented in Table 1.

DIETARY RISK FACTORS

The role of diet in the aetiology of CRA is yet to be elucidated and thus remains an area of active investigation. Dietary risk factors include any type of food, nutrients or other constituents of food that are related to the risk of a disease. Evidence from case-control and cohort studies and some intervention trials suggest a correlation between dietary intake and incidence of CRA. Dietary fat, red meat, fibre, resistant starch, fruits and vegetables in particular, as well as other dietary factors have been associated with the risk for this condition (World Cancer Research Fund, 2007).

Dietary Fat

Epidemiological studies have provided inconsistent data on the role of dietary fats in colorectal cancer, while a few studies have investigated their roles in colorectal adenoma. Mathew *et al*. (2004), in a case-control study from 1994-1996 on 239 cases and 228 control subjects, found an increased risk of seven percent for every five percent increase in energy intake from total fat (OR = 1.07, 95% CI = 0.94 – 1.22). In the same study, the type of fat and sources of fat were also found to influence the risk for CRA. For every additional five percent increase in oleic acid intake, the risk for CRA increased significantly by 115% (OR = 2.15, 95% CI = 1.05 – 4.39). Specifically, red meat fat was found to increase the risk by 20% (OR = 1.20, 95% CI = 0.71 – 2.04), while white meat fat decreased risk by 67% (OR = 0.33, 95% CI = 0.19 – 0.95) for every additional five percent increase in the intake per day.

A randomized, partially double-blind, placebo-controlled trial conducted over four years found that a low fat diet (< 25% of calories from fat) was able to reduce the risk for large adenomas > 10mm in diameter (MacLennan *et al*., 1995). After 24 months into the trial, the OR for the low fat group was found to be 0.4 (95% CI = 0.1 – 1.1) and after 48 months, it further reduced to 0.3 (95% CI = 0.1 – 1.0). The reduction however was not statistically significant. In another arm of the trial, participants were subjected to both low fat and high fibre (25 g of wheat bran supplementation), and these subjects were found to have zero large adenomas at 24 and 48 months, a statistically significant finding (p = 0.03). These observations suggest that a combination of low fat and high fibre diet may reduce the rate of transition from smaller to larger adenomas. However, affirmative conclusions cannot be made from these findings as only a small number of subjects were enrolled in this study.

In another prospective study on the effect of dietary marine n-3 fatty acids on distal CRA in women, no significant relationship was found between these two variables (Oh *et al*., 2005). However, higher intakes of dietary marine n-3 fatty acids were inversely but not significantly associated with large adenomas (RR = 0.74, 95% CI = 0.54 – 1.01), but were directly associated with small adenomas (RR = 1.36, 95% CI = 1.02 – 1.81). Once again, the results of this study suggest that higher intakes of marine n-3 fatty acids may reduce the progression of small adenomas to larger ones.

The effect of dietary fat on the risk for CRA continues to be elusive. Diergaarde *et al.* (2005) reported that the high intake of fat seemed to only increase the risk of APC(-) polyps (OR = 1.9, 95% CI = 1.0-3.7). On the other hand, Vinikoor *et al.* (2008) reported that it increased the prevalence of CRA in those in the highest quartile of trans-fatty acid intake as compared to those with the lowest (OR = 1.86, 95% 1.04 – 3.33). A newer study was carried out by Methy *et al*. (2008) to further assess the risks of overall adenoma recurrence associated with dietary consumption of total fat, sub-types of fat, and specific fatty acids (oleic acid, linoleic acid, alpha-linolenic acid). The

study comprised 523 patients with confirmed adenomas at the index colonoscopy, aged between 35 to 75 year old. The overall 3-rear recurrence rate was 22.6%. Nonetheless, this study failed to observe significant associations between overall adenoma recurrences with either total fat, sub-type of fats, or specific fatty acids. Polyunsaturated fatty acids and linoleic acid were both moderately and significantly associated with distal and multiple recurrence. No significant association was observed with the recurrence of proximal or advanced adenomas. The study by Methy *et al.* (2008) did not support the hypothesis of a strong association between dietary fatty acids and the recurrence of colorectal adenomas. It was concluded that the differential role of specific fatty acids according to colorectal subsites deserves further investigation.

As much of the evidence on the role of fat in the CRA risks resulted from case-control studies, more cohort and experimental studies are warranted to examine this association. However, special focus should be placed on determining the ability of dietary fat to influence the progression of smaller adenomas to larger adenomas, and the possible role of dietary fat in the progression of adenomas to carcinoma.

Dietary Fibre

The role of dietary fibre in the prevention of CRC was first proposed by Burkitt (1969), following the clinical observation that colon cancer was rare among the Africans whose diet was high in unrefined foods. Studies on CRA are generally now supportive of a protective association with dietary fibre, although some contradictory results have been published (Fuchs *et al.,* 1999; Schatzkin *et al*., 2000; Robertson *et al.,* 2005).

Intake of fibre from vegetables and cereals has been associated with a clear reduction in the risk for CRA in a prospective study by Giovannucci *et al.* (1992), where the relative risk for the lowest quintile of dietary fibre intake versus the highest was 8.4 (95% CI = 0.2 – 0.6). This finding was confirmed by a study conducted by Peters *et al.* (2004), which was conducted within the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. High intakes of dietary fibre were associated with a 27% lower risk (95% CI = 14 – 38) of CRA, after adjusting for other dietary and non-dietary risk factors. The inverse relationship was strongest for fibre from grains and cereals (OR =0.75), and from fruits (OR=0.58). Risks were similar for advanced and non-advanced adenoma. Risk of rectal adenoma however, was not significantly associated with fibre intake.

Results from the Health Professionals Follow-up Study showed that there was a modest 19% reduced risk of distal colon adenoma with the increase in the intake of fibre from fruits, but not from cereals or vegetables (Platz *et al.,* 1997). The RR comparing the highest intake (median, 8.4 g/day) to the lowest quintile of fibre intake (1.3 g/day) was 0.81 (95% CI, 0.59-1.11). The reduction in risk, however, was observed only for soluble fibre. A latter study within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (PLCO) by Peters *et al*. (2003) noted a similar finding. Risk of adenoma was lowest at the highest quintile of dietary fibre intake in comparison to the lowest quintile. The inverse association observed was most significant for fibre from grains, cereals, and fruits. Risks were similar for advanced and non-advanced adenomas. These results suggested that soluble fibre might be particularly important in reducing risk of adenomatous polyps of the distal colon. The Wheat Bran Fibre Trial (Jacobs *et al.,* 2002), prior to the Polyp Prevention Trial (Lanza *et al.,* 2007) also found a reduction in risk with the intake of fibre, but the reduction was not statistically significant.

Potential mechanisms that may explain the protective effect of dietary fibre include dilution of faecal carcinogens and procarcinogens, reduction of transit time of faeces through the bowel, production of short chain fatty acids which promote anticarcinogenic action, and binding of carcinogenic bile acids (Lipkin *et al*., 1999).

On the other hand, there are studies which have shown no association between dietary fibre and risk for CRA. A prospective study, which was carried out among 88,000 women who had been followed up for 16 years, found the lack of a protective effect of dietary fibre against CRA (Fuchs *et al*., 1999). The Polyp Prevention Trial (PPT), a well-publicised large-scale intervention trial, found no significant association between dietary fibre intakes and recurrence of adenomatous polyps (Schatzkin *et al*., 2000). One of the most plausible explanations for the lack of effect was that the population studied had only low intakes of dietary fibre from cereals (4.8 g/day in the highest intake group). The subjects were further followed up for 4 years and yet no significant association was found between their dietary fibre intakes and recurrence of adenoma (Lanza *et al*., 2007). The authors' explanations for the null observation included inadequate trial length, inappropriate timing in the life course for such a trial, inappropriate end point, and inappropriate intervention.

As some of the recent findings are not encouraging, more studies should be done to establish the relationship between different types of dietary fibre and the risks for CRA at various subsites. Thus, the role of fiber in the etiology of colorectal cancer and precursor adenomatous polyps continues to be controversial.

Red Meat

Western diets containing high amounts of red meat have been associated with a high risk for CRA. A German case-control study, which compared patients with previous adenomas with hospital and population controls, found a positive association between red meat intake and risk for CRA, but not for fat or protein from red meat (Breuer-Katschinski *et al*., 2001). Those in the highest quintile of red meat intake were found to have more than three-fold increase in risk (OR = 3.6, 95% CI = 1.7 – 7.5) as compared to the hospital controls, and over four-fold increase in the risks (OR = 4.4, 95% CI = 1.6 – 12.1) than the control population.

Chiu and Gapstur (2004) reported that the risk for CRA was higher for those with the smallest reduction in red meat intake after the age of 30 years (OR = 2.8, 95% CI = 1.1-7.3). High intakes of red meat appeared to increase the risk of APC(-) polyps only (APC(-) vs. controls OR = 1.8, 95% CI = 1.0-3.1) (Diergaarde *et al*., 2005). Processed meat could specifically contribute to risk at the highest quartile of intake, by a two-fold increase in risk (Ward *et al*., 2007) as compared to the lowest intake.

Sinha *et al.* (1999) suggested that besides total red meat intake, cooking method such as well-done, grilled red meat might also increase the risk of CRA. An increased risk of 11% per 10 g/day of red meat consumption (OR = 1.11, 95% CI = 0.96 – 1.26) while high-temperature cooking methods were reported to increase the risk even further. Consumption of about 10 g/day of grilled red meat was associated with 26% risk (OR = 1.26, 95% CI = 1.06 – 1.50) and 15% per 10 g/day (OR = 1.15, 95% CI = 0.97 – 1.36) for pan-fried red meat. A larger case-control study published six years later confirmed this finding (Sinha *et al.* 2005).

Gunter *et al*. (2005) estimated that an incremental increase of 10 g of barbecued red meat per day might be associated with a 29% increased risk of large adenoma (OR = 1.29, 95% CI = 1.02-1.63). The consumption of oven-broiled red meat was inversely related to adenoma risk compared with non-consumers (OR = 0.49, 95% CI = 0.28-0.85). Furthermore, higher consumption of mutagens from meats cooked at higher temperature and longer duration may be associated with higher risk of distal colon adenoma independent of the overall meat intake (OR highest versus lowest quintile of meat-derived mutagenity = 1.29, 95% CI = 0.97-1.72) (Wu *et al*., 2006). These results are consistent with the hypothesis that carcinogenic compounds, such as heterocyclic amines and polycyclic aromatic hydrocarbons, formed by high-temperature cooking techniques, may contribute to the risk of developing colorectal tumours.

Although an overwhelming number of studies have shown positive correlations between red meat intake and the risk for CRA, Tiemersma *et al.* (2004) reported otherwise. HCAs were present in habitually prepared meat, although meat consumption (7 versus < 5x/week) did not increase the risk of colorectal adenomas (OR = 1.2, 95% CI = 0.8-1.9). Besides, presumed unfavourable preparation habits of meat did not increase adenoma risk (OR = 0.8 and 0.9, respectively).

In recent years, dietary effects on risk of diseases have been studied in relation to genetic polymorphisms in biotransformation genes. A study by Skelbred *et al*. examined the role of dietary factors in combination with genetic factors in the different stages of colorectal carcinogenesis in a Norwegian population. The results suggested an increased risk of colorectal adenomas in individuals for some of the higher ratios of total meat to total fruit, berry, and vegetable intakes. In addition, the study supports the notion that the biotransformation enzymes GSTM1, GSTP1, and EPHX1 may modify the effect of dietary factors on the risk of developing colorectal carcinoma and adenoma.

Evidence continues to mount proving that red meat intake affects risk of developing CRA. Although no study has been reported on Malaysians' risk for adenomas associated with intake of red meat, the current evidence should be taken into consideration, as Malaysian diets are increasingly becoming more westernized coupled with a high demand for animal foods.

Fruits and Vegetables

The presumed beneficial effects of fruit and vegetables have been the core of many large-scale public health campaigns such as the well-known "Five a Day" program and guidelines on cancer prevention, especially CRC (National Cancer Institute 2006). Meanwhile, consumption of fruit and vegetables may confer protection from colorectal adenomas, but the observational and interventional evidence is rather inconclusive.

Witte *et al.* (1996) conducted a case-control study in Southern Carolina and found inverse relationships between high carotenoid vegetables, cruciferous vegetables, high vitamin C fruit, garlic and tofu, and the risk for CRA. This finding supported the hypothesis that high intakes of vegetables, fruit and grains decreased the risk of adenomatous polyps.

A high-fruit, low-meat diet also appears to be protective against CRA compared with a dietary pattern of increased vegetable and meat consumption (Austin *et al.,* 2007). After adjusting for potential confounders, the high vegetable-moderate meat cluster (OR = 2.17, 95% CI = 1.20 – 3.90) and high meat cluster (OR = 1.70, 95%CI = 1.04 – 2.80) were at significantly increased odds of having had an adenoma compared with the high fruit-low meat cluster.

A cross-sectional study within the Nurses' Health Study (Michels *et al.,* 2006) found that a frequent consumption of fruit was inversely related to the risk of being diagnosed with polyps (OR >5 servings vs <1 servings = 0.60, 95% CI = 0.44 – 0.81), whereas little association was found for vegetable consumption (OR = 0.82, 95% CI = 0.65 – 1.05). However, another case-control study reported that individuals in the highest quartile of increased consumption vegetables (OR = 0.5; CI = 0.3-1.1) had a lower risk compared with those with minimal increase in consumption (Chiu and Gapstur, 2004).

On the other hand, Smith-Warner *et al*. (2002) found only juice consumption reduced the risk of CRA, but this was only evident in women subjects (OR = 0.50, 95% CI = 0.27 – 0.92) when cases were compared to negative-controls and (OR = 0.56, 95% CI = 0.30 – 1.06) community-controls. The association was stronger for adenomas with moderate and severe dysphasia.

A three-year endoscopic follow-up study concluded that fruit and vegetables might play an early but weak role in the development of CRC by influencing the growth and recurrence of adenoma (Almendingen *et al*., 2004). Dietary intake which was assessed by a five-day dietary record and food frequency questionnaire (FFQ) revealed a weak inverse association between growth of adenoma

and fruit and berries (adjusted OR = 0.3, 95% CI = 0.1 – 0.9). Moreover, a weak association was found between adenoma recurrence and vegetable intake (crude OR = 0.4, 95% CI = 0.1 – 0.9).

The protective effect of vegetable intake was observed on the recurrence of adenomas but not on the appearance of new adenoma; this suggests that vegetables may have a stronger role in preventing the progression of adenomas to carcinomas rather than in the initial appearance of adenomatous polyps. Meanwhile, research was found an inverse link between high plant-based food intake and the risk for adenomas, but several other studies did not find any relationship. Thus, further investigations are warranted to affirm the protective role of these food items.

Vitamin A

Vitamin A, which is involved in normal tissue growth and differentiation, was one of the earliest vitamins studied with respect to carcinogenesis (Sporn *et al*., 1983). *In vivo* experiments suggested that vitamin A deficiency might enhance the susceptibility of cells to certain chemical carcinogens. The hypothesized mechanisms through which vitamin A may influence carcinogenesis include action on the cell nucleus involving the expression of genetic information that controls cell differentiation. Preformed vitamin A is obtained from animal products, but pro-vitamin A carotenoids are derived largely from fruit and vegetables (Olson, 1994; Ross and Temus, 1993).

Unfortunately, studies indicating the relationship between vitamin A and CRA are few in number and are under-researched compared to research on vitamin A and CRC. An early study by Enger *et al.* (1996) suggested that vitamin A from dietary sources is associated with a decreased risk of CRA (crude OR = 0.60, 95% CI = 0.4 – 0.9) when the highest quartile of intake was compared to the lowest, but the relationship no longer existed after adjusting for potential confounders (adjusted OR = 0.90, 95% CI = 0.5 – 1.5). Nevertheless, the association between supplemented vitamin A and risk was not significant (adjusted OR = 1.4, 95% CI = 0.9 – 2.3). Similarly, Giovannucci *et al*. (1993) found that higher intake of vitamin A did not protect from the risk of CRA (OR = 0.91, 95% CI = 0.69 – 1.19). A case-control study revealed no significant relationship between dietary retinol (vitamin A) and risk of CRA (Lubin *et al.,* 1997). The adjusted odds ratio for the intake of retinol was 0.9 (95% CI = 0.5 – 1.6) when the highest tertile of intake was compared with the lowest, while adjustment was made for energy intake and physical activity. Data from a Japanese cohort study, comprising both male and female subjects, noted a relative risk (RR) of (RR = 1.42, 95% CI = 1.00 – 2.20), indicating an increased risk of adenomas with animal protein and vitamin A intake (RR = 1.51, 95% CI = 1.04 – 2.20) for the highest tertile versus the lowest (Nagata *et al*., 2001).

It is important to note that studies revealing relationships between dietary vitamin A (or even plasma vitamin A) and CRA are sparse. Moreover, very few clinical trials or epidemiological studies have explored the association between vitamin A and its derivates with risk of developing CRA. Thus, the available data are insufficient to conclude any association between vitamin A and risk of CRA, and thus requires further research.

Carotenoids

Carotenoids are pigments found primarily in plants, and the predominant carotenoids in the human diet are β-carotene, lycopene, lutein, β-cryptoxanthin and α-carotene. Carotenoids are related to cancer through their antioxidant properties, modulation of gene expression, regulation of cell growth and possible immune response (Rock *et al*., 1997).

Lubin and co-workers (1997) identified specific nutrients as independent factors which are associated with CRA, while carotene was identified as one of the nutrients with potential benefits. Increased intake of carotene was suggested to reduce the risk of CRA by 40% when the highest tertile of intake was compared with the lowest (OR = 0.6, 95% CI = 0.3 – 1.0).

Senesse *et al.* (2005) investigated the effect of β-carotene on the risk of CRA and the potential interaction with smoking status. The researchers found a significant interaction between β-carotene and smoking habit (p = 0.04). In non-smokers, β-carotene was inversely associated with the risk, of colon adenomas (OR in low vs. high consumers = 0.4, 95% CI = 0.2 – 0.9), whereas in past or current smokers, β-carotene was associated with a non-significant increase in the risk of colon adenomas (OR = 1.9, 95% CI = 0.9 – 4.1). The authors stressed that although β-carotene seemed to be protective in non-smokers, the adverse effect of the nutrient in smokers should be taken as a caution.

Other carotenoids have shown little or almost no significant relationship with the risk of CRA. Enger *et al.* (1996) found that in univariate-matched analysis, α-carotene, β-carotene, β-cryptoxanthin, lutein and zeaxanthin were all associated with decrease in risk, but only β-carotene was found to be significantly associated with adenomas (p = 0.04) after adjusting for potential confounding factors. An observational study carried out among the White subjects with history of hyperplastic polyps and controls revealed that plasma lycopene was the only carotenoid which lowered the risk for CRA (Erhardt *et al*., 2003). The median plasma lycopene concentration was significantly lower in the adenoma group than in the control group (-35%, p = 0.016). In addition, the median plasma β-carotene was also found to be lower in the adenoma group (-25.5%), but the difference was not significant. In the multiple logistic regression, only smoking (OR = 3.02, 95% CI = 1.46 – 6.25) and plasma lycopene concentration (OR = 2.31, 95% CI = 1.12 – 4.77) were risk factors for adenomatous polyps.

Shikany *et al.* (1997) showed that there is no association between individual plasma carotenoids and the prevalence of adenomatous polyps. This study did not stratify the subjects according to their smoking status but carotenoids were suggested as a probable protective factor only in smokers. This might explain the reason for the non-association found between carotenoids and risk of CRA. In a RCT conducted within Alpha – Tocopherol, Beta–Carotene Cancer Prevention Study (ATBC Study), supplementation with β-carotene had no effect on risk for CRA (RR = 0.98; 95% CI = 0.71 - 1.35) among middle-aged male smokers (Malila *et al*., 1999).

Even β-carotene, lycopene and lutien, the well-studied carotenoids of all, have shown inconsistent findings. On the other hand, other carotenoids such as zeaxanthin and cryptoxanthin are under-studied. Therefore, future studies should focus on these less studied carotenoids.

Vitamin C

Vitamin C is a water soluble vitamin that occurs mainly in fruit and vegetables. Its potent anti-oxidative properties are thought to contribute to its possible cancer preventive potential. As an antioxidant, vitamin C is considered to have a protective effect on cellular biopolymers, including genetic material and could thus be protective in the initiation and promotional stages of carcinogenesis (Van Poppel and Van Den Berg, 1997).

A high rate of apoptosis has been linked to a reduced risk of CRA in a study conducted within the Diet and Health Study III (Connelly *et al*., 2003). Among individuals with adenomas, there was an inverse linear association between apoptosis and total vitamin C intake. Similarly, individuals with adenomas in the highest quintile of total vitamin C intake were substantially less likely to have increased colonic apoptosis than those in the lowest quintile (OR = 0.05, 95% CI = 0.01–0.46). High vitamin C intake was associated with reduced colorectal apoptosis, but this was only among individuals with adenomas in this population.

Meanwhile, Benito *et al.* (1993) found higher intake of vitamin C to significantly lower the risk for CRA by 63% (p for trend <0.01), whereas Tseng *et al.* (1996) found a significant reduction in risk exclusively among women subjects. Other studies found insignificant results as well. Enger *et al.* (1996), for example, found that dietary vitamin C only managed to yield a weak association

after adjusting for confounding factors (OR = 0.8, 95% CI = 0.5 – 1.5). This concludes that dietary vitamin C may not always be protective of CRA.

Antioxidant vitamins, such as vitamin C, have been suggested as potential anticancer agents because they fight free radicals which may cause oxidative damage to DNA, possibly leading to development of cancer (Byers and Perry, 1992). The ability of ascorbic acid to inhibit the formation of carcinogenic nitrosamines is the best documented cancer-protecting effect of vitamin C (Block, 1991). This protective mechanism of vitamin C could provide the explanation for numerous studies which found a protective effect of fruit and vegetables against cancer, as vitamin C is one of the most commonly occurring antioxidant vitamins in this particular food group.

Although fruit and vegetables have been consistently shown to be related to the risk of CRA and CRC, the same could not be said about vitamin C per se which is a commonly found micronutrient in these foods. Instability of this vitamin in food and plasma is one of the reasons; thus, methodological and study design may also be partly to be blamed for the inconsistent evidence. More studies which take these issues into account should be done in the future to strengthen the current available evidence.

Vitamin E

Vitamin E is a predominant antioxidant nutrient in the lipid phases of circulating lipoproteins and cell membranes. This potent peroxyl radical scavenger is a chain-breaking antioxidant that prevents the propagation of free radical damage in biological membranes (Traber and Packer, 1995). Just like vitamin C, this vitamin also seems to provide protection from various types of cancer, especially CRC. However, there are some limitations when interpreting the results of plasma vitamin E values in prospective studies. These include person-to-person variation in diet, the effects of non-dietary determinants of blood concentrations and the effects of preclinical disease on blood concentrations.

The use of vitamin E supplements was found to be associated with a lower incidence of recurrent adenomas (OR = 0.62, 95% CI = 0.39 – 0.98) in a population of patients with history of previous colonic neoplasia (Whelan *et al*., 1999). However, Tseng *et al.* (1996) demonstrated a protective effect of vitamin E only among men, whereby those in the highest quartile of vitamin E intake had a risk of 0.35 (95% CI- 0.14 – 0.92) relative to those in the lowest intake.

Plasma α- and γ-tocopherol concentrations for subjects with CRA were compared with healthy controls in order to examine the protective effect of vitamin E in plasma against CRA (Ingles *et al*., 1998). Increasing α-tocopherol and decreasing γ-tocopherol levels were associated with decreased occurrence of large adenomas; however, after adjusting for potential confounding variables, these trends were not statistically significant. Subjects in the highest versus lowest quintile of α-tocopherol:γ-tocopherol ratio had an OR of 0.36 (95% CI = 0.14-0.95) for large adenomas, which had higher probability to progress to CRC. The finding that indicated a high α-tocopherol:γ-tocopherol ratio in association with decreased occurrence of only large CRA is consistent with the previous findings that suggested α-tocopherol might be protective against CRC.

As reported for other antioxidant vitamins, the evidence for vitamin E and its association with CRA is also unequivocal and little. A study focusing on both dietary intake and plasma vitamin E will be able to add more information to the available data, particularly in the Asian community.

Vitamin D and Calcium

There has been a considerable interest in the protective role of vitamin D and calcium. Although evidence exists for the protective effects of vitamin D against CRC, there was no study linking vitamin D, calcium and CRA prior to 1999 (Holt, 1999). However, results of the on-going Nurses'

Health Study indicated that women, whose plasma $1,25(OH)_2D$ concentration was below 26.0 μg/ml, were at increased risk of distal CRA (Platz *et al*., 2000).

Peters *et al*. (2004) showed that serum 25-(OH)D was inversely associated with CRA, in which they found that the risk of CRA decreased by 26% (OR 0.74) with each 10 mg/ml increase of serum 25-(OH)D. However, the inverse association between serum 25-(OH)D and CRA has been suggested to be stronger in subjects with calcium intake above the median. Jacobs *et al*. (2007) also suggested insignificant reduction in the risk with higher serum 25-(OH)D levels.

The findings by Grau *et al*. *(*2003) indicated a protective role of vitamin D and calcium against CRA. They demonstrated the synergistic effect by looking at the participants' status of vitamin D in a trial which showed that calcium supplements protected against recurrence of CRA. Among people with 25-(OH)D levels at or below the overall median, calcium was found to have no effect on the risk of recurrence of adenomas. However, the risk was lowered in those with high levels of vitamin D. Therefore, vitamin D was associated with a reduced risk only among those taking calcium.

Supplementation with calcium has also been shown to be protective against CRA. The strongest evidence for the use of calcium in preventing CRA came from a trial by Baron *et al.* (1999), where calcium or placebo was given to adenomatous polyp patients for 4 years resulting in a moderate, but significantly reduced risk for adenomatous polyp recurrence in the intervened group. The daily dosage used, 3 g of calcium carbonate, added 1200 mg of calcium ion to the daily intake of dietary calcium. Two other studies showed a significant reduction in adenoma recurrence after given calcium supplements (Hofstad *et al.,* 1998; Bonitton-Kopp *et al.,* 2000).

However, there were studies which did not find any significant association. For instance, Hartman *et al.* (2005) did not find any significant association between adenoma recurrence and dietary calcium, total calcium, and dietary vitamin D intake. Kesse *et al.* (2005) suggested a decreasing trend in risk with the increase in calcium intake (RR = 0.80, 95% CI ==0.62-1.03), but this trend was not significant, and no effect was seen with vitamin D intake. Little association was observed by Miller *et al*. (2007) when they compared total calcium intake of ≥900 mg/day to < 500 mg/day (adjusted OR = 0.85, 95% CI = 0.53-1.37). However, Miller *et al*. (2007) reported a lower prevalence of adenomas among patients with calcium intake ≥ 900mg/day and lower fat intake.

The role of vitamin D and calcium have been (but not always) found to be related to adenoma appearance. However, a considerable number of large studies are required before accepting the role of these micronutrients in adenoma appearance.

Folate

Several studies have found a link between lower levels of folate intake and a higher incidence of adenomas, suggesting that folate may play a protective role in the carcinogenic process.

In a case-control study of diet and colorectal adenoma risk, Benito *et al.* (1993) found that subjects with folate intakes greater than 222 μg per day were approximately one fourth as likely to have adenomas as compared to those with intakes below 141 μg per day. Unfortunately, the only dietary factor the data were adjusted for was total calorie intake. Folate seemed to be a risk factor, especially when vitamin B12 intake was low, while vitamin B12 was inversely associated with adenomas, especially with relatively high folate intake (van den Donk *et al*., 2005). The adjusted OR (95% CI) for the highest compared with the lowest sex-specific tertile of intake was 1.32 (95% CI = 1.01 - 1.73) for folate and this was 0.51 (95% CI = 0.36 - 0.73) for vitamin B12. Among non-multivitamin users, Martinez *et al.* (2006) reported results from two major RCTs, namely Wheat Bran Fibre Trial and Ursodeoxycholic Acid Trial, and found that the OR for those in the highest

versus the lowest folate quartile was 0.65 (95% CI = 0.40-1.06) for the WBF study and 0.56 (0.31-1.02) for the UDCA trial.

Tseng *et al.* (1994) pursued this possible cancer-folate connection by conducting a similar case-control study to evaluate the relationship between micronutrients and CRA risk. Although their results did not achieve statistical significance, they observed a gender-specific trend. After adjusting for other dietary factors, their results showed a 60% decrease in the adenoma risk for women in the highest quartile of folate intake compared with the lowest quartile. The cause of the observed sex specificity is unclear, but the authors suggested that there might be other physiological factors involved that changed the risk pattern between men and women.

A prospective study of similar subjects from two large cohorts, namely the Nurses' Health Study and the Health Professionals Follow-up Study, was conducted by Giovannucci *et al.* (1993). They were interested in the association with folate because they found a mechanism by which low folate levels might contribute to the development of adenomas by decreasing the availability of methyl groups. The link including methionine in this equation was suggested because folate is responsible for methylization of homocysteine to methionine. This is particularly important as a low level of folate is hypothesized to disrupt DNA methylation as well.

Similar to other micronutrients studied, the relationship between folate and risk for CRA and CRC needs to be examined further. A prospective study should be able to provide more concrete evidence.

CONCLUSIONS

In conclusion, the dietary intake of an individual may influence the risk of developing CRA. While most of the available evidence suggests a role for certain foods, such as vegetables and fruits especially greens, cruciferous vegetables, citrus fruit and garlic for reducing risk, evidence for other dietary factors remains unequivocal. In addition, international variations in the distribution of the disease may also be a contributing factor to the differences derived in the observations of adenoma status (advanced or small), while position (distal or proximal) may also confound the association. Thus, future epidemiological studies and clinical trials of CRA should take into account the interaction of ethnicity, adenoma size and site into their study design.

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TABLE 1
Summary of studies on dietary factors and risk of colorectal adenomas

Factor	Authors	Year	Study design	Sample size	Results
Dietary fat	Mac Lennan *et al*.	1995	RCT	411 subjects	Low fat diet insignificantly reduced the risk of large adenomas after 48 mo (OR = 0.3, 95% CI = 0.1 – 1.0).
	Mathew *et al*.	2004	Case-control	239 subjects with history of CRA & 238 healthy controls	Total fat (OR = 1.07, 95% CI = 0.94 – 1.22) and red meat fat (OR = 1.20, 95% CI = 0.71 – 2.04) increased the risk. White meat fat reduced the risk (OR = 0.33, 95% CI = 0.19 – 0.95).
	Diergaarde *et al*.	2005	Case-control	278 cases and 414 polyp-free controls	High intake of fat seemed to increase the risk of APC(-) polyps only (OR = 1.9, 95% CI = 1.0-3.7).
	Oh *et al*.	2005	Cohort	34,451 US women followed up for 18 years	Dietary marine n-3 fatty acids reduced the risk of small adenomas (RR = 1.36, 95% CI = 1.02 – 1.81).
	Methy *et al*.	2008	RCT	523 patients with confirmed adenomas	There were no significant associations between overall adenoma recurrence and either total fat, subtypes of fat, or specific fatty acids. Polyunsaturated fatty acids and linoleic acid were both moderately but significantly associated with distal and multiple recurrence.

	Vinikoor *et al*.	2008	Cross-sectional	622 subjects	Increased prevalence of CRA in those with the highest compared to the lowest quartile of trans-fatty acids (OR = 1.86, 95% 1.04 – 3.33).
Dietary fibre	Giovannucci *et al*.	1992	Cohort (part of Health Professionals Follow-up Study)	7284 male health professionals	Low intake of dietary fibre increased the risk (RR = 8.4, 95% CI = 0.2 – 0.6).
	Platz *et al*	1997	Case-control (part of Health Professional Follow-up Study)	159 men with adenomatous polyps, 327 men with hyperplastic polyps and 16,448 healthy men as controls	Reduction in the risk for distal adenomas by 19% with increased intake of soluble fibre from fruit.
	Fuchs *et al*.	1999	Cohort (part of Nurses' Health Study)	88,000 women (16 years follow-up)	Lack of protective effect of dietary fibre (OR = 0.91, 95% CI = 0.71 – 1.16).
	Schatzkin *et al*.	2000	RCT (Polyp Prevention Trial)	2079 subjects with history of CRA	No significant association between dietary fibre and recurrence of adenomas (unadjusted OR = 1.00, 95% CI = 0.90 -1.12). Similar findings after 4 years of follow up (Lanza *et al*., 2007).

	Jacobs *et al*.	2002	RCT (Wheat Bran Trial)	1208 subjects	Compared with individuals consuming less than 1.8 g/ day of supplemental fibre, the adjusted OR (95% CI) for adenoma recurrence for those consuming greater than 11.0 g/day was 0.94 (0.66-1.33). The OR (95% CI) for participants whose total fibre intake was greater than 30.3 g/day was 0.98 (0.68-1.42) compared with those whose intake was less than 17.9 g/day.
	Peters *et al*.	2004	Case -control (part of PLCO trial)	3696 cases and 34 817 controls	High intake of dietary fibre reduced the risk by 27% (95% CI = 14 – 38).
	Lanza *et al*.	2007	RCT (PPT-Continued Follow-up Study)	405 intervention participants and 396 control participants	RR of recurrent adenoma in the intervention group compared with the control group was 0.98 (95% CI = 0.88-1.09). There were no significant intervention-control group differences in recurrence of an advanced adenoma (RR = 1.06, 95% CI = 0.81-1.39) or multiple adenomas (RR = 0.92, 95% CI = 0.77-1.10).
Red meat	Sinha *et al*.	1999	Case-control	149 cases with history of CRA and 228 healthy controls	Total red meat consumption (OR = 1.11, 95% CI = 0.96 – 1.26), grilled red meat (OR = 1.26, 95% CI = 1.06 – 1.50) and pan-fried red meat (OR – 1.15, 95% CI = 0.97 – 1.36) increased the risk.

	Breuer-Katschinski *et al*.	2001	Case-control (Colorectal Adenoma Study Group)	184 cases with history of CRA and matched controls	Red meat from increase the risk in cases compared to hospital controls (or = 3.6, 95% CI = 1.7 – 7.5) and population controls (OR = 4.4, 95% CI = 1.6 – 12.1).
	Chiu and Gapstur	2004	Case-control	146 colorectal adenomas and 226 controls	Risks were higher for those with the smallest reduction in red meat intake (OR = 2.8, 95% CI = 1.1-7.3).
	Tiemersma *et al*.	2004	Case-control	431 adenoma cases and 433 polyp-free controls	HCAs were present in habitually prepared meat, although meat consumption (7 versus < 5x/week) did not increase the risk of colorectal adenomas (OR = 1.2, 95% CI = 0.8-1.9). Presumed unfavourable preparation habits of meat did not increase adenoma risk (OR 0.8 and 0.9, respectively).
	Diergaarde *et al*.	2005	Case-control	278 cases and 414 polyp-free controls	Red meat consumption was significantly and differently related to polyps with truncating APC mutation (APC(+) polyps) (highest vs. lowest tertile, OR = 0.5, 95% CI= 0.3-1.0). High intake of red meat seemed to increase the risk of APC(-) polyps only (APC(-) vs. controls: red meat, OR = 1.8, 95% CI = 1.0-3.1).

	Gunter *et al*.	2005	Case-control	261 cases and 304 controls	Consistent with this finding, an incremental increase of 10 g of barbecued red meat per day was associated with a 29% increased risk of large adenoma (OR = 1.29, 95% CI = 1.02-1.63). Individuals in the top quintile of barbecued red meat intake were at increased risk of large adenoma (OR = 1.90, 95% CI = 1.04-3.45) compared with those who had never consumed barbecued red meat. The consumption of oven-broiled red meat was inversely related to adenoma risk compared with non-consumers (OR = 0.49, 95% CI = 0.28-0.85).
	Sinha *et al*.	2005	Case-control	3,696 left-sided adenoma cases and 34,817 endoscopy-negative controls	Intake of red meat, with known doneness/cooking methods, was associated with an increased risk of adenoma in the descending and sigmoid colon (OR =1.26, 95% CI = 1.05-1.50 comparing extreme quintiles of intake) but not rectal adenoma. Well-done red meat was associated with increased risk of colorectal adenoma (OR = 1.21, 95% CI = 1.06-1.37).

	Wu *et al*.	2006	Cohort (Health Professionals Follow-up Study cohort)	581cases with distal adenoma	Higher consumption of mutagens from meats cooked at higher temperature and longer duration may be associated with higher risk of distal colon adenoma independent of overall meat intake (OR highest versus lowest quintile of meat-derived mutagenity = 1.29, 95% CI = 0.97-1.72).
	Ward *et al*.	2007	Case-control	146 cases of colorectal adenoma and 228 polyp-free controls	Two-fold increased risk in the highest compared to the lowest quartile of processed meat intake (95% CI = 1.0-4.0).
Fruits and vegetables	Witte *et al*.	1996	Case-control	488 matched pairs.	High carotenoid and cruciferous vegetables, high vitamin C fruits, garlic and tofu reduced the risk.
	Smith-Warner *et al*.	2002	Case-control	564 cases with history of CRA, 682 polyp-free controls and 535 community controls	Juice consumption reduced the risk in women (OR = 0.50, 95% CI = 0.27 – 0.92).
	Almendingen *et al*.	2004	Case-control	28 cases with history of CRA and 34 matched controls followed up for 3 years	Weak association between adenomas growth and fruit/ berries (OR = 0.3, 95% CI = 0.1 – 0.9) and between adenoma recurrence and vegetable intake (OR = 0.4, 95% CI = 0.1 – 0.9).
	Chiu and Gapstur	2004	Case-control	146 colorectal adenomas and 226 controls	Individuals in the highest quartile of increased consumption vegetables (OR = 0.5; CI = 0.3-1.1) had a lower risk compared with those with minimal increase in consumption.

	Michels *et al*.	2006	Cross-sectional (Nurses' Health Study)	1720 prevalent cases in women	Frequent consumption of fruit was inversely related to the risk of being diagnosed with polyps (OR >5 servings vs <1 servings = 0.60, 95% CI = 0.44 – 0.81), whereas little association was found for vegetable consumption (OR = 0.82, 95% CI = 0.65 – 1.05).
	Austin *et al*.	2007	Case-control	203 cases with history of CRA and 522 controls without CRA	High vegetable-moderate meat cluster (OR = 2.17, 95% CI = 1.20 =- 3.90) and high meat cluster (OR 1.70, 95% CI = 1.04 – 2.80) increased the risk.
Vitamin A	Giovannucci *et al*.	1993	Case-control (using subjects from Nurses' Health Study and Health Professionals Follow-up Study)	564 cases of women with CRA and 15,984 control women. 331 cases of men with CRA and 9490 control men	Higher intake of vitamin A did not protect from the risk (OR = 0.91, 95% CI = 0.69 – 1.19).
	Enger *et al*.	1996	Case-control	488 matched pairs	Dietary vitamin A decreased the risk only before adjusting for confounders (OR = 0.60, 95% CI = 0.4 – 0.9).
	Lubin *et al*.	1997	Case-control	196 cases with CRA and matched healthy controls.	No significant relationship was found between dietary retinol and the risk (OT = 0.9, 95% CI = 0.5 – 1.6).
	Nagata *et al*.	2001	Case-control (part of the cohort of Takayama Study, Japan)	279 cases with CRA and 28361 polyp-free controls	Higher vitamin A intake was significantly associated with increased risk (RR = 1.51, 95% CI = 1.04 – 2.20).

Carotenoids	Enger *et al*.	1996	Case-control	488 matched pairs	Only b-carotene was associated with the risk (p=0.04).
	Lubin *et al*.	1997	Case-control	196 cases with CRA and matched healthy controls	Highest tertile of carotene intake reduced the risk by 40% (OR = 0.6, 95% CI = 0.3 – 1.0) compared to the lowest.
	Shikany *et al*.	1997	Case-control	472 cases with CRA and 502 matched controls	No association between individual plasma carotenoids and the risk.
	Malila *et al*.	1999	RCT (ATBC Study)	15,538 ATBC study participants with 146 cases with CRA	Supplementation with b-carotene had no effect on the risk (RR = 0.98, 95% CI = 0.71 – 1.35).
	Erhardlt *et al*.	2003	Observational study	73 white subjects with history of adenomas, 63 without any polyps, and 29 with hyperplastic polyps	Plasma lycopene significantly lowered the risk by 35%.
	Senesse *et al*.	2005	Case-control	362 cases with CRA and 427 polyp-free controls stratified according to smoking status	β-carotene intake was inversely associated with the risk in non-smokers OR = 0.4, 95% CI = 0.2 – 0.9) but increased the risk in smokers (OR = 1.9, 95% CI = 0.9 – 4.1).

Vitamin C	Benito *et al*.	1993	Case-control	79 cases with history of CRA and 242 healthy controls	Higher intake of vitamin C lowered the risk by 63% ($p<0.01$).
	Enger *et al*.	1996	Case-control	488 matched pairs	Insignificant weak association between vitamin C intake and the risk (OR = 0.8, 95% CI = 0.5 – 1.5).
	Tseng *et al*.	1996	Case-control	236 cases with CRA or cancer and 409 controls	Significant reduction in the risk only in women.
	Connelly *et al*.	2003	Cross-sectional (within Diet and Health Study III)	503 participants who underwent rectal biopsy	High vitamin C intake was associated with reduced colorectal apoptosis only among individuals with adenomas.
Vitamin E	Tseng *et al*.	1996	Case-control	236 cases with CRA or cancer and 409 controls	Protective effect of vitamin E intake only in men (OR = 0.35, 95% CI = 0.14 – 0.92).
	Ingles *et al*.	1998	Case-control	332 subjects with history of CRA and 363 healthy controls	No significant association with plasma tocopherols and the risk, but higher ratio of α-tocopherol:γ-tocopherol lowered the risk for large adenomas (OR = 0.36, 95% CI = 0.14 – 0.95).
	Whelan *et al*.	1999	Case-control	448 cases with history of CRA and 714 healthy controls	Vitamin E supplements lowered the risk (OR – 0.62, 95% CI = 0.39 – 0.98).

Vitamin D and calcium	Hofstad *et al*.	1998	RCT	42 in the intervention group and 51 in the placebo group. All subjects with history of CRA	Significant reduction in risk with calcium supplementation compared to placebo (Mean difference = 2.3 mm, 95% CI = 0.26-4.36).
	Baron *et al*.	1999	RCT (Polyp Prevention Study Group)	409 in the calcium group and 423 in the placebo group. All subjects with history of CRA	Moderate but significant reduction in risk with calcium supplementation (OR = 0.76, 95% CI = 0.60 - 0.96).
	Bonitton-Kopp *et al*.	2000	RCT (ECPO Study Group)	176 in calcium group, 198 in fibre group and 178 in placebo group. All subjects with history of CRA	Significant reduction in risk with calcium supplementation (OR = 0.66, 95% CI 0.38-1.17).
	Platz *et al*.	2000	Case-control (within Nurses' Health Study)	326 matched women case and control pairs	Plasma $1,25(OH)_2D$ concentration below 26.0μg/ml increased the risk of distal adenoma.
	Grau *et al*.	2003	RCT	398 in intervention group and 405 in placebo group	High level of vitamin D together with calcium supplementation lowered the risk (RR = 0.71, 95% CI = 0.57 to 0.89, P for interaction=0.012).
	Peters *et al*.	2004	Case-control (within PLCO Trial)	3693 cases with history of CRA and 34 817 healthy controls	The risk decreased by 26% for every 10ng/ml increase in serum 25-(OH)D.

	Hartman *et al*.	2005	Cross-sectional (within PPT)	754 adenoma cases	There were no overall significant associations between adenoma recurrence and dietary calcium, total calcium and dietary vitamin D intake. Total vitamin D intake was weakly and inversely associated with adenoma recurrence (OR = 0.84, 95% CI = 0.62-1.13). Supplemental calcium and vitamin D use during follow-up was also inversely associated with adenoma recurrence (OR for any compared with no use = 0.82, 95% CI = 0.68-0.99; and OR = 0.82, 95% CI = 0.68-0.99 for calcium and vitamin D, respectively).
	Kesse *et al*.	2005	Case-control	516 adenoma cases and of 4,804 polyp-free subjects	There was a decreasing trend in the risk of adenoma (p=0.04) with increasing calcium intake (RR = 0.80, 95% CI ==0.62-1.03 in the fourth quartile compared to the first). No vitamin D effect was identified.
	Jacobs *et al*.	2007	Cross-sectional	568 subjects	Insignificant reduction in risk for recurrence of CRA in highest tertile compared to the lowest tertile of serum 25(OH) D levels (OR = 0.78, 95% CI = 0.49 – 1.24). Insignificant reduction in risk was seen in women (OR 25(OH)D above median vs. below median = 0.59 (95% CI = 0.30 – 1.16).

	Miller *et al*.	2007	Case-control	222 cases and 479 adenoma-free controls	Little association was observed comparing total calcium intake of ≥ 900 mg/day to < 500 mg/day (adjusted OR = 0.85, 95% CI = 0.53-1.37). Total calcium intake of ≥ 900 mg/day was associated with a lower prevalence of adenomas among patients with lower fat intake (OR = 0.47, 95% CI = 0.25-0.91).
Folate	Benito *et al*.	1993	Case-control	79 cases with history of CRA and 242 healthy controls	Reduction of risk by 25% in those with folate intakes > 222μg/day as compared to those with < 141μg/day.
	Martinez *et al*.	2004	Cross-sectional	1014 subjects	Lower odds of recurrence were shown for higher plasma folate (OR = 0.66, 95% CI = 0.46 -0.97) and higher total intakes (dietary plus supplemental) of folate (OR = 0.61, 95% CI = 0.42 - 0.89).
	Van den Donk *et al*.	2005	Case-control	768 cases with history of CRA and 709 healthy controls	Folate is a risk factor when vitamin B12 intake is low (OR = 1.32, 95% CI = 1.01 – 1.73).
	Martinez *et al*.	2006	RCT (wheat bran fiber (WBF) and the ursodeoxycholic acid (UDCA) trials)	WBF trial – 1014 subjects. UDCA trial – 1111 subjects	Among non-multivitamin users, the OR for those in the highest versus the lowest folate quartile was 0.65 (95% CI = 0.40-1.06) for the WBF study and 0.56 (0.31-1.02) for the UDCA.