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Colorectal Cancer and the Preventive Effects of Food Components

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1. Introduction

It has been reported that the cause of 30% of cancer is associated with eating habits (Anand et al., 2008). Colorectal cancer is one of the most common causes of death all over the world, and there is a strong association between this type of cancer and food intake. Despite this statement, the preventive effects of foods and nutrients on colorectal cancer have not completely elucidated yet.

It has been proposed that some biologically active nutrients suppress colon carcinogenesis through the mechanisms of cytostatic properties, inhibition of cell growth, induction of apoptosis, an anti-inflammation effect or modification of DNA in *in vitro* studies.

Although the positive effects of these nutrients have been shown in *in vitro* studies, it is still difficult to apply the effects of these nutrients in *in vivo* studies, due to modifications to foods during the process of absorption and delivery within the body. There might be two possible active sites, where foods and their components affect colon epithelium cells, where nutrients are distributed hematogenously after absorption, or retained in the lumen without absorption. Absorbed foods and nutrients might show the effects of anti-inflammation, anti-oxidant, and anti-proliferative par hematogenously in cancer epithelial cells and stromal cells, while on the other hand, the regulation of enterobacteria might be provided by the component in a poorly-absorbed form. Recent studies have focused on resistant carbohydrates functioning as prebiotics that prevent colorectal cancer (Davis & Milner, 2009).

The normal human intake of food has a great advantage for oral administration and safety, compared with the administration of medicine, because safety has been proven by long food experience. Thus, the prevention of colorectal cancer through the intake of specific foods and nutrients might have a great potential, however further studies are required, especially in regard to absorption and disposition. In this paper, we focused on foods, and their components, with cancer preventive aspects.

2. The preventive effects of food components against colorectal cancer

Colorectal cancer is one of the most common cancers in the world and it has been proposed that it is strongly associated with dietary habits (Anand et al., 2008; Jemal et al., 2011). Red and processed meat may convincingly increase the risk, and physical activity is only the

proven method of prevention. Avoiding body fatness, especially abdominal fatness, and the consumption of an excessive amount of alcohol are also important for colorectal cancer prevention (World Cancer Research Fund, 2007b). Despite the confirmation of cancer inducing foods, foods or nutritional elements that have protective qualities against colorectal cancer have not yet been fully confirmed.

2.1 Epidemiology

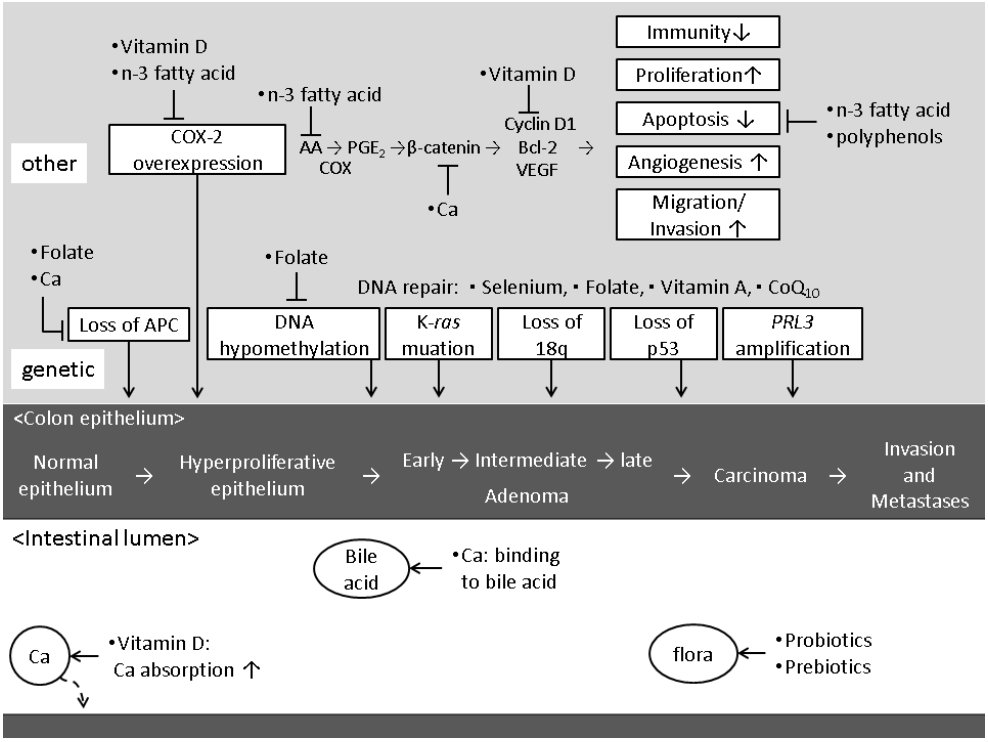
Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females, and it is the fourth common cause of death in males and third in females, according to a survey conducted in 2008 (Jemal et al., 2011) . The increasing rate of colorectal cancer is considered to be due to the combination of changes in dietary patterns, obesity and smoking (Jemal et al., 2011). Approximately only 5-10% of all colorectal cancers are a consequence of recognized hereditary conditions (Lynch & de la Chapelle, 2003). Since dietary habits play an important role in the incidence of colorectal cancer, this subject must be employed as one of the main strategies to investigate components derived from foods with cancer prevention properties.

It has been reported that dietary patterns are associated with the onset of colorectal cancer. The Mediterranean diet was associated with a reduced risk of recurrence of colorectal adenomas in woman. The Mediterranean diet is characterized by a high consumption of breads, vegetables, fruit, fish and olive oil (World Cancer Research Fund, 2007c, as cited in Cottet et al., 2005). The Japanese traditional diet is characterized by a high consumption of fish and seafood with a high salt content. Japanese cohort studies demonstrated that both the Japanese traditional diet and western diet were associated with an increased risk of colon cancer in women, but not in men (Kim et al., 2005). The 'Pork, processed meats and potatoes' diet was associated with an increased risk of colon cancer in women and also with rectal cancer in men. 'Pork, processed meats and potatoes' diet pattern was characterized as intakes of energy, protein carbohydrate, fat, saturated and monounsaturated fatty acids, cholesterol, B vitamins, and minerals (Dixon et al., 2004). Vegetarian diets might moderately reduce the risk of colon cancer, which is due to not only to no or low consumption of meat, but also to a high consumption of plant foods (Sanjoaquin et al., 2004; World Cancer Research Fund, 2007c), although there is a negative result of colorectal cancer prevention (Key et al., 1996).

2.2 Adenoma-to-carcinoma sequence and pathology

A genetic model for colorectal tumorigenesis has been proposed in the following procedures (Fearon & Vogelstein, 1990). 1) The mutation of APCTS gene transform normal colonic epithelia tissue to multiple polyps, 2) DNA hypomethylation is related to the onset and development of and early adenoma, 3) The K-*ras* oncogene play an important role in the progression from early to intermediate adenomas, 4) A mutation of the Thymidylate synthase gene plays an important role in the development from intermediate to late adenoma, 5) A mutation of TP53 gene is highly found in late adenomas and colorectal cancers (Tammariello & Milner, 2010) (Figure 1).

Oxidative stress, which provided by both exogenous (irradiation, chemicals, and drugs) and endogenous (O2 metabolism, immune response, and inflammation) origin, plays a critical



Abbreviations: COX, cyclooxygenase; AA, arachidonic acid; VEGF vascular endothelial growth factor; Ca, calcium; CoQ_{10}, coenzyme Q_{10}

Fig. 1. Proposed anticarcinogenetic effects of nutrients on colorectal cancer. Selenium, folate, vitamin A and CoQ_{10} have been reported to repair damaged DNA. Vitamin D and n-3 fatty acid may suppress the COX-2 mediated carcinogenesis. Ca plays a diverse role, including the inhibition of *APC* mutation, suppression of β-catenin and binding to bile acid. Probiotics and/or prebiotics reduce colorectal cancer to modify the proportion of gut microflora.

role in DNA damage (Kryston et al., 2011). Reactive oxygen spices (ROS) and DNA interactions induce DNA damage, which causes mutation via either double-strand break (DSB) or non-DSB lesions (Sedelnikova et al., 2010). Carcinogenesis of oxidative stress also involve immune cell activation via CCL2/MCP-1, pro-inflammatory factor (Martin et al., 2011).

The methods of accurate measurement of oxidative stress have been brought by HPLC, tandem mass spectrometry (MS/MS) electrochemical detector (Cadet et al., 2010). There are also biomarkers to assess the level of oxidative stress, such as 8-oxo-2'deoxyguanosine (8-oxo-dG) (Ziech et al., 2010). These can allow us precise studies of anti-oxidative property by food.

Cyclooxygenase (COX) also plays an important role in carcinogenesis, e.g. to induce prostaglandin E_2 (PGE_2). PGE_2 has diverse functions to promote cell proliferation, migration,

invasion and angiogenesis, and also to suppress immunity and apoptosis through inducing cyclin D1, Bcl-2 and vascular endothelial growth factor (VEGF) (Chan & Giovannucci, 2010). Figure 1 demonstrates the possible anti-tumor mechanisms of nutrients in the process of colorectal carcinogenesis (Janne & Mayer, 2000; Lamprecht & Lipkin, 2003; World Cancer Research Fund, 2007a; Chan & Giovannucci, 2010; Vilar & Gruber, 2010).

2.3 Digestion, absorption, delivery and distribution, and the site of mechanisms of action

For the clinical application of foods and nutrients for the prevention of colorectal cancer, we need to elucidate thoroughly how each food is digested, absorbed, delivered, and distributed to every organ or tissue, and determine what is the biologically active component, similar to the pharmacokinetics of drugs. Food constituents showed anti-tumor properties when they are distributed hematogenously to pre-cancer or cancer epithelial cells.

We often find that there is a big gap in the effective concentration between *in vitro* and *in vivo* studies. It sometimes happens that *in vitro* studies need a much higher concentration to demonstrate significant anti-tumor effects, compared with the biological concentration. When the ingestion of a nutrient shows a cancer prevention effect in an *in vivo* study, this does not directly mean the nutrient affect will be imported into the cells, as it may change to another form after digestion and absorption. Each article of food includes a lot of constituents, so that various constituents may demonstrate additive action or synergetic effects. In addition, active constituents affect not only cancer epithelium cells, but also the cancer stromal environment, e.g. angiogenesis or the interaction between epithelial and stromal cells, since the paracrine interaction between epithelial and stroma cells affect each other for tumor progression (Ko et al., 2002; Adegboyega et al., 2004; Martinez-Outschoorn et al., 2011).

For cancer prevention of the alimentary tract, active food components can have an effect not only hematogenously, but also from the gut lumen side. This indicates that indigestible constituents, as well as easily absorbed components, can function as potent anti-cancer agents against colorectal cancer. As mentioned above, resistant starches have cancer prevention properties as prebiotics that modify intestinal microorganism (Tuohy et al., 2005). Calcium may reduce the colorectal cancer risk associated with the combination to bile acid, the risk profile in intestinal lumen (Boursi & Arber, 2007). The effective site of food components has been proposed in Figure 1 (Lamprecht & Lipkin, 2003).

Some of the blood levels of active components after the ingestion of foods have been reported, but those amounts in the gut or stool have been rarely reported. For colorectal cancer prevention in humans, we need to investigate the systemic function of food ingredients, how the food is digested, absorbed and remains in the gut, as well as the blood concentration and delivery in each organ. Further studies are necessary to illuminate the mechanisms of food components on colorectal cancer prevention.

2.4 Food, nutrition, physical activity and the prevention of cancer: a global perspective, 2007

The Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective was produced by the World Cancer Research Fund and the AIRC, in order to generate a

comprehensive series of recommendations on food, nutrition, and physical activity, for reducing cancer risk for all populations worldwide (World Cancer Research Fund, 2007b).

The World Cancer Research Fund and the American Institute for Cancer Research judged that the evidence that physical activity protects against colorectal cancer was convincing, and the evidence that foods containing dietary fibre, garlic, milk and calcium protect against colorectal cancer was probable. On the other hand, the evidence that red meat, processed meat, alcoholic drinks for men, body fatness, abdominal fatness and adult attained height caused colorectal cancer was convincing, and the evidence that alcoholic drinks in women caused this cancer was probable.

Table 1 shows the positive and negative results on colorectal cancer protection of foods and nutrition.

2.4.1 Foods judged to "probably" reduce the risk of colorectal cancer

The 4 foods that affected the judgement that the evidence on the reduction of the risk of colorectal cancer was probable were food containing dietary fibre, garlic, milk and calcium.

2.4.1.1 Dietary fibre

Dietary fibre was associated with a reduced risk of colon cancer (Mastromarino et al., 1976). A meta-analysis of eight studies of dietary fibre estimated that the relative risk was 0.90 (95% confidence interval (CI) 0.84-0.97) per 10 g/day increment (World Cancer Research Fund, 2007c).

A few negative results have been demonstrated. There was no association shown between dietary fibre consumption and the onset of colorectal cancer or adenoma by a 16-year follow-up prospective study (Fuchs et al., 1999). In the paper, a higher consumption of vegetable fibre was even associated with an increased risk of colorectal cancer in women. There was another negative result shown for dietary fibre, i.e., a high-fibre cereal supplement did not reduce recurrent colorectal adenomas (Alberts et al., 2000).

The mechanisms of the action of dietary fibre are not clearly elucidated yet, but it has been suggested that it dilutes faecal contents, decrease transit time, and increase stool weight (World Cancer Research Fund, 2007c, as cited in Cummings, 1981). Short-chain fatty acids, like butyrate, are produced by the gut flora from dietary carbohydrates that reach the colon, induce apoptosis and cell cycle arrest, and promote differentiation (World Cancer Research Fund, 2007c). Dietary fibre intake is important for lipid and glucose metabolism or for acting as prebiotics on microflora health in preventing colonic cancer (Donini et al., 2009). The consumption of fibre is associated to the consumption of folate (World Cancer Research Fund, 2007c), which has also been reported to be associated with a reduced risk of colorectal cancer (Sanjoaquin et al., 2005).

2.4.1.2 Garlic

In the "Global Perspective", the World Cancer Research Fund and American Institute for Cancer Research judged that garlic probably protects against colorectal cancer (World Cancer Research Fund, 2007c). Ally sulphur, which is considered to be an effective component of garlic, inhibited colon tumors in animal studies. The biologically active compounds derived from garlic have been proposed as allicin, diallyl sulphide (DAS),

Food and nutrition	Human studies	RR (95% CI) highest vs lowest exposure whcn it is not mentioned	ref.
Foods containing dietary fibre			
positive			
	Dietary fibre was associated with a reduced risk of recurrence of colorectal adenomas in woman /meta-analysis from 8 studies	0.90 (0.84-0.97) per 10g/day increment	World Cancer Research Fund, 2007c
negative			
	Dietary fibre was not associated with colorectal cancer risk in women/16-year follow-up cohort study	0.95 (0.73-1.25)	Fuchs et al., 1999
	Dietary fibre from vegetable was associated with an increased risk of colorectal cancer in women/16-year follow-up cohort study	1.35 (1.05-1.72)	Fuchs et al., 1999
	Dietary supplement of wheat-bran fibre was not associated a reduced risk of recurrent colorectal adenomas/randomized trial	0.88 (0.70-1.11)	Alberts et al., 2000
garlic			
positive			
	Garlic intake was probably associated with a reduced risk of colon cancer/2 cohort studies and 6 case-control studies	0.77 (0.51-1.16) 0.68 (0.46-1.01)	World Cancer Research Fund, 2007c
milk			
positive			
	Milk intake was associated with a reduced risk of colorectal cancer/meta-analysis from 4 cohort studies	0.94 (0.85-1.03) per serving/day	World Cancer Research Fund, 2007c
	Milk intake was associated with a reduced risk of colorectal cancer/meta-analysis from 10 cohort studies	0.85 (0.78-0.94)	Cho et al., 2004
	Milk intake was associated with a reduced risk of colorectal cancer/meta-analysis from 19 cohort studies	0.91 (0.85-0.94) per 200 g/day of milk	Aune et al., 2011
calcium			
positive			
	Calcium supplementation was associtated with a reduced risk of adenomas/meta-analysis from 2 cohort studies	0.95 (0.92-0.98) per 200 mg/day	World Cancer Research Fund, 2007c
	Total calcium intake and intake of calcium from food sources was was associtated with a reduced risk of colorectal cancer/meta-analysis from 10 cohort studies	0.78 (0.69-0.88) for total calcium 0.86 (0.78-0.95) for calcium from food sources	World Cancer Research Fund, 2007c, as cited in Samad et al., 2005

Table 1.

non-starchy vegetables and fruits			
possitive			
	Conssumption of fruit was associated with a reduced risk of colorecatl cancer/meta-analysis from 8 cohort studies	0.97 (0.92-1.03) per serving/day	World Cancer Research Fund, 2007c
	Conssumption of fruit was associated with a reduced risk of colorecatl cancer in women/meta-analysis from 5 cohort studies	0.81 (0.85-0.98) per serving/day	World Cancer Research Fund, 2007c
	Consumption of fruit was associtated with a reduced risk of colorectal cancer/cohort study	0.57 (0.34-0.97)	Sanjoaquin et al., 2004
	A high consumption of vegetable and fruit was association with a reduced risk of colorectal and colon cancer/cohort study	0.86 (0.75-1.00) for colorectal cancer 0.76 (0.63-0.91) for colon cancer	van Duijnhoven et al., 2009
	There is limited evidence suggesting that non-starchy vegetables protect against colorectal cancer	1.00 (0.90–1.11) per 2 servings/day	World Cancer Research Fund, 2007c
negative			
	Vegetarians diet was not significantly associated with a reduced risk of colorectal cancer/cohort study	0.85 (0.55-1.32) vegetarians vs non-vegetarians	Sanjoaquin et al., 2004
	A high consumption of vegetable was not associated with recuded risk of rectal cancer/cohort study	0.92 (0.79-1.06)	van Duijnhoven et al., 2009
	A high consumption of fruit was not associated with recuded risk of colorectal cancer/cohort study	0.88 (0.76-1.01)	van Duijnhoven et al., 2009
Foods containing folate			
positive			
	Dietary folate intake was associated with the recuced risk of colorectal cancer/meta-analysis of 7 cohort studies	0.75 (0.64-0.89)	Sanjoaquin et al., 2005
	Total folate intake was associated with a recuced risk of colorectal cancer/metanalysis of 7 cohort studies	0.95 (0.81-1.11)	Sanjoaquin et al., 2005
Selenium and foods containing selenium			
positive			
	Dietary selenium was associated with a reduced risk of colorectal cancer/A meta-analysis from 5 case-control studies	0.86 (0.78-0.95) per 10 µg/dl serum	World Cancer Research Fund, 2007c
Fish			
positive			
	Fish consumption was associated with a reduced risk of colorectal cancer/meta-analysis from 7 cohort studies	0.96 (0.92-1.00) per serving/week	World Cancer Research Fund, 2007c
negative			

Table 1. (continued)

	Consumption of salmon or cod was not associtated with local markers of inflammation, genotoxicity markers in colonocyte, and apoptotic and mitotic rate in colonic mucosa/randomized controlled study		Pot et al., 2009; Pot et al., 2010a; Pot et al., 2010b
Foods containing vitamin D			
positive			
	Food containing vitamin D was associated with a reduced risk of colorectal cancer/meta-analysis from 9 cohort studies	0.99 (0.97-1.00) per 100 IU/day	World Cancer Research Fund, 2007c
Vitamins (except vitamin D)			
positive			
	A high consumption of vitamin C and E from both food and supplements (total) was associated with a reduced risk of colon cancer risk/pooled analysis of cohort studies	0.80 (0.71-0.90) for total vitamin C 0.82 (0.74-0.91) for total vitamin E	Park et al., 2010
	Multivitamin intake was associated with a reduced risk of colon cancer/pooled analysis of cohort studies	0.88 (0.81-0.96)	Park et al., 2010
	A high intake of either dietary nutrients (vitamin C, vitamin E, β-carotene, selenium, folate, vitamin B6, and vitamin B12) was associated a reduced the risk of distal colorectal cancer in the caucasian/case-control study	0.58 (0.42-0.80) for vitamin C 0.65 (0.48-0.89) for vitamin E 0.52 (0.38-0.71) for β-carotene 0.55 (0.39-0.77) for selenium 0.50 (0.36-0.69) for folate 0.48 (0.35-0.67) for vitamin B6 0.59 (0.42-0.81) for vitamin B12	Williams et al., 2010
	A high intake of dietary selenium was associated with a reduced risk of distal coloredtal cancer in African Americans/case-control study	0.55 (0.29-1.02)	Williams et al., 2010
	β-carotene intake was associated with a reduced risk of colorectal cancer in men/cohort study	0.77 (0.763-0.95)	Park et al., 2009
negative			
	lycopene intake was associated with an increased risk of rectal cancer in men/cohort study	1.50 (1.04-2.16)	Park et al., 2009

Table 1. (continued)

Vitamin A, vitamin C, and vitamin E intake from food only were not associated with colon cancer risk /pooled analysis of cohort studies	0.92 (0.81-1.05) for vitamin A 1.06 (0.95-1.18) for vitamin C 0.99 (0.89-1.11) for vitamin E	Park et al., 2010
A high consumption of carotenoid (except for β-carotene) was not associated with a reduced resk of colorecatl cancer/cohort study	0.86 (0.71-1.04) for total carotenoids in men0.83 (0.67-1.04) for total carotenoids in men	Park et al., 2009

Abbreviations: RR, relative risk; 95% CI, 95% confidence interval

Table 1. Positive and negative result of food and nutrition on colorectal cancer protection.

diallyl disulphide (DADS), diallyl trisulfide (DATS) and ajoene. DAS, DADS and S-allylcysteie (SAC) demonstrated the inhibitory effect on colon cancer in the rat (Shukla & Kalra, 2007).

In colon tumor cells, the induction of apoptosis, cell cycle modification and inhibition of tubulin polymerisation were suggested as the mechanism of the action of DATS, and the anti-proliferative effect, G2/M cell cycle arrest, decrease of polyamine biosynthesis, inhibition of histone deacetylase activity were suggested as the mechanisms of the actions of DADS (Filomeni et al., 2003; Shukla & Kalra, 2007). It also has been reported that garlic and its constituents inhibit DNA adduct formation, scavenge free radicals and modulate P-glycoprotein-mediated multidrug resistance (Shukla & Kalra, 2007).

2.4.1.3 Milk and other dairy products

A meta-analysis of "a global perspective" produced a summary effect estimate for relative risk of 0.94 (95% CI 0.850-1.03) per serving/day (World Cancer Research Fund, 2007c). An analysis of data obtained from 10 cohort studies demonstrated that higher milk intake (≧ 250 g/day) was related to a statistically significant reduced risk of colorectal cancer with relative risk 0.85 (95% CI 0.78-0.94) compared with the lowest intake (< 70 g/day) (Cho et al., 2004). According to the latest meta-analysis study, nineteen cohort studies concluded that the summary relative risk was 0.91 (95% CI 0.85-0.94) per 200 g/day of milk, and 0.83 (95% CI 0.78-0.88) per 400 g/day of total dairy products intake. There was no significant association between the consumption of cheese and a reduced risk (Aune et al., 2011).

Dietary milk fat globule membrane reduced the incidence of aberrant crypt foci in Fisher-344 rats (Snow et al., 2010).

The cancer prevention effect of milk and dairy products is at least partly associated with the intake of calcium, which may bind to bile acids and ionized fatty acids to reduce cell proliferation and promote cell differentiation (Aune et al., 2011).

2.4.1.4 Calcium (supplemented at a dose of 1200 mg/day)

The main dietary sources of calcium in Europe and America are milk and dairy products. The meta-analysis estimate for the summary effect for colon cancer was 0.95 (95% CI 0.92-0.98) per 200 mg/day of dietary calcium (World Cancer Research Fund, 2007c). Analysis from 10 cohort studies demonstrated that the total calcium had a greater correlation (relative risk 0.78; 95% CI 0.69-0.88) to colorectal cancer than calcium from food sources (relative risk 0.86; 95% CI 0.78-0.95) (World Cancer Research Fund, 2007c, as cited in Samad et al., 2005).

On the other hand, there was a negative report regarding the chemoprevention effects of calcium, 2.5 g/kg calcium reduced the number of small intestinal tumors, but increased the number of colon tumors (Huerta et al., 2003).

Calcium binds bile acids in the bowel lumen to inhibit their proliferative and carcinogenic effects, since bile acids might promote hyper-proliferation of the colorectal epithelium and carcinogenesis. Calcium may also act directly on the colonic epithelial cells to inhibit *ras* mutation (Bautista et al., 1997; Janne & Mayer, 2000). Extracellular dietary calcium is associated with the activation of calcium-sensing receptors in intestinal epithelial cells, and then the activation of intracellular signalling pathways, including proliferation, differentiation, and apoptosis (Lamprecht & Lipkin, 2001).

2.4.2 Food judged to be "limited-suggestively" reduced cancer risk

Since there was not sufficient evidence to judge, the factors below were concluded as limited-suggestive; non-starchy vegetables (not including salted and/or pickled products), fruits, foods containing folate, foods containing selenium, fish, foods containing vitamin D, and selenium (supplements at the dose of 1200 mg/day).

2.4.2.1 Fruit and vegetable

It is quite complicated to investigate which nutrient has the most effective properties for colorectal cancer prevention, since non-starchy vegetables are a source of dietary fibre, carotenoids, folate, selenium, glucosinolates, and so on, and fruits are sources of vitamin C, carotenoids, phenols, flavonoids and other anti-oxidants. The results of the anti-cancer effects of fruit and vegetable are heterogeneous.

Dietary cruciferous vegetable intake was associated with a reduced colon risk of approximately 25% (Marshall, 2008), There was an inverse association between the consumption of fruits and the risk of colorectal cancer, although the vegetarians showed a moderate, but non-significant, decrease in the risk (Sanjoaquin et al., 2004). A high consumption of vegetable and fruit showed an inverse association with colorectal and colon cancer, but not rectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). There was no significant inverse association shown between vegetable consumption or fruit consumption and colorectal, colon, or rectal cancer (Key et al., 2009; van Duijnhoven et al., 2009).

Vegetable-fruit mixture intake did not decrease the number of colon polyps both in low in fat (20% of energy) and high in fat (40% of energy) in the *Apc*^{Min} mice which are genetically predisposed to intestinal polyps (van Kranen et al., 1998).

It has been reported that several fruits have a specific potency for cancer prevention. Apple is rich in quercetin (World Cancer Research Fund, 2007c). Apple juice also showed the potency of preventing colon carcinogenesis in mice, but this effect was not found under the cancer promoting conditions associated with obesity (Koch et al., 2009). On the other hand, Nandir et al. showed apple pomace increased the number and diameter of colon polyps in *Apc*^{Min} mice (Mandir et al., 2008). Citrus fruits are sources of antioxidants, such as vitamin C, phenols, flavonoid and bioactive phytochemicals. Vitamin C traps free radicals and reactive oxygen species, and protects DNA from mutagenic damage (World Cancer Research Fund, 2007c). Cruciferous vegetables, such as broccoli, cabbage and cauliflower, reduced the colorectal cancer risk (Marshall, 2008), although there was also a negative report (Graham et al., 1988).

2.4.2.2 Foods containing folate and folate

According to the meta-analysis study, there was strong association between folate consumption and colorectal cancer risk in 7 cohort studies. Dietary folate showed a stronger association (relative risk for high vs. low intake = 0.75; 95% CI 0.64-0.89) than total folate (relative risk for high vs. low =0.95; 95% CI 0.81-1.11) (Sanjoaquin et al., 2005). Folate intake was strongly correlated with dietary fibre intake (World Cancer Research Fund, 2007c).

Animal studies also supported the cancer prevention properties of folate, however, intervention with exceptionally high doses of folate (2.0-5.0 g of folic acid/kg diet) after the formation of microscopic neoplastic foci may have promoted colorectal carcinogenesis (Kim, 2003). Folate reduced the number of small intestinal tumors in mice, although the timing of folate intervention was critical in preventive properties. In contrast, this effect was not found in colon (Song et al., 2000).

Folate deficiency has the potential to modulate DNA synthesis, DNA methylation, DNA damage and impaired DNA repair, increase mutagenesis, hyperproliferation, abnormal apoptosis, and methylenetetrahydrofolate reductase (MTHFR) polymorphisms and related gene-nutrient interactions (Prinz-Langenohl et al., 2001; Kim, 2003).

Under certain conditions, folate potentialy has an inverse effect on cancer prevention. In DNA polymerase β deficiency mice, folate deficiency provided protection against tumorigenesis, the induction of apoptosis, and the suppression of cell proliferation (Ventrella-Lucente et al., 2010)

2.4.2.3 Selenium and foods containing selenium

A meta-analysis of "a global perspective" produced a summary effect estimate of 0.86 (95% CI 0.78-0.95) per 10 μg/dl serum, with high heterogeneity (World Cancer Research Fund, 2007c). Dietary selenium deficiency has been reported to cause a lack of selenoprotein expression, and some of these selenoproteins play important roles in anti-inflammatory and antioxidant properties (Ganther, 1999).

Selenium-enriched broccoli reduced the number of small intestinal tumors in multiple intestinal neoplasia mice (Davis et al., 2002). In the study, selenium-enriched diet for 10 weeks significantly increased the plasma concentration of selenium, and reduced small intestinal (46.3 ± 3.7 vs 65.6 ± 6.1) and large intestin (0.43 ± 3.7 vs 1.93 ± 6.1) tumors than control diet.

Several mechanisms have been suggested for the cancer preventiion effect of selenium, including the induction of apoptosis, cell cycle modulation (inhibition of cdk2 and protein kinase C), and the activation of thioredoxin redactase (Combs, 2004).

2.4.2.4 Fish

A meta-analysis of "a global perspective" produced a summary effect estimate of 0.96 (95% CI 0.92-1.00) per serving/week. A high consumption of fish is associated with low consumption of meat (World Cancer Research Fund, 2007c).

Increasing salmon or cod consumption for 6 months resulted in a lower concentration of the systemic inflammation marker C-reactive protein (CRP), but showed no effect on the local

markers of inflammation in the colonic biopsies or feces, the genotoxicity markers in colonocyte, and apoptotic and mitotic rate in colonic mucosa (Pot et al., 2009; Pot et al., 2010a; Pot et al., 2010b).

An animal study showed that fish oil significantly reduced colon tumors (Rao et al., 2001). A diet including fish oil and pectin protects against colon cancer, compared with that of corn oil and cellulose azoxymethane, which induced colon cancer in model rats (Cho et al., 2011).

The preventive mechanisms of fish have been proposed to include the effects on gene expression, decreasing adhesion genes such as *B44galt1* at the initiation stage, lowering the expression of both cell promoters and suppressors at the aberrant crypt foci (ACF) stage, and increasing apoptosis inducing genes at the tumor stage. These modifications may be associated to the induction of apoptosis and the suppression of proliferation (Cho et al., 2011). Fish n-3 polyunsaturated fatty acids (PUFAs) may reduce eicosanoid biosynthesis derived from n-6 PUFA to protect tissue from inflammation, and inhibit COX-2 (Rao et al., 2001).

On the other hand, it has been reported that dietary fish oil containing docosahexaenoic acid (DHA) promotes inflammation through the modification of CD4+ and CD8+ T-cell populations in SMAD-/- mice and that chronic inflammation is the risk factor for colorectal cancer (Woodworth et al., 2010).

2.4.2.5 Foods containing vitamin D

A meta-analysis of "a global perspective" produced a summary effect estimate of 0.99 (95% CI 0.97-1.00) per 100 IU/day (World Cancer Research Fund, 2007c). Higher vitamin D levels are associated with a lower risk of colon cancer and overall mortality. UV exposure stimulates vitamin D production, but it may increase the risk of skin cancer. Therefore it is recommended that high-risk populations with a low level of vitamin D intake increase the consumption of fish, or take vitamin D supplements (Zeeb & Greinert, 2010).

Vitamin D induces differentiation, apoptosis and induces G1 phase arrest in intestinal cells. It also increases the absorption of calcium in the small and large intestine. Most of the pleiotropic, long-term actions of [1,25 $(OH)_2D_3$] are mediated by binding to vitamin D receptors (VDR), which are high-affinity receptors in the nucleus of cells. Activated VDR induces gene transcription, and VDR density in colonic mucosa was higher in hyperplastic polyps and in early stages of carcinogenesis, compared with normal mucosa (Lamprecht & Lipkin, 2001; Lamprecht & Lipkin, 2003; World Cancer Research Fund, 2007c).

2.4.3 Limited-non conclusive and others

There was not enough evidence for cancer prevention at the time of when "a grovel Perspective" was drawn up in 2007, so the following foods and nutrition were judged limited-non conclusive: Cereals (grains) and their products, potatoes, poultry, shellfish and other seafood, other dairy products, total fat, fatty acid, cholesterol, sugar (sucrose), coffee, tea, caffeine, total carbohydrate, starch, vitamin A, retinol, vitamin C, vitamin E, multivitamins, non-dairy sources of calcium, methionine, beta-carotene, alpha-carotene, lycopene, meal frequency, and energy intake.

Some of the latest research has demonstrated new knowledge, or confirmed the previous results.

2.4.3.1 Vitamins (except vitamin D)

A pooled analysis of cohort studies concluded that a high consumption of vitamin C and E from both food and supplements showed an inverse association with colon cancer risk, although there were some interactions with folate intake. Multivitamin intake also significantly decreases the risk of colon cancer. On the other hand, vitamin A, vitamin C, and vitamin E intake from food only were not associated with colon cancer risk (Park et al., 2010).

In the Caucasian race, a high intake of each anti-oxidant nutrient (vitamin C, vitamin E, β-carotene, selenium) and DNA methylation-related nutrients (folate, vitamin B6, vitamin B12) reduced the risk of distal colorectal cancer, and only selenium showed a lower risk in African Americans. In this study, both intake from food only and total intake (food and supplements) demonstrated cancer prevention potency (Williams et al., 2010).

In colorectal cancer patients, the level of vitamin A, vitamin C, and vitamin E were reduced, and urinary 8-oxo-dG, a biomarker of DNA oxidation, was elevated (Obtulowicz et al., 2010).

A high consumption of carotenoid did not reduce the risk of colorectal cancer, except for β-carotene intake among men, which showed an inverse association (relative risk 0.77, 95% CI 0.763-0.95). On the other hand, lycopene intake was significantly associated with an increase in the risk of rectal cancer among men (relative risk 1.50, 95% CI 1.04-2.16) (Park et al., 2009).

2.4.3.2 Other dietary factors

Avenanthraide (Avns) polyphenols from oats showed anti-proliferative effects independent of Cox-2 expression in COX-2 positive HT29, Caco-2 and LS174T cells, and COX-2 negative HCT116 cells. Avns may also reduce the colon cancer risk inhibiting PGE2 production derived from macrophage (Guo et al., 2010).

In animal studies, the oral administration of flavone (400mg/kg over 4 weeks) increased apoptosis and reduced the rate of aberrant crypt formation in mice. The down-regulation of the tricarboxylic acid cycle may be a part of the action mechanism (Winkelmann et al., 2010). In a human study, a case-control study of dietary flavonoid showed that flavonoid, especially quercetin, was significantly associated with a reduction in the colorectal cancer risk (Kyle et al., 2010).

In an SD rat study, Coenzyme Q10 reduced the number of APFs, possibly by modulating COX-2 and iNOS gene expression in colonic mucosa, and DNA damage in leukocytes (Kim & Park, 2010).

It has been reported that an increased consumption of n-3 fatty acid, Sulforaphane, Chafuroside, Curcumin and Dibenzoylmethane decreased the number of small intestinal tumors in *Apc*^{Min} mice. On the other hand, there are a few reports on colonic tumor that showed that 31 g/kg of steridonic acid or 600 ppm of sulforaphane demonstrated an inhibitory effect on colonic tumors in *Apc*^{Min} mice (Petrik et al., 2000; Shen et al., 2007).

2.5 The latest proposed action mechanisms

Various mechanisms, such as DNA repair, proapoptosis, cell cycle modification, immunity promotion, and the mediation of chemomediators, have been proposed as the effects of

foods and nutrition. Recently, the focus has been on the prebiotic and probiotic effects, insulin-like growth factor (IGF) regulation, and calorie restriction.

2.5.1 Prebiotic and probiotic effects

Feeding specific food products with a prebiotic effect have been reported to reduce the incidence of tumors and cancers (Roberfroid et al., 2010). There are 100 trillion microbial organisms, called the microbiota, in human adult gut (Davis & Milner, 2009). Carbohydrate and proteolytic fermentation are the two main types of anaerobic fermentation in the gastrointestinal tract (Davis & Milner, 2009, as cited in (McIntosh et al., 1999).

Prebiotics are non-digestible food ingredients which stimulate beneficial gut microbiota (Lim et al., 2005), e.g. inulin and other oligosaccharides, lactulose and resistant starch, such as fructooligosaccharides, inulin, lactulose and galactooligosaccharides (Tuohy et al., 2005). Probiotics are live bacteria found in processed foods or in dietary supplements, e.g. yogurt, cheese, fermented milks, juices, smoothies, cereal, and nutrition bars (Penner et al., 2005; Davis & Milner, 2009). Synbiotics are a combination of a probiotic with a prebiotic. A prebiotic can support the activity of a probiotic (Gibson & Roberfroid, 1995).

Prebiotics must survive acidic conditions in the stomach and resist digestion in the small intestine. Then they need to be selectively fermented, and stimulate beneficial bacteria, usually bifidobacteria or lactobacilli, in the colon (Tuohy et al., 2005). In the randomized, double-blind, placebo-controlled trial for 12 weeks, dietary synbiotics reduced colon cancer risk, through increasing *Bifidobacterium* and *Lactobacillus*, and decreasing *Clostridium perfringens* (Rafter et al., 2007).

A 4-year supplementation regime employing *Lactobacillus casei* decreased the recurrence of atypical colonic polyps (Ishikawa et al., 2005).

Several animal studies and human trials showed that prebiotics, probiotics and synbiotics reduced toxic metabolite production, like caecal β-glucuronidase, nitrate reductase activities and caecal pH, in the gut, resulting in the prevention of colorectal cancer. On the other hand, some human studies denied the beneficial effects of prebiotics (Tuohy et al., 2005).

An increased number of bifidobacteria and/or lactobacilli may also play an important role in DNA protective modification and chemically-induced DNA damage (Tuohy et al., 2005). An increased number of biofidobacteria and/or lactobacilli in the gut may suppress the number or activity of putative enteropathogens such as *Escherichia coli* and *Clostridium perfingens* (Reddy, 1999). Prebiotics may also stimulate protective enzyme activities within the intestinal mucosa or reduce the immune inflammatory response (Burns & Rowland, 2000).

Since prebiotics are mostly oligosaccharides, it is considered that they reduce blood glucose. Increasing glycosylated hemogloin (HbA1c), which is a biomarker of glucose control for diabetes, was associated with an increased risk of colorectal cancer in women (Chan & Giovannucci, 2010). However, the consumption of short-chain fructooligosaccharides did not have a significant affect on the glucose level in blood (Luo et al., 2000).

Transplantation of the gut microflora from normal mice into germ-free recipients resulted in increasing their body fat without increasing food consumption (Bajzer & Seeley, 2006). A 1-

year low calorie diet in obese people modified the proportion of gut microbes, increasing bacteroidestes and decreasing firmicutes, while obese people had fewer bacteroidetes and firmicutes, compared with a lean control group (Ley et al., 2006).

Supplementation employing a drink fortified with short-chain fructooligosaccharides and inulin (1.5 g/day) significantly increased the absorption of calcium in adolescent girls (Griffin et al., 2002). The consumption of oligosaccharides also improved the magnesium absorption in humans and animals (Coudray et al., 2003). An optimum well-tolerated dose of prebiotics might be 10 g/day and a high dose (e.g. > 20 g/day) of some prebiotics might have a laxation effect, such as stool frequency or stool weight (Bouhnik et al., 1999).

2.5.2 IGF regulation

IGF play important roles in proliferation, differentiation and transfomation in a variety of cell types, and thus it has been suggested that dysregulation of the IGF is an important cancer risk factor (Park, 2008).

A study on colon adenocarcinoma showed that n-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), increased IGFBP-6 in human colon adenocarcinoma Caco-2 cells, and the authors proposed that low IGF-II/IGFBP-6 ratios have resulted in less free IGF-II and a resulting slower proliferation of Caco-2 cells (Roynette et al., 2004). All-trans retinoic acid (tRA) showed an anti-proliferative effect in Caos-2 cells, and it was considered that this was due to a partly increased IGFBP-6 expression (Kim et al., 2002).

A low-calcemic vitamin D analogus decreased the secretion of IGF-II and suppressed HT-29 cell proliferation (Oh et al., 2001).

2.5.3 Calorie restriction

Calorie restriction in *Apc*^{Min} mice at the rate of 40% reduced the number of intestinal polyps by 57%, compared with mice fed ad libium. The serum levels of IGF-1 and leptin, and urinary corticosterone output were significantly reduced in the calorie restriction group, compared with that of the ad libium group. Supplementation of freeze-dried fruit and vegetable extract with a diet high in olive oil also reduced the number of polyps, even though this group had a calorie intake of about 90% of ad libium. The supplementation of fruit and vegetables significantly reduced the urinary corticosterone output levels, but did not show any effect on the serum levels of IGF-1 and leptin (Mai et al., 2003).

These results indicate that calorie restriction has a great potency for colon cancer prevention, and a diet in high fruit and vegetable without calorie restriction showed less, but still significant, intestinal tumorigenesis preventive effects.

Calorie restriction or increased exposure to n-3 fatty acid, sulforaphe, chafrroside, curcumin and dibenzoylmethane reduced the risk of colon cancer, while total fat, a diet high in calories and all-trans retinoic acid increased the risk (Tammariello & Milner, 2010).

However, even considering these interesting results, the frequency of colon polyps in the calorie restriction group and the fruit and vegetable group did not show any significant changes, compared with the ad libium group (van Kranen et al., 1998).

3. Conclusion

The contribution of diet in all cancer-related death estimates was 30-35% in the environmental factors, greater than tobacco, which was 25-30%. Colorectal cancer was strongly associated with diet, and linked to 70% of cancer related-deaths (Anand et al., 2008). Eating habits are the most important factor for colorectal cancer prevention, however, it is still difficult to specify how we should eat. It has been proposed that an increase in the consumption of fruit and vegetables and less intake of red and processed meat will comprise a better diet. However, it has not been proven yet how much of a respective increase and decrease is the best quantity, and which nutrients exactly play a key role in carcinogenesis and anti-carcinogenesis. Plenty of studies have been published on food components or nutrients to protect from carcinogenesis *in vitro*, describing the molecular action mechanisms involved. In human trials, individual nutrients, such as supplements, often showed no or less intended function, while nutrients contained in food functioned as expected. Accordingly, the judgement from a global perspective concluded that it was not appropriate to recommend the usage of supplements for cancer prevention at the present (World Cancer Research Fund, 2007d). The ideal diet for cancer prevention may be a well-balanced diet, and no one food or ingredient should be considered a miracle food. Further studies are required to elucidate precisely the disposition and safety of nutrients and the interaction of each nutrient.

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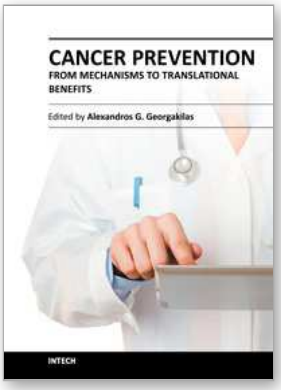

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This unique synthesis of chapters from top experts in their fields targets the unique and significant area of cancer prevention for different types of cancers. Perspective readers are invited to go through novel ideas and current developments in the field of molecular mechanisms for cancer prevention, epidemiological studies, antioxidant therapies and diets, as well as clinical aspects and new advances in prognosis and avoidance of cancer. The primary target audience for the book includes PhD students, researchers, biologists, medical doctors and professionals who are interested in mechanistic studies on cancer prevention and translational benefits for optimized cancer treatment.

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