11. DIETARY PREVENTION OF COLORECTAL CANCER

Comprehensive summary of results and discussion

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Introduction

In the developed countries colorectal cancer is the second most common malignancy in both sexes and although it is widespread in the world rather universally, there is a higher incidence of this cancer in prosperous industrialized countries, such as North America or Europe and lower in South America, Southeast Asia or Africa (1, 2). The data on the overall anatomical distribution of colorectal tumours show that about one third is in the rectum, one third in left colon, about 20% in right colon and 10% in transverse colon and flexures (3). In western European and US data, tumours of the right colon are more prevalent among women and it partly results from the fact that right-sided tumours are more common in older persons among whom there is a greater number of women than men.

The gradual change of colorectal cancer incidence over generations in the Japanese that migrated to the USA has clearly pointed to the overwhelming impact of environmental factors in colorectal cancer etiology (4). Since long causes of colorectal cancer have been linked to lifestyle and choices of particular dietary habits (5, 6). Many correlation studies have established an inverse association between a greater intake of vegetables, fruits and cereals and colorectal cancer occurrence. Although the studies do not provide a strong evidence for causal relationship, it is generally believed that 60% to 80% of colorectal cancer in the industrialized countries may be linked to dietary preferences. A survey of epidemiologic case-control studies that investigated the relationship between colorectal cancer and diet confirmed a significant protective effect of fruits and vegetables against different types of cancers (7–9). It has been estimated that the risk of colorectal cancer was twice as high in persons, who consumed low amounts of fruits and vegetables. However, recent pooled analysis of fourteen epidemiologic cohort studies has not confirmed strong correlation between fruit and vegetables consumption and the overall risk of colon cancer but pointed to the association with a lower risk of distal colon cancer (10).

Despite the assumption that diet may have a major role in cancer, up to now the studies failed to identify the specific dietary components causally involved in colorectal cancer etiology. Beneficial properties of fiber of vegetable sources were documented in

many case-control studies (11–14), however, it may be also true that high consumption of saturated fats and animal proteins coupled with low fiber intake might play a role in colon cancer etiology (15). It is understood that fiber action on the colon epithelium may imply several mechanisms such as alteration of intestinal transit time, dilution of fecal bolus/colonic contents, physical or chemical adherence to mutagenic agents combined with resultant effects in forming products of bacterial fermentation such as short – chain fatty acids (SCFA), and changes of the luminal pH (16). An increased production of SCFA in the course of bacterial fermentation may also have an important role in colon metabolic processes. As low intake of fiber with food reduces intestinal transit time and increases the concentration of carcinogenic agents in colon contents, the colonic mucosa remains in a longer contact with harmful and carcinogenic agents. Among such agents, fatty acids metabolites (bile salts), the products of the metabolism of animal fat and protein, may change colonic epithelium and give rise to neoplasic colon cells.

Red meat (beef, lamb, pork) and processed meats (sausage, hamburger, ham and bacon) and refined carbohydrates are also high on the list of suspected food products that may play a role in colon cancer etiology (17). It has been postulated that the increased risk of colon cancer due to high red meat consumption probably results from the greater production of bile acids and formation of carcinogenic agents or other toxic compounds possibly inducing the proliferation of colonocytes. It was estimated that daily increase of 100 grams of meat was associated with a 14% increase in colon cancer risk, however, a daily increase of 25 grams of processed meat was associated with a 49% greater risk.

Higher levels of physical activity are also associated with reduced colon cancer risk (18). Overweight and obesity may increase the risk and 10% of colon cancers in both sexes may be attributable to this (19). Some recent studies also suggest that tobacco smoking elevates the risk of colorectal cancer (20, 21). Relative risks for long-terms smokers, compared with those who have never smoked, are in the range 1.5–3.0. However, the findings are not confirmed by other studies.

A major role of the phytochemicals in protection against oxidation stress in colorectal cancer was assumed by many studies. Human body is constantly exposed to a variety of oxidizing agents, and many metabolism processes may also lead to the formation of oxidants. For optimal physiological and metabolism processes it is very important that the levels of oxidants and antioxidants in human bodies remained in equilibrium. Overload of human body with oxidants may cause an imbalance and subsequently lead to oxidative damage of large biomolecules such as lipids, DNA, and proteins (22).

There is an evidence that the potentially cancer-inducing oxidative damage might be prevented or restricted largely by the presence of dietary antioxidants of plant origin such as fruits or vegetables. Protective antioxidant effect of fruits and vegetables is thought to be attributed to phytochemicals, which are the nonnutrient plant compounds as the carotenoids, flavonoids, isoflavonoids, and phenolic acids. (23–24).Many phytochemicals present in various food products, have been found to possess also other biochemical properties, which are important in protecting against cancer. It was demonstrated that phytochemicals might inhibit cancer cell proliferation, regulate inflammatory and immune response, and protect against lipid oxidation (25–27).

Several commonly consumed foods and beverages, including cranberries, apples and onions, but also tea, wine and cocoa, have been considered as particularly beneficial

dietary components due to their high content of antioxidants. A major class of phytochemicals found commonly in fruits and vegetables are the flavonoids that belong to polyphenolic compounds and occur naturally in various foods and beverages of plant origin. Flavonoids are categorized into subgroups, such as flavonols and flavones. Flavonols among others include quercetin, myricetin and kaempferol, which are present in various common fruits, vegetables, and beverages. Flavones include compounds such as apigenin and luteolin, which are found in parsley and thyme. Because of the differences in their chemical structures, flavonoid compounds may have different effects on human health. The flavonoid compounds have been demonstrated *in vitro* to inhibit colon cancer cell proliferation, possibly due to the involvement in reducing mRNA levels of tumor-promoting enzymes such as cyclooxygenase-2. It is important that many flavonoids act also as antioxidants, because they scavenge free radicals.

It is estimated that apples are very rich source of flavonoids (28–30) and if compared to many other commonly consumed fruits, apples have the second highest level of antioxidant power (Fig. 11.1). Apples are also ranked as the second for total concentration of phenolic compounds, and more importantly, apples had the highest content of free phenolics in comparison to other fruits. It means that these substances are not bound to other chemical compounds present in the fruits, and therefore the phenolics are more easily absorbed into the bloodstream. Interestingly, it has been shown that apple peels have a stronger antioxidant activity than apple flesh and apple peels alone inhibited the growth and cell proliferation of liver cancer and colon cancer cells more significantly than whole apples (31, 32). The total antioxidant activity of apples with the peel has approximately 83 µmol vitamin C equivalents, which means that the antioxidant activity of 100 g apples (about one serving of apple) is equivalent to about 1500 mg of vitamin C. However, the content of vitamin C in 100 g of apples is only about 5.7 mg (32). Although vitamin C is a powerful antioxidant, the major part the antioxidant activity attributed to apples comes from other compounds present in apples and it is believed that vitamin C present in apples contributed to less than 0.4% of total antioxidant activity attributed to apples.

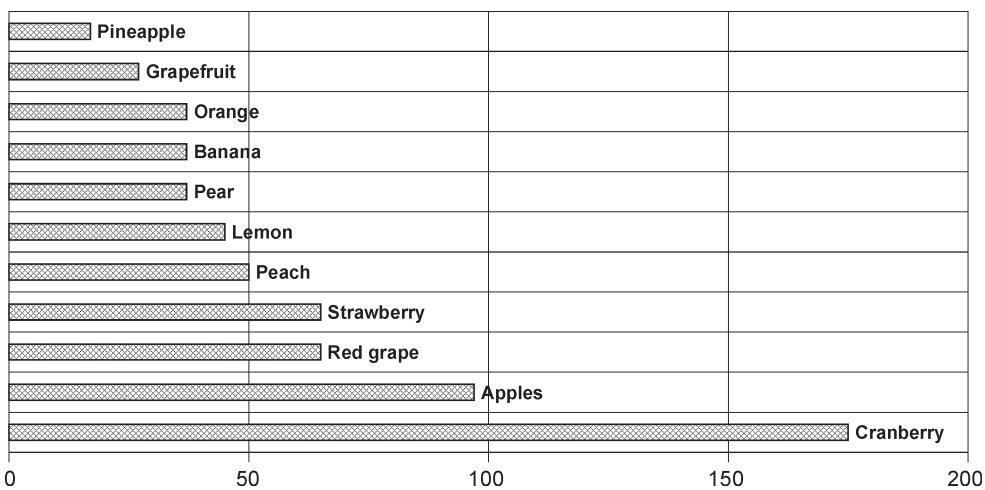

Figure 11.1. Total antoxidant acivity (µmol vitamin C equivalents/g fruits), modified from Boyer J, Liu RH. Apple phytochemicals and their health benefits. *Nutrition Journal* 2004; 25

The concentration of the phytochemicals in apples depends not only on cultivars of the apple, its storage or processing procedures. The most well recognized antioxidant compounds in apples include quercetin-3-galactoside, quercetin-3-glucoside, quercetin-3-rhamnoside, catechin, epicatechin, procyanidin, cyanidin-3-galactoside, coumaric acid, chlorogenic acid, gallic acid, and phloridzin. The compounds most commonly found in apple peels consist of the procyanidins, catechin, epicatechin, chlorogenic acid, phloridzin, and the quercetin conjugates (Fig. 11.2). In the apple flesh, there is also catechin, procyanidin, epicatechin, and phloridzin, but these compounds occur in much lower concentrations in comparison with that observed in peels. Because the apple peels contain more antioxidant compounds, especially quercetin, apple peels show much higher antioxidant activity than the apple flesh. Recent research has shown that apple peels contain from two to six times (depending on the variety) more phenolic compounds than in the flesh, and two to three times more flavonoids in the peels when compared to the flesh. Accordingly, the antioxidant activity of the peels was also much greater, ranging from two to six times greater in the peels when compared to the flesh, depending on the variety of the apple (31). It was documented that apples with the peels were better inhibitor of cancer cell proliferation when compared to apples without the peels (32). Experiments done on rats consuming apple peels showed greater inhibition of lipid peroxidation and greater plasma antioxidant capacity when compared to rats fed with apple flesh.

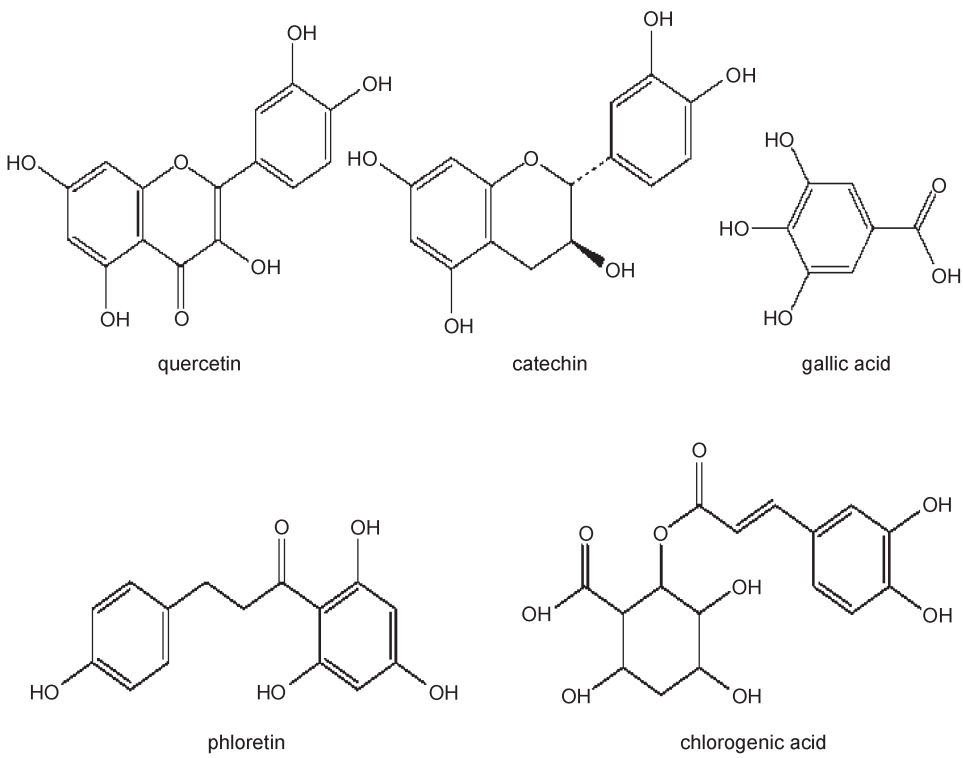

Figure 11.2. Chemical structures of selected apple antioxidants

Many research performed *in vitro* and in animal experiments showed that potential health benefits from apples may be attributed to specific phytochemicals. For example, the procyanidins, epicatechin and catechin, have been found to inhibit low density lipoprotein (LDL) oxidation *in vitro* (33). In mice, catechin inhibits intestinal tumor formation and delays tumors onset (34). Quercetin is also a strong antioxidant, and is thought to have potential protective effects against both cancer and heart disease. Quercetin has been found to down regulate expression of mutant p53 in breast cancer cells, arrest human leukemic T-cells. In mice liver treated with ethanol, quercetin decreased lipid oxidation and increased glutathione, protecting the liver from oxidative damage. Recently, it has been found that high doses of quercetin inhibit cell proliferation in colon carcinoma cell lines and in mammary adenocarcinoma cell lines. Low doses of quercetin inhibited cell proliferation of Human Leukemia cells, induced apoptosis inhibited platelet aggregation, calcium mobilization, and tyrosine protein phosphorylation in platelets (35–37).

Bioavailability of phytochemicals is important issue for understanding of the beneficial effect of phytochemicals on human health. Up to now, there is a scarcity of data on the bioavailability of phytochemicals from the apple. One of the few studies addressing bioavailability of apple products assessed the bioavailability of polyphenolic compounds from alcoholic apple cider in volunteers. After drinking 1.1 liters of apple cider, no quercetin was found in the volunteers' plasma but low levels of 3'-methyl quercetin and 4'-methyl quercetin were seen after 60 minutes following consumption. Caffeic acid was rapidly absorbed, but within 90 minutes the caffeic levels in the plasma were undetectable. Catechin, epicatechin, and phlorizin were not seen in the plasma, possibly because the concentration in the cider was too low. Hippuric acid and phloretin were both increased in the subjects' urine following the consumption of the cider, but there was no evidence of quercetin, catechin, or epicatechin in the urine (38). In another study involving human subjects, quercetin bioavailability from apples was only 30% of the bioavailability of quercetin from onions (39). In this latter study, quercetin levels reached a peak after 2.5 hours in the plasma. The differences in bioavailability of flavonoids between apples and onions most likely result from the differences in quercetin conjugates in various foods. Onions contain more quercetin aglycone and more quercetin glucosides, whereas apples tend to contain more quercetin monogly cosides and quercetin rutinoside, which may be less bioavailable.

Some bacterial degradation of quercetin conjugates most likely occurs in the human intestinal tract. Both *Enterococcus casseliflavis* and *Eubacterium ramulus*, microorganisms isolated from human feces, were found to degrade quercetin-3-glucoside as a carbon and energy source. *Enterococcus casseliflavis* utilized only the sugar moiety of the glucoside, whereas *Eubacterium ramulus* was also capable of degrading the aromatic ring system with phloroglucinol produced as an intermediate (40).

The genetic traits of colon cancer have aroused interest in recent years as a result of developments in genetics and molecular biology. The genetic alterations that lead to CoReCa may either be acquired (generating the so-called sporadic cancer) or hereditary. During this process, the increase of genetic alterations is necessary and mutations in at least 4 or 5 genes are needed for the development of a malignant tumor. It is assumed that the great majority (75 to 85%) of patients have sporadic CoReCa, exhibiting no evidence of a genetically inherited disease in which the risk of developing CoReCa is high.

Nowadays it is well recognized that a complex interaction between individual genetic features and environmental factors, especially diet, is involved in the etiology of colon cancer (41).

Based on the animal and human studies, it appears that apples, which are rich in flavonoids may play an important role in reducing the risk of a wide variety of chronic diseases and maintaining good general health. Apples were most consistently associated with reduced risk of various cancers (42–45), cardiovascular diseases (46–50), asthma (51), and chronic obstructive pulmonary disease (52) when compared to other fruits and vegetables or other sources of flavonoids. Apple consumption was also positively associated with better lung function (53) and increased weight loss (54).

A case-control study from Uruguay found an inverse relationship between apple consumption and colorectal cancer (55). It was followed by the very recent reanalysis of several case-control studies in Italy, which demonstrated a consistent inverse association between apple consumption and risk of various cancers, and among them of colorectal cancer (56).

Epidemiologic evidence supporting the health benefits from fruits and apples encouraged us to assess the potential protective impact of apples on the risk of colorectal cancer in the course of the recently completed hospital based case-control study in the country with dietary habits very different from that of Mediterranean region. Earlier results of our study presented in the first part of the monograph documented the distribution of cases and controls according to basic demographic variables. Cases consisted in greater proportion of males and older patients (> 50 years). Greater proportion of cases than controls were born in rural areas, had lower education level and was residents of villages or small towns. Now, we will present the detailed multivariable statistical analysis of the group effect of dietary elements and its specific importance for the occurrence of colorectal cancer.

Summary results of Krakow case-control study

Fruits

In total, mean number of fruit servings reported was 2.3 per day and was lower by about 27% in cases than in controls (Table 11.1). In total, mean amount of fruits consumed was 77.2 g/day and was lower by about 11% in cases compared with controls (Table 11.2). Consumption of specific fruits was consistently lower in cases than in controls. Apples were most frequent fruit consumed in the study subjects and about 80% of variability in the total fruit consumption resulted from intake of apples. Hence, only 20% variability in consumption of total fruits was explained by intake of berries, stone fruits and citruses. As expected, there was the significant correlation between reported number of servings and amount of fruits consumed daily by both controls and cases (Fig. 11.3).

Although mean number of fruit servings such as apples, stone fruits, citrus and berries reported by cases was lower than in controls but the nonparametric trend (for ranks) was statistically significant in univariable analysis only for total intake of fruits ($z = -3.13$, p for trend = 0.002) and apples ($z = -3.36$, p for trend = 0.003) (Table 11.3). Statistical analysis performed with multivariable logistic regression model provided adjusted risk

estimates (ORs) for the number of fruit servings consumed daily (Table 11.4a). It does show that OR of colorectal cancer inversely and significantly correlated with the number of fruit servings (OR = 0.90; 95% CI: 0.84–0.95). Percent change of the risk estimates in terms of an increase in predictor variables by one unit or by one SD unit was presented in Table 11.4b. It tells that the increase in fruit servings by one unit leads to lower risk estimates by about 10%. Predicted probability of cases related to fruit intake (number of daily servings is presented in Figure 11.4.

Table 11.1. Frequency of fruit servings consumed daily by controls and cases

	Fruits total	Berries	Citrus	Stone fruits	Apples
Controls (N = 745)					
Mean	2.6	0.6	0.3	0.3	1.2
Percentile 25	0.8	0.05	0.02	0.01	0.3
Median	1.6	0.2	0.1	0.01	0.7
Percentile 75	3.4	0.8	0.3	0.3	1.5
Cases (N = 584)					
Mean	1.9	0.4	0.2	0.2	0.9
Percentile 25	0.8	0.07	0.04	0.16	2.5
Median	1.4	0.2	0.1	0.08	0.7
Percentile 75	2.5	0.6	0.3	0.22	1.0
Total (1329)					
Mean	2.3	0.6	0.2	0.3	1.0
Percentile 25	0.8	0.01	0.02	0.02	0.3
Median	1.5	0.2	0.1	0.08	0.7
Percentile 75	3.0	0.7	0.3	0.3	1.1

Table 11.2. Amount of fruits (g/day) consumed by controls and cases

	Fruits total	Berries	Citrus	Stone fruits	Apples
Controls (N = 745)					
Mean	81.3	15.9	5.6	11.2	39.7
Percentile 25	32.7	2.0	0.6	0.6	11.5
Median	54.2	8.3	3.1	5.4	25.7
Percentile 75	107.2	22.5	6.7	12.4	46.8
Cases (N = 584)					
Mean	72.0	14.5	5.7	9.6	34.3
Percentile 25	33.3	3.6	1.0	0.9	9.9
Median	49.9	8.3	3.4	5.3	23.7
Percentile 75	94.4	18.0	7.3	11.1	43.3
Total (N = 1329)					
Mean	77.2	15.3	5.6	10.5	37.3
Percentile 25	33.2	2.8	0.73	0.8	11.0
Median	51.9	8.3	3.2	5.4	24.8
Percentile 75	100.9	20.7	7.1	12.0	46.0

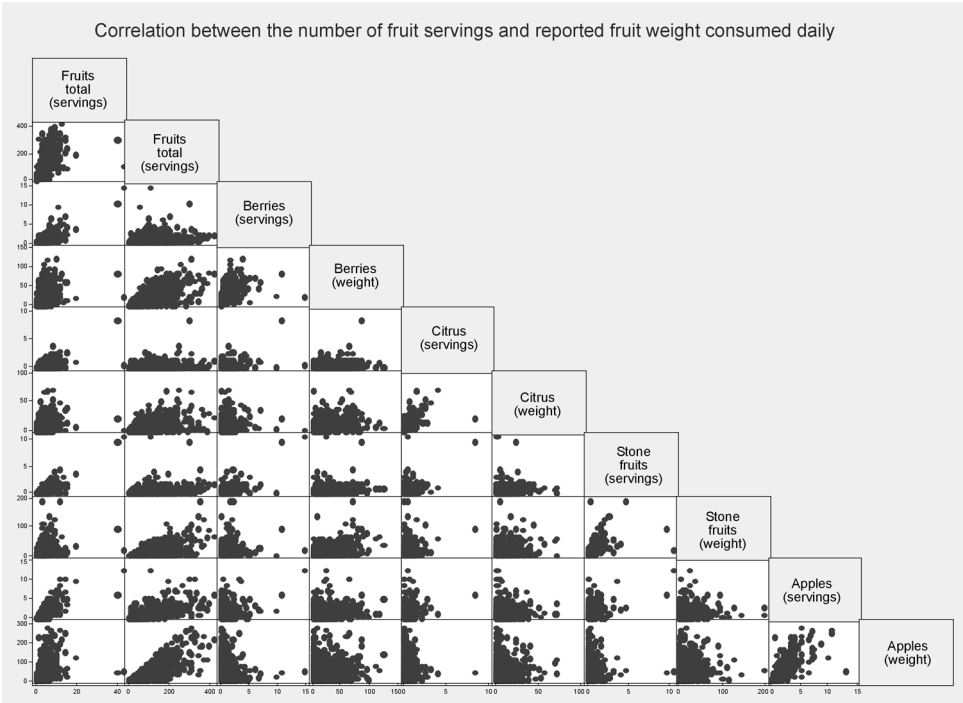

Figure 11.3. Correlation between amount of fruits consumption (g/day) and the number of daily servings

Table 11.3. Nonparametric Wilcoxon test for the number of fruit servings in controls and cases

Variables	obs	Sum of ranks	Significance level
Fruits total	745	517556.5	z = –3.13
Controls	585	367558.5	Prob > |z| = 0.002
Cases			
Berries	745	499911.5	z = –0.59
Controls	585	385203.5	Prob z = 0.88
Cases			
Citrus			
Controls	745	489699	z = 0.88
Cases	585	395416	Prob > |z| = 0.379
Stone fruits			
Controls	745	500126.5	z = –0.63
Cases	585	384988.5	Prob > |z| = 0.532
Other fruits (including apples)			
Controls	745	519137.5	z = –3.36
Cases	585	365977.5	Prob > |z| = 0.001
Only Apples			
Controls	745	516626	z = –3.00
Cases	585	368489	Prob > |z| = 0.003

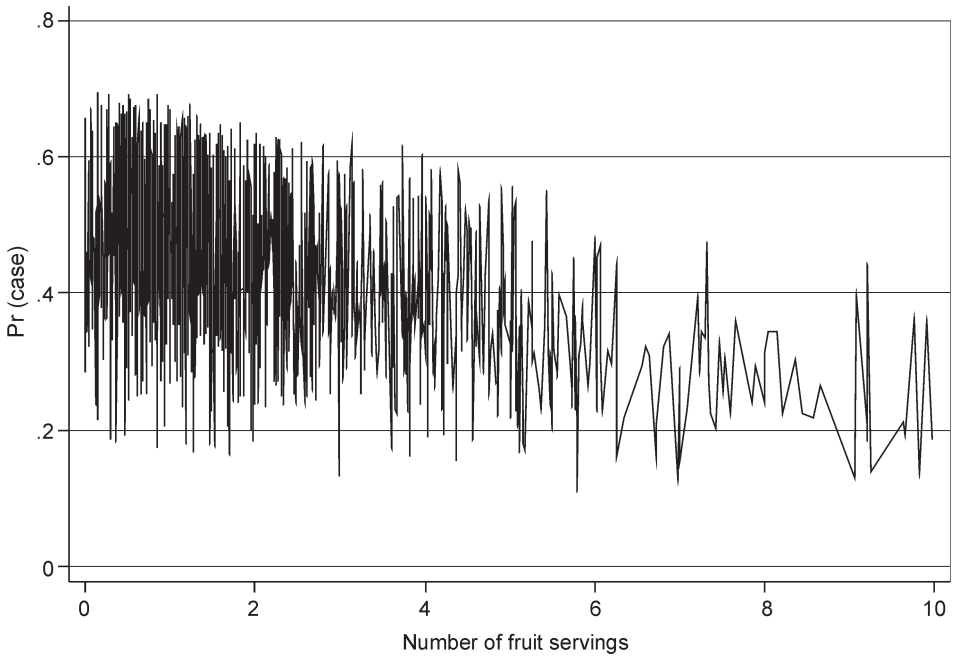

Figure 11.4. Predicted ORs of colorectal cancer related to daily intake of fruits

Table 11.4a. Estimated risk (OR) of colorectal cancer related to the amount of total fruits consumed (number of daily servings) adjusted for potential confounders

Predictors	**Odds Ratio**	**Std. Err.**	**z**	**P > z**	**[95% Conf. Interval]**	
Age (years)	1.02	0.01	3.25	0.001	1.01	1.03
Gender	0.90	0.12	–0.83	0.406	0.69	1.16
Marital status	0.55	0.08	–4.01	0.000	0.42	0.74
Residence	1.85	0.22	5.28	0.000	1.47	2.33
Smoking status	1.09	0.08	1.13	0.259	0.94	1.25
BMI (tertiles)	1.04	0.07	0.48	0.631	0.90	1.19
Energy intake (tertiles)	0.93	0.08	–0.85	0.393	0.80	1.09
Fruits total (number of daily servings)	0.90	0.03	–3.74	0.000	0.84	0.95

Table 11.4b. Percent change in odds for change in predictor variables (X) related to the amount of total fruits consumed (number of daily servings) and other potential risk factors

Predictors	Raw coefficient	z-score for test of b = 0	P value for z-test	Percent change in odds for unit increase in X	Percent change in odds for SD increase in X	Standard deviation of X
Age (years)	0.02	3.25	0.001	1.9	21.9	10.6
Gender	–0.11	–0.83	0.406	–10.3	–5.3	0.5
Marital status	–0.59	–4.01	0.000	–44.5	–21.8	0.4
Residence	0.62	5.28	0.000	85.2	35.6	0.5
Smoking status	0.08	1.13	0.259	8.5	7.2	0.8
BMI (tertiles)	0.04	0.48	0.631	3.5	2.9	0.8
Energy intake (tertiles)	–0.07	–0.85	0.393	–6.6	–5.4	0.8
Fruits, total (number of daily servings)	–0.11	–3.74	0.000	–10.5	–25.9	2.7

Tables 11.5 and 11.6 present the adjusted estimates of colorectal cancer risk in quartiles of apple consumption. The results supported earlier findings that reflected consistently reduced risk estimates of colorectal cancer with daily amount of apples consumed in g/day (Table 11.5) and those for the number of daily apple servings (Table 11.6). It is important to mention, however, that the significant reduction of OR estimates was only observed for higher intake of apples. The adjusted OR of colorectal cancer was lowest at the consumption of more than 46 g of apples per day (OR = 0.71; 95% CI: 0.52–0.98) and one or more servings daily (OR = 0.61; 95% CI: 0.43–85.3). Predicted probability of cases related to intake of apples (g/day) is presented in Figure 11.5.

Table 11.5. Estimated risk (OR) of colorectal cancer related to the amount of apple consumed daily (g/day in quartiles) adjusted for potential confounders

Predictors	Odds Ratio	Std. Err.	z	P > z	[95% Conf. Interval]	
Age (years)	1.02	0.01	3.55	0.000	1.01	1.03
Marital status	0.55	0.08	–4.14	0.000	0.42	0.73
Residence	1.94	0.22	5.75	0.000	1.55	2.44
Smoking status	1.05	0.04	1.23	0.218	0.97	1.13
BMI (tertiles)	1.02	0.07	0.30	0.762	0.89	1.17
Energy intake (tertiles)	0.91	0.07	–1.29	0.197	0.78	1.05
Apples (quartiles)						
Q1 < 10.9 g/day	1.00					
Q2 (10.9–24.8 g/day)	0.88	0.14	–0.79	0.428	0.64	1.21
Q3 (24.9–46.0 g/day)	0.79	0.13	–1.48	0.139	0.58	1.08
Q4 (> 46.0 g/day)	0.71	0.12	–2.05	0.004	0.52	0.98

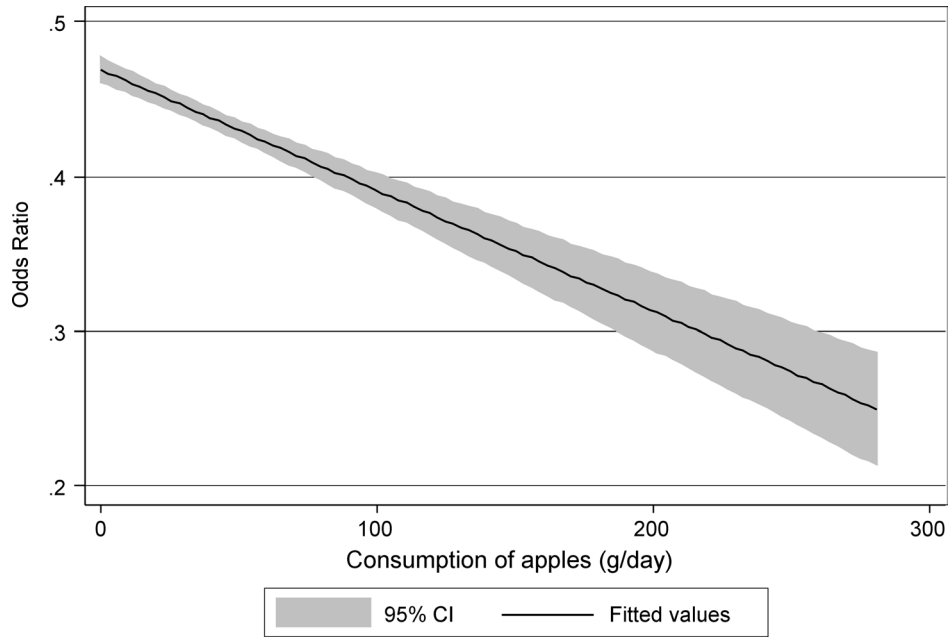

Figure 11.5. Predicted ORs of colorectal cancer related to the consumption of apples (g/day)

Table 11.6. Estimated risk (OR) of colorectal cancer related to the number of apple servings consumed daily (in quartiles) adjusted for potential confounders

Predictors	**Odds Ratio**	**Std. Err.**	**z**	**P > z**	**[95% Conf. Interval]**	
Age (years)	1.02	0.01	3.20	0.001	1.01	1.03
Marital status	0.55	0.08	–4.06	0.000	0.42	0.74
Residence	1.90	0.22	5.51	0.000	1.51	2.40
Smoking	1.06	0.04	1.40	0.161	0.98	1.14
BMI (tertiles)	1.04	0.08	0.61	0.544	0.91	1.20
Energy intake (tertiles)	0.91	0.07	–1.29	0.197	0.78	1.05
Apple servings/day in quartiles						
Q1 (< 0.25) servings/day	1.00					
Q2 (0.26–0.68) servings/day	1.00	0.16	0.02	0.987	0.73	1.37
Q3 (0.69–1.08) servings/day	1.01	0.16	0.04	0.972	0.73	1.38
Q4 (> 1.08) servings/day	0.61	0.11	–2.87	0.004	0.43	0.85
Vegetables servings (quartiles)	0.99	0.079	–0.11	0.910	0.85	1.16

Additional statistical analysis performed for the number of daily fruit servings (tables 11.7a and 11.7b) revealed that percent change of the OR estimates with the increase of apple intake by one unit, decreased the risk estimates by about 20%. All statistical models considered the set of potential confounding variables such as demographic characteristics of subjects (age, gender, place of residency, marital status smoking habit, BMI (in tertiles), total energy intake (in tertiles) and in addition the total intake of vegetables (daily number of servings).

Table 11.7a. Estimated risk (OR) of colorectal cancer related to the amount of apple consumed (number of daily servings) adjusted for potential confounders

Predictors	Odds Ratio	Std. Err.	z	P > z	[95% Conf.	Interval]
Age (years)	1.02	0.01	3.22	0.001	1.01	1.03
Gender	0.88	0.11	–0.99	0.324	0.68	1.14
Marital status	0.55	0.08	–4.02	0.000	0.42	0.74
Residence	1.90	0.22	5.50	0.000	1.51	2.39
Smoking status	1.09	0.08	1.23	0.219	0.95	1.26
BMI (tertiles)	1.05	0.08	0.67	0.504	0.91	1.21
Energy intake (tertiles)	0.90	0.07	–1.42	0.157	0.77	1.04
Apple servings daily	0.81	0.04	–3.85	0.000	0.73	0.90

Table 11.7b. Percentage change in Odds for change in predictor variables (X) related to the amount of apples consumed (number of daily servings) and other potential risk factors

Predictors	Raw coef-ficient	z-score for test of b = 0	P value for z-test	Percent change in odds for unit increase in X	Percent change in odds for SD increase in X	Standard deviation of X
Age (years)	0.02	3.22	0.001	1.9	21.7	10.6
Gender	–0.13	–0.99	0.324	–12.1	–6.2	0.5
Marital status	–0.59	–4.02	0.000	–44.7	–21.9	0.4
Residence	0.64	5.50	0.000	90.0	37.3	0.5
Smoking status	0.09	1.23	0.219	9.3	7.9	0.9
BMI (tertiles)	0.05	0.67	0.504	4.9	4.0	0.8
Energy intake (tertiles)	–0.11	–1.42	0.157	–10.4	–8.6	0.8
Apple servings daily	–0.21	–3.86	0.000	–19.1	–23.2	1.3

In the subsequent nested logistic multivariable models (Table 11.8) we were able to show that except apples, no other fruits recorded were significantly associated with the risk of colorectal cancer. Summary statistics of the latter analysis has shown that only the consumption of apples significantly contributed to explaining the occurrence of cases ($Chi^2 = 17.76$, $p < 0.0001$) and the effect of other fruits was of border significance. Out of all demographic variables considered in the statistical models, the higher risk of colorectal cancer was observed among older persons ($Chi^2 = 11.15$, $p = 0.0008$), residents of villages or small towns ($Chi^2 = 38.03$, $p = 0.0000$) and married persons ($Chi^2 = 17.12$, $p < 0.0001$).

Table 11.8. Estimated risk of colorectal cancer related to dietary factors (number of various fruit servings daily in tertiles) adjusted for confounders. The nested (hierarchical) logistic regression

Case	Odds Ratio	Std. Err.	z	P > z	[95% Conf.	Interval]
Block 1 (Apples)						
Apples	0.80	0.042	–4.21	0.000	0.73	0.89
Block 2 (Apples, stone fruits)						
Apples	0.83	0.05	–3.34	0.001	0.75	0.93
Stone fruits	0.77	0.12	–1.74	0.083	0.57	1.04
Block 3 (Apples, stone fruits, citrus)						
Apples	0.83	0.05	–3.38	0.001	0.74	0.92
Stone fruits	0.74	0.12	–1.83	0.068	0.54	1.02
Citrus	1.11	0.19	0.58	0.565	0.79	1.55
Block 4 (Apples, stone fruits, citrus, berries)						
Apples	0.84	0.05	–3.11	0.002	0.75	0.94
Stone fruits	0.87	0.16	–0.76	0.445	0.61	1.24
Citrus	1.20	0.21	1.01	0.310	0.85	1.70
Berries	0.83	0.08	–1.91	0.056	0.69	1.01
Block 5 (Apples, stone fruits, citrus, berries, age)						
Apples	0.84	0.05	–3.20	0.001	0.75	0.93
Stone fruits	0.86	0.16	–0.84	0.398	0.60	1.22
Citrus	1.23	0.22	1.15	0.251	0.87	1.74
Berries	0.84	0.08	–1.81	0.071	0.70	1.02
Age	1.02	0.01	3.34	0.001	1.01	1.03
Block 6 (Apples, stone fruits, citrus, berries, age, residence)						
Apples	0.83	0.05	–3.20	0.001	0.74	0.93
Stone fruits	0.81	0.15	–1.16	0.248	0.57	1.16
Citrus	1.37	0.25	1.75	0.081	0.96	1.95
Berries	0.87	0.085	–1.39	0.165	0.72	1.06
Age	1.02	0.01	3.65	0.000	1.01	1.03
Residence	2.05	0.24	6.17	0.000	1.63	2.57
Block 7 (Apples, stone fruits, citrus, berries, age, residence, marital status)						
Apples	0.83	0.05	–3.21	0.001	0.74	0.93
Stone fruits	0.81	0.15	–1.15	0.249	0.57	1.16
Citrus	1.36	0.25	1.70	0.088	0.95	1.95
Berries	0.87	0.09	–1.41	0.159	0.72	1.06
Age	1.02	0.01	3.87	0.000	1.01	1.03
Residence	1.93	0.23	5.60	0.000	1.53	2.43
Marital status	0.55	0.08	–4.14	0.000	0.42	0.73

Summary statistics

Block	Chi²	Df	Pr > F
1. (Apples)	17.76	1	0.0000
2. (Apples, stone fruits)	3.01	1	0.0826
3. (Apples, stone fruits, citrus)	0.33	1	0.5652
4. (Apples, stone fruits, citrus, berries)	3.64	1	0.0563
5. (Apples, stone fruits, citrus, berries, age)	11.15	1	0.0008
6. (Apples, stone fruits, citrus, berries, age, residence)	38.03	1	0.0000
7. (Apples, stone fruits, citrus, berries, age, residence, marital status)	17.12	1	0.0000

To reach a deeper understanding of the interrelationship between consumption of fruits and vegetables, the additional nested logistic multivariable regression model was performed, which accounted for both variables together (fruits and vegetables) with other potential risk factors (Table 11.9). The results of the latter analysis clearly indicated that the potential effect of vegetable intake was insignificant after simultaneous controlling for fruit intake. Interestingly, the effect of cigarette smoke on the occurrence of colorectal cancer was confirmed only in persons with the low intake of fruits (Table 11.10).

Table 11.9. Estimated risk of colorectal cancer related to dietary factors (number of fruit and vegetable servings daily in tertiles) adjusted for confounders. The nested (hierarchical) logistic regression

Predictors	Odds Ratio	Std. Err.	z	P > z	[95% Conf. Interval]	
Block 1 (Fruits)						
Fruits	0.80	0.05	–3.28	0.001	0.70	0.91
Block 2 (Fruits and vegetables)						
Fruits	0.82	0.06	–2.62	0.009	0.71	0.95
Vegetables	0.95	0.07	–0.68	0.499	0.82	1.10
Block 3 (Fruits, vegetables and age)						
Fruits	0.80	0.06	–2.87	0.004	0.69	0.93
Vegetables	0.98	0.08	–0.26	0.798	0.84	1.14
Age (years)	1.02	0.01	3.31	0.001	1.01	1.03
Block 4 (Fruits, vegetables, age and place of residence)						
Fruits	0.81	0.06	–2.65	0.008	0.70	0.95
Vegetables	1.00	0.79	0.03	0.976	0.86	1.17
Age (years)	1.02	0.01	3.60	0.000	1.01	1.03
Residence	2.02	0.23	6.15	0.000	1.62	2.53
Block 5 (Fruits, vegetables, age, place of residence and marital status)						
Fruits	0.82	0.06	–2.54	0.011	0.70	0.96
Vegetables	0.98	0.08	–0.32	0.749	0.84	1.14
Age (years)	1.02	0.01	3.79	0.000	1.01	1.03
Residence	1.91	0.23	5.58	0.000	1.52	2.39
Marital status	0.55	0.08	–4.13	0.000	0.42	0.73

Summary statistics

Block	Chi²	Df	Pr > F
1. (Fruits)	10.74	1	0.001
2. (Fruits, vegetables)	0.46	1	0.499
3. (Fruits, vegetables and age)	10.93	1	0.001
4. (Fruits, vegetables, age and place of residence)	17.88	1	0.000
5. (Fruits, vegetables, age, place of residence and marital status)	17.02	1	0.000

Table 11.10. Estimated risk (OR) of colorectal cancer related to cigarette smoking status adjusted for potential confounders (by strata of fruit consumption)

Predictors	Odds Ratio	Std. Err.	z	P > z	[95% Conf.	Interval]
A. One or more fruit servings a day						
Age (years)	1.01	0.01	1.58	0.114	1.00	1.03
Gender	1.01	0.16	0.08	0.937	0.74	1.38
Marital status	0.63	0.12	–2.56	0.011	0.44	0.90
Residence	1.87	0.27	4.30	0.000	1.41	2.48
Smoking status	1.05	0.17	0.31	0.758	0.77	1.44
BMI (tertiles)	1.05	0.09	0.60	0.550	0.89	1.25
Energy intake (tertiles)	0.81	0.08	–2.16	0.031	0.67	0.98
B. Less than one fruit serving a day						
Age (years)	1.03	0.01	3.04	0.002	1.01	1.05
Gender	0.59	0.13	–2.39	0.017	0.39	0.91
Marital status	0.43	0.11	–3.38	0.001	0.27	0.70
Residence	1.97	0.39	3.43	0.001	1.34	2.90
Smoking status	1.56	0.35	2.03	0.043	1.02	2.41
BMI (tertiles)	0.96	0.12	–0.33	0.739	0.75	1.23
Energy intake (tertiles)	0.99	0.14	–0.11	0.910	0.75	1.29

Vegetables

On average, vegetable servings were consumed twice daily and fresh mixed salads were most frequent vegetable dish consumed in the study population. Most of the variability (80%) in the total vegetable consumption resulted from consumption of mixed fresh salads. In total, mean number of vegetable servings reported was 2.2 per day, and was lower by about 15% in cases than in controls (Table 11.11). Mean amount of vegetables (g/day) consumed was 96.2 and lower by about 17% in cases compared with controls (Table 11.12). As expected, there was the significant correlation between reported daily number of servings and amounts of vegetables consumed by both controls and cases. Although mean number of vegetable servings and their amount reported by cases were generally lower than in controls, but the nonparametric test for ranks of intake was statistically significant in univariate analysis only for total vegetables ($z = –2.41$, $p = 0.016$) and pickled vegetables ($z = –4.18$, $p < 0.0001$) (Table 11.13).

Table 11.11. Frequency of vegetable servings consumed daily by controls and cases

	Vegetables total	Vegetables fresh	Cucumbers	Tomatoes sweet pepper	Mixed salads	Vegetables cooked	Vegetables pickled
Controls (N = 745)							
Mean	2.3	1.4	0.2	0.85	0.09	0.6	0.3
Percentile 25	1.2	0.6	0.08	0.25	0.0	0.3	0.1
Median	1.8	1.0	0.14	0.52	0.07	0.5	0.2
Percentile 75	2.8	1.7	0.2	1.04	0.14	0.7	0.4
Cases (N = 584)							
Mean	2.0	1.2	0.15	0.65	0.09	0.6	0.2
Percentile 25	1.2	0.6	0.08	0.26	0.0	0.3	0.08
Median	1.7	1.0	0.14	0.51	0.08	0.5	0.2
Percentile 75	2.5	1.5	0.18	1.0	0.14	0.7	0.3
Total (N = 1329)							
Mean	2.2	1.3	0.16	0.77	0.09	0.6	0.3
Percentile 25	1.2	0.6	0.08	0.25	0.0	0.3	0.08
Median	1.8	1.0	0.14	0.51	0.07	0.5	0.2
Percentile 75	2.6	1.6	0.19	1.0	0.14	0.7	0.4

Table 11.12. Amount of vegetable servings (g) consumed daily by controls and cases

	Vegetables total	Vegetables fresh	Cucumbers	Tomatoes sweet pepper	Mixed salads	Vegetables cooked	Vegetables pickled
Controls (N = 745)							
Mean	102.3	43.6	3.6	22.2	10.8	41.3	16.1
Percentile 25	61.6	19.6	0.4	8.9	2.8	21.9	4.9
Median	83.3	33.0	2.3	15.2	6.7	34.1	11.7
Percentile 75	123.0	54.6	4.6	29.1	13.5	50.7	20.0
Cases (N = 584)							
Mean	88.5	36.8	3.4	18.2	8.7	38.7	11.7
Percentile 25	58.4	19.5	0.4	8.5	3.1	23.9	3.3
Median	78.6	29.5	2.2	14.3	6.8	34.2	9.7
Percentile 75	105.8	46.1	4.6	25.3	11.5	47.7	16.1
Total (N = 1329)							
Mean	96.2	40.6	3.5	20.5	9.9	40.2	14.2
Percentile 25	59.6	19.5	0.4	8.7	2.9	22.8	4.2
Median	81.2	31.0	2.3	14.8	6.7	34.1	10.7
Percentile 75	115.4	50.4	4.6	27.2	12.4	49.6	18.5

Table 11.13. Nonparametric Wilcoxon rank test for the number of vegetable servings in controls and cases

Variables	obs	Sum of ranks	Significance level
Vegetables, total			
Controls	745	512523	z = –2.41
Cases	585	372592	Prob > |z| = 0.016
Raw vegetables, total			
Controls	745	507290.5	z = –1.65
Cases	585	377824.5	Prob > |z| = 0.098
Lettuce			
Controls	745	486760	z = 1.32
Cases	585	398355	Prob > |z| = 0.185
Cabbages, cucumbers, radish			
Controls	745	505018.5	z = –1.33
Cases	585	380096.5	Prob > |z| = 0.184
Carrot			
Controls	745	489068.5	z = 1.14
Cases	585	396046.5	Prob > |z| = 0.255
Tomato/sweet pepper			
Controls	745	506565.5	z = –1.55
Cases	585	378549.5	Prob > |z| = 0.121
Onions, chives			
Controls	745	497810.5	z = –0.29
Cases	585	387304.5	Prob > |z| = 0.768
Mixed salads			
Controls	745	492350	z = 0.51
Cases	585	392765	Prob > |z| = 0.612
Cooked vegetables			
Controls	745	504039.5	z = –1.19
Cases	585	381075.5	Prob > |z| = 0.236
Pickled vegetables			
Controls	745	524800.5	z = –4.18
Cases	585	360314.5	Prob > |z|=0.000
Potatoes			
Controls	745	499146	z = –0.48
Cases	585	385969	Prob > |z| = 0.630

Table 11.14 presents the adjusted estimates of ORs of colorectal cancer for the consumption of total vegetables (quartiles of servings) based on the standard unconditional multivariable logistic statistical model. The results show that OR of colorectal cancer inversely correlated with daily number of servings, however, insignificant reduction of OR estimates was observed. In other approach, we repeated the analysis using other statistical model substituting variable *total vegetables* by *pickled* ones (Table 11.15). This time it was possible to point out that the preventive effect was significant both for moderate (OR = 0.73; 95% CI 0.53–1.00) and higher consumption of pickled vegetables in comparison with the lowest intake level (OR = 0.58; 95% CI: 0.41–0.82). As earlier,

the statistical models considered the set of potential confounding variables such as demographic characteristics of subjects (age, gender, place of residency, marital status and occupational activity, BMI, total energy intake. The predicted ORs of colorectal cancer related to daily intake of vegetables (total) were displayed in Figure 11.6 and those for the intake of pickled vegetables in Figure 11.7.

Table 11.14. Estimated risk (OR) of colorectal cancer related to the number of vegetable servings consumed daily (in quartiles) adjusted for potential confounders

Predictors	Odds Ratio	Std. Err.	z	P > z	[95% Conf. Interval]	
Age (years)	1.02	0.01	3.12	0.002	1.01	1.03
Marital status	0.55	0.79	–4.21	0.000	041	072
Residence	1.90	0.22	5.50	0.000	1.51	2.38
Smoking	1.04	0.04	1.03	0.302	0.97	1.12
BMI (tertiles)	1.03	0.07	0.43	0.668	0.90	1.19
Energy intake (tertiles)	0.89	0.07	–1.53	0.126	0.77	1.03
Vegetable servings in quartiles						
Q1 (< 1.19 servings/day)	1.00					
Q2 (1.20–1.75 servings daily)	0.98	0.16	–0.12	0.901	0.71	1.35
Q3 (1.76–2.62 servings a day)	1.03	0.17	0.19	0.850	0.75	1.42
Q4 (> 2.62 servings a day)	0.83	0.14	–1.10	0.273	0.59	1.16

Table 11.15. Estimated risk (OR) of colorectal cancer related to the number of vegetable servings consumed daily (in quartiles) adjusted for potential confounders

Predictors	Odds Ratio	Std. Err.	z	P > z	[95% Conf.	Interval]
Age (years)	1.02	0.01	2.99	0.003	1.01	1.03
Marital status	0.54	0.08	–4.31	0.000	0.40	0.72
Residence	1.89	0.22	5.46	0.000	1.50	2.37
Smoking status	1.04	0.04	0.97	0.331	0.96	1.12
BMI (tertiles)	1.04	0.08	0.57	0.570	0.91	1.20
Energy intake (tertiles)	0.94	0.07	-0.88	0.377	0.81	1.08
Picked vegetables (servings/day)						
Q1 (< 0.08 servings a day)	1.00					
Q2 (0.09–0.16 servings a day)	0.86	0.14	–0.96	0.337	0.63	1.17
Q3 (0.17–0.37 servings a day)	0.73	0.12	–1.97	0.049	0.54	1.00
Q4 (> 0.37 servings a day)	0.58	0.10	–3.13	0.002	0.41	0.82

In the subsequent analysis, besides variable *total vegetables* we introduced *total fruits* (Table 11.16) and afterwards we substituted the variable *total vegetables* by *pickled vegetables* (Table 11.17). While the effect of fruits remained significant (OR = 0.65; 95% CI: 0.47–0.88), there was revealed the independent inverse effect of pickled vegetables on the colorectal cancer risk estimates. Table 11.18 shows similar significant effect of combined intakes of apples and pickled vegetables. Using the nested logistic multivariable model we were able to confirm that both pickled vegetables (OR = 0.68; 95% CI:

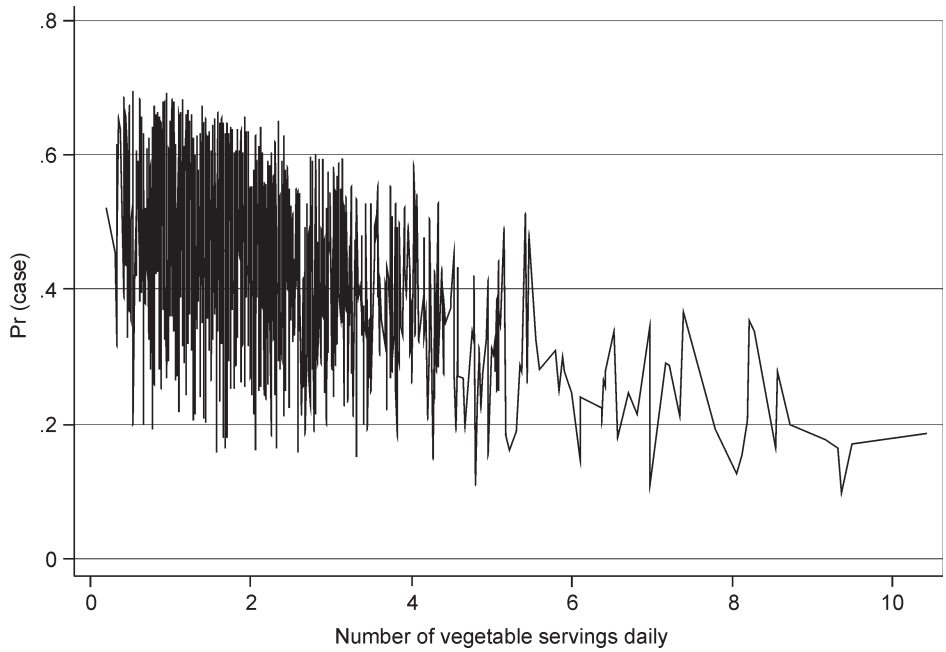

Figure 11.6. Predicted ORs of colorectal cancer related to daily intake of vegetables

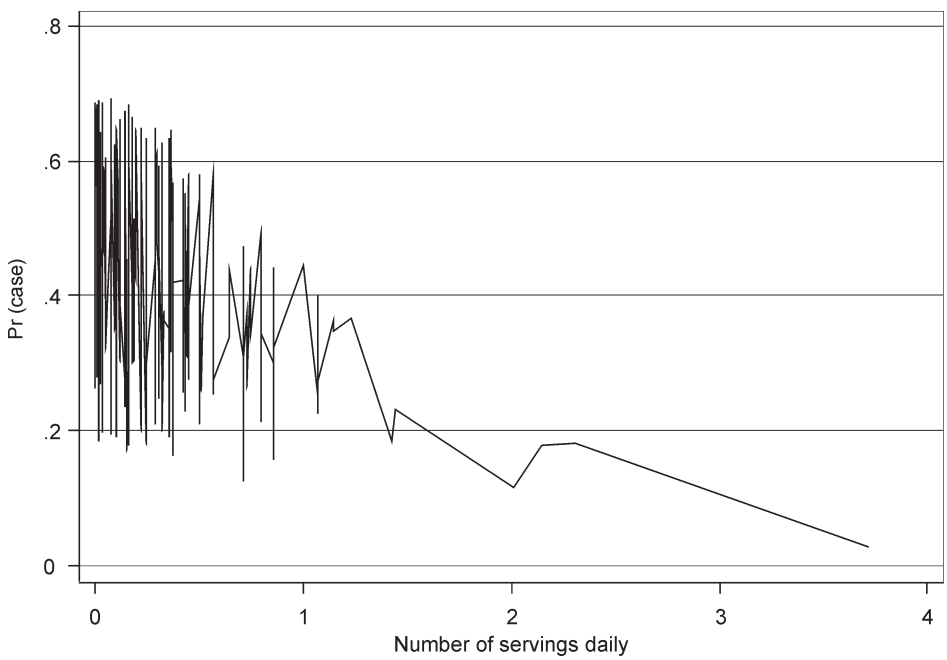

Figure 11.7. Predicted ORs of colorectal cancer related to daily intake of pickled vegetables

0.51–0.91) and apples (OR = 0.62; 95% CI: 0.46–0.84) were independently associated with the lower risk of colorectal cancer (Table 11.19). Summary statistics of the latter analysis has indicated that besides consumption of apples, which significantly contributed to explaining the occurrence of cases ($chi^2 = 10.91$, $p = 0.001$) the preventive effect of pickled vegetables appeared to be significant as well ($chi^2 = 9.10$, $p = 0.003$). Out of all demographic variables considered in the statistical models, the higher risk of colorectal cancer was observed among older persons, residents of villages or small towns, and married persons.

Table 11.16. Estimated risk (OR) of colorectal cancer related to the number of fruit servings consumed daily (in tertiles) adjusted for vegetables servings and other potential confounders

Case	Odds Ratio	z	P > z	[95% Conf. interval]	
Age (years)	1.02	3.47	0.001	1.01	1.03
Gender	0.95	–0.44	0.661	0.75	1.20
Marital status	1.77	3.87	0.000	1.32	2.35
Residence	1.88	5.39	0.000	1.49	2.36
Smoking status	1.07	1.63	0.103	0.99	1.15
BMI (tertiles)	1.02	0.30	0.760	0.89	1.18
Total fruit servings (tertiles)					
Q1	1.00				
Q2	0.96	–0.26	0.793	0.73	1.27
Q3	0.65	–2.74	0.006	0.47	0.88
Total vegetable servings (tertiles)					
Q1	1.00				
Q2	1.09	0.62	0.534	0.82	1.45
Q3	0.95	–0.33	0.742	0.69	1.30

Table 11.17. Estimated risk (OR) of colorectal cancer related to the number of fruit servings consumed daily (in tertiles) adjusted for pickled vegetables (servings) and other potential confounders

Case	Odds Ratio	z	P > z	[95% Conf. interval]	
Age (years)	1.02	3.20	0.001	1.01	1.03
Gender	0.90	–0.84	0.398	0.72	1.14
Marital status	1.78	3.92	0.000	1.34	2.38
Residence	1.87	5.38	0.000	1.49	2.35
Smoking status	1.06	1.48	0.140	0.98	1.14
BMI (tertiles)	1.03	0.44	0.662	0.90	1.19
Total fruit servings (tertiles)					
Q1	1.00				
Q2	1.00	–0.01	0.997	0.76	1.31
Q3	0.69	–2.51	0.012	0.52	0.92
Pickled vegetables (tertiles)					
Q1	1.00				
Q2	0.86	–1.12	0.262	0.66	1.12
Q3	0.67	–2.66	0.008	0.50	0.90

Table 11.18. Estimated risk (OR) of colorectal cancer related to the number of apple servings consumed daily (in tertiles) adjusted for pickled vegetables (tertiles of servings) and other potential confounders

Case	Odds Ratio	z	P > z	[95% Conf.	Interval]
Age (years)	1.02	3.21	0.001	1.01	1.03
Gender	0.90	–0.86	0.387	0.71	1.14
Marital status	1.78	3.88	0.000	1.33	2.37
Residence	1.88	5.43	0.000	1.50	2.37
Smoking	1.06	1.44	0.150	0.98	1.14
BMI (tertiles)	1.04	0.61	0.545	0.91	1.20
Apple servings (tertiles)					
Q1	1.00				
Q2	1.04	0.29	0.771	0.80	1.35
Q3	0.62	–3.09	0.002	0.46	0.84
Pickled vegetables (tertiles)					
Q1	1.00				
Q2	0.87	–1.05	0.294	0.66	1.13
Q3	0.68	–2.61	0.009	0.51	0.91

Table 11.19. Estimated risk of colorectal cancer related to dietary factors (number of apple and pickled vegetable servings consumed daily – in tertiles) adjusted for potential confounders. The nested (hierarchical) logistic regression

Case	Odds Ratio	Std. Err.	z	P > z	[95% Conf.	Interval]
Block 1 (Apples)						
Apples	0.79	0.056	–3.30	0.001	0.69	0.91
Block 2 (Apples and pickled vegetables)						
Apples	0.83	0.06	–2.61	0.009	0.72	0.95
Pickled vegetables	0.81	0.06	–3.02	0.003	0.71	0.93
Block 3 (Apples, pickled vegetables and age)						
Apples	0.82	0.06	–2.77	0.006	0.71	0.94
Pickled vegetables	0.83	0.06	–2.66	0.008	0.72	0.95
Age	1.02	0.01	3.09	0.002	1.01	1.03
Block 4 (Apples, pickled vegetables, age and place of residdence)						
Apples	0.82	0.06	–2.71	0.007	0.71	0.96
Pickled vegetables	0.85	0.06	–2.34	0.019	0.73	0.97
Age	1.02	0.01	3.39	0.001	1.01	1.03
Residence	2.03	0.23	6.16	0.000	1.62	2.54
Block 5 (Apples, pickled vegetables, age, place of residence and marital status)						
Apples	0.82	0.06	–2.73	0.006	0.71	0.94
Pickled vegetables	0.83	0.06	–2.62	0.009	0.72	0.95
Age	1.02	0.01	3.60	0.000	1.01	1.03
Residence	1.91	0.22	5.56	0.000	1.52	2.39
Marital status	0.54	0.08	–4.30	0.000	0.41	0.71

Summary statistics

Block	Chi^2	Df	Pr > F
1. (Apples)	10.91	1	0.001
2. (Apples and pickled vegetables)	9.10	1	0.003
3. (Apples, pickled vegetables and age)	9.52	1	0.002
4. (Apples, pickled vegetables, age place of residence)	37.96	1	0.000
5. (Apples, pickled vegetables, age, place of residence and marital status)	18.45	1	0.000

Final multivariable logistic regression model for the number of fruit servings consumed daily (Tables 11.20a and 11.20b) indicated that percent change of the risk estimates in terms of an increase in vegetable servings by one unit decreased the risk estimates by about 14%. However, the percent change of the risk estimates in terms of an increase in pickled vegetables intake by one unit reduced the risk estimates by about 59% (Tables 11.21a and 11.21b). The pattern of demographic host risk factors for colorectal cancer in comparison with daily intake of total vegetables was presented in Figure 11.8 and that for pickled vegetables in Figure 11.9.

Table 11.20a. Estimated risk (OR) of colorectal cancer related to the amount of vegetables consumed (number of daily servings) adjusted for potential confounders

Predictors	Odds Ratio	Std. Err.	z	P > z	[95% Conf. Interval]	
Age (years)	1.02	0.01	3.01	0.003	1.01	1.03
Gender	0.87	0.11	–1.06	0.290	0.68	1.13
Marital status	0.54	0.08	–4.15	0.000	0.41	0.73
Residence	1.85	0.22	5.25	0.000	1.47	2.32
Smoking status	1.07	0.08	0.95	0.344	0.93	1.23
BMI (tertiles)	1.05	0.08	0.61	0.542	0.91	1.20
Energy intake (tertiles)	0.93	0.08	–0.85	0.393	0.80	1.09
Vegetable servings	0.86	0.04	–3.31	0.001	0.79	0.94

Table 11.20b. Percentage change in Odds for change in predictor variables (X) related to the amount of total vegetables consumed (number of daily servings) and other potential risk factors

Predictors	Raw coefficient	z-score for test of b = 0	P value for z-test	Percent change in odds for unit increase in X	Percent change in odds for SD increase in X	Standard deviation of X
Age (years)	0.02	3.007	0.003	1.7	20.1	10.6
Gender	–0.14	–1.059	0.290	–12.9	–6.6	0.5
Marital status	–0.61	–4.150	0.000	–45.7	–22.5	0.4
Residence	0.61	5.246	0.000	84.7	35.4	0.5
Smoking status	0.07	0.946	0.344	7.1	6.0	0.9
BMI (tertiles)	0.04	0.609	0.542	4.5	3.6	0.8
Energy intake (tertiles)	–0.07	–0.854	0.393	–6.7	–5.5	0.8
Vegetable servings	–0.15	–3.306	0.001	–14.0	–20.2	1.5

Table 11.21a. Estimated risk (OR) of colorectal cancer related to the amount of pickled vegetables consumed (number of daily servings) adjusted for potential confounders

Predictors	Odds Ratio	Std. Err.	z	P > z	[95% Conf.	Interval]
Age (years)	1.012	0.01	2.85	0.004	1.01	1.03
Gender	0.82	0.11	–1.57	0.117	0.63	1.05
Marital status	0.55	0.08	–4.02	0.000	0.42	0.74
Residence	1.88	0.22	5.39	0.000	1.49	2.36
Smoking status	1.08	0.08	1.02	0.308	0.93	1.24
BMI (tertiles)	1.05	0.08	0.68	0.493	0.91	1.21
Energy intake (tertiles)	0.93	0.07	–0.92	0.356	0.80	1.09
Pickled vegetable servings	0.41	0.09	–4.04	0.000	0.27	0.64

Table 11.21b. Percentage change in Odds for change in predictor variables (X) related to the amount of pickled vegetables consumed (number of daily servings) and other potential risk factors

Predictors	Raw coefficient	z-score for test of b = 0	P value for z-test	Percent change in odds for unit increase in X	Percent change in odds for SD increase in X	Standard deviation of X
Age (years)	0.02	2.847	0.004	1.7	18.9	10.6
Gender	–0.20	–1.567	0.117	–18.4	–9.7	0.5
Marital status	–0.59	–4.017	0.000	–44.6	–21.8	0.4
Residence	0.63	5.391	0.000	87.7	36.5	0.5
Smoking status	0.07	1.019	0.308	7.6	6.5	0.9
BMI (tertiles)	0.05	0.685	0.493	5.1	4.1	0.8
Energy intake (tertiles)	–0.07	–0.923	0.356	–7.1	–5.8	0.8
Pickled vegetables	–0.88	–4.040	0.000	–58.5	–25.9	0.3

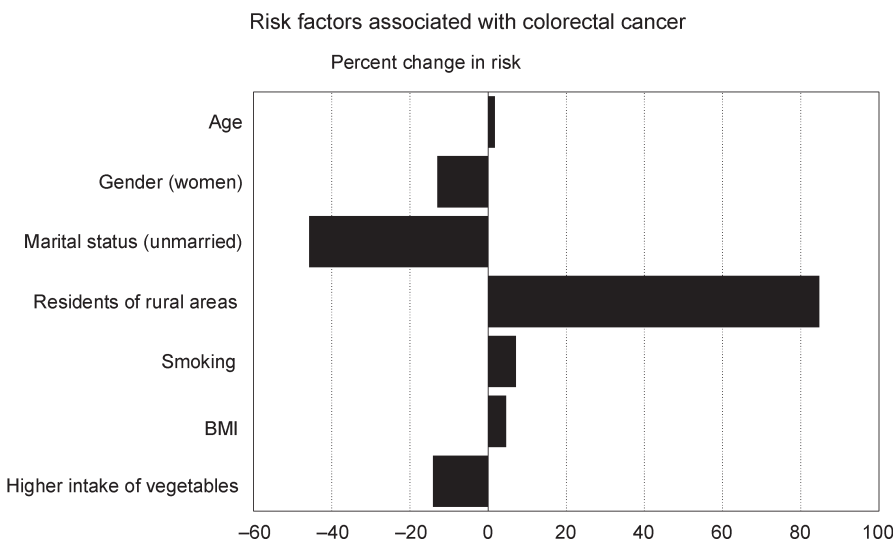

Figure 11.8. Impact of selected risk factors on the occurrence of colorectal cancer

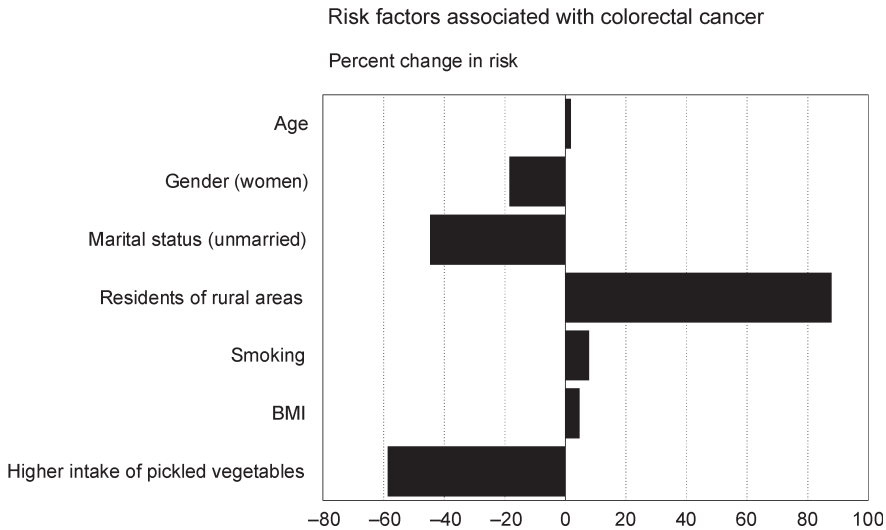

Figure 11.9. Impact of selected risk factors on the occurrence of colorectal cancer

Table 11.22 presents OR estimates related to high-fiber diet adjusted for all confounding variables considered in the earlier analyses. It demonstrates that high intake of dietary fiber has a protective action against colorectal cancer (OR = 0.67; 95% CI: 0.50––0.89). Predicted risk of colorectal cancer related to intake of dietary fiber was shown in Figure 11.10.

Table 11.22. Estimated risk of colorectal cancer related to dietary factors (high-fiber intake) adjusted for potential confounders. Multivariable logistic regression

Predictors	Odds Ratio	Std. Err.	z	P > z	[95% Conf. Interval]	
Gender	0.86	0.11	–1.20	0.232	0.66	1.10
Age (years)	1.02	0.01	3.12	0.002	1.01	1.03
Marital status	0.56	0.08	–3.95	0.000	0.42	0.75
Residence	1.9	0.22	5.40	0.000	1.49	2.36
Smoking status	1.09	0.08	1.17	0.242	0.94	1.25
BMI (tertiles)	1.04	0.07	0.60	0.547	0.91	1.20
Energy intake (tertiles)	0.92	0.08	–0.96	0.338	0.79	1.09
High-fiber diet*	0.67	0.10	–2.74	0.006	0.50	0.89

* above 75th percentile of distribution (5.5 g/day)

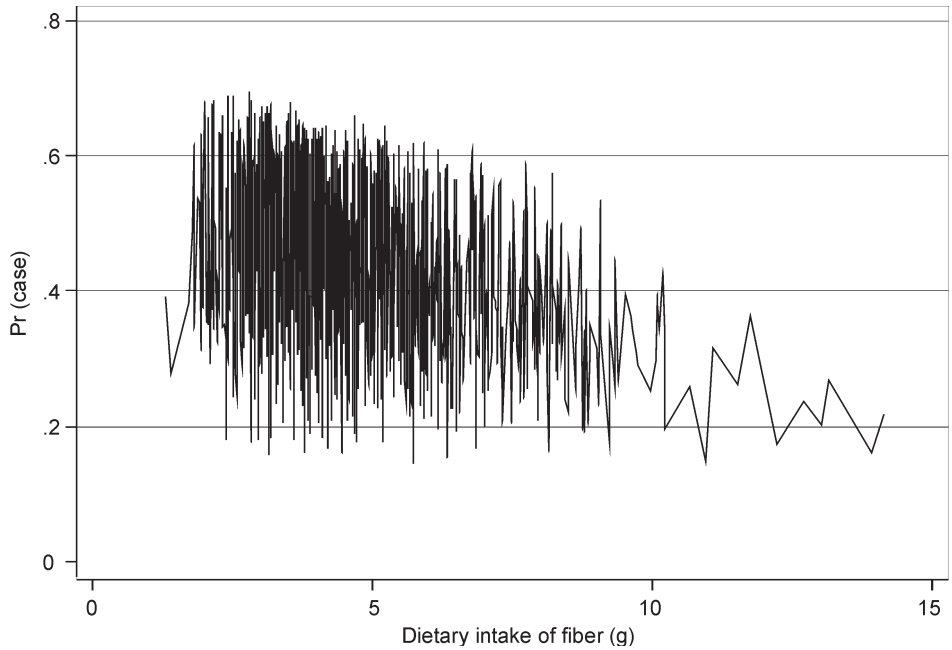

Figure 11.10. Predicted ORs of colorectal cancer related to daily intake of dietary fiber

Meat and fish consumption

Red meat (beef, lamb, pork) and processed meats (sausage, hamburger, ham and bacon) are high on the list of suspected food products that may play a role in colon cancer etiology. Fat also seems to be one of the risk components and the association of saturated and animal fat with colorectal cancer risk seems quite strong (15), but unsaturated fatty acids may have different effects. Some of the studies reported negative association between fish consumption and colorectal cancer mortality (112, 113), while others did not support these findings for neither colorectal cancer mortality (114, 116), nor incidence (117, 118).

The hypothesis on the important role of the long-chain n-3 polyunsaturated fatty acids (PUFAs), being present in fatty cold-water fish and fish oils has been supported in animal experiments and *in vitro* studies showing that the PUFAs suppress the development of major cancers (119). Since current evidence on fish intake and reduced colorectal cancer risk based on epidemiologic studies is scarce, therefore the important purpose of the study was to provide some insight into the relationship between fish consumption and colorectal cancer risk from the European region, where consumption of fish is rather low.

For this particular analysis, meats were grouped into red meat, processed meat, and poultry. Red meat included all fresh, minced, and frozen beef, veal, pork, and lamb. Processed meats were mostly pork and beef that were preserved by methods other than freezing, such as salting (with and without nitrites), smoking, marinating, or heating (i.e., ham, bacon, sausages, blood sausages, salami, tinned meat, luncheon meat, corned beef, and others). Poultry included all fresh, frozen, and minced chicken (including rabbit), and fish included fried, and processed (canned, salted, and smoked fish).

There are 3 types of naturally occurring fats classified by the number of double bonds present in their fatty acid side chains: saturated, monounsaturated, and polyunsaturated (Fig. 11.11). The food industry created a fourth class, trans fats, by adding hydrogen ions to polyunsaturated fats through a process called hydrogenation. Polyunsaturated fats can be further classified into 2 groups based on the position of the first double bond site: omega-3 fatty acids and omega-6 fatty acids. The most prominent omega-6 fatty acids in the human diet are arachidonic acid (found in animal meat) and linoleic acid (found in vegetable oils, seeds, and nuts), which can be converted into arachidonic acid by a desaturase enzyme (Fig. 11.12). Major dietary sources of omega-3's are fish containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and nuts, seeds, and vegetable oils containing a-linolenic acid (ALA), which can be converted to EPA and then DHA by the same desaturase enzyme that converts linoleic acid to arachidonic acid.

On average, median intake of various fish servings was significantly higher in controls than cases (1.70/week vs. 1.25/week, $z = 2.273$, $p = 0.023$). Meatscore (average number of servings of cooked, stewed, fried meat and poultry) was higher in cases than

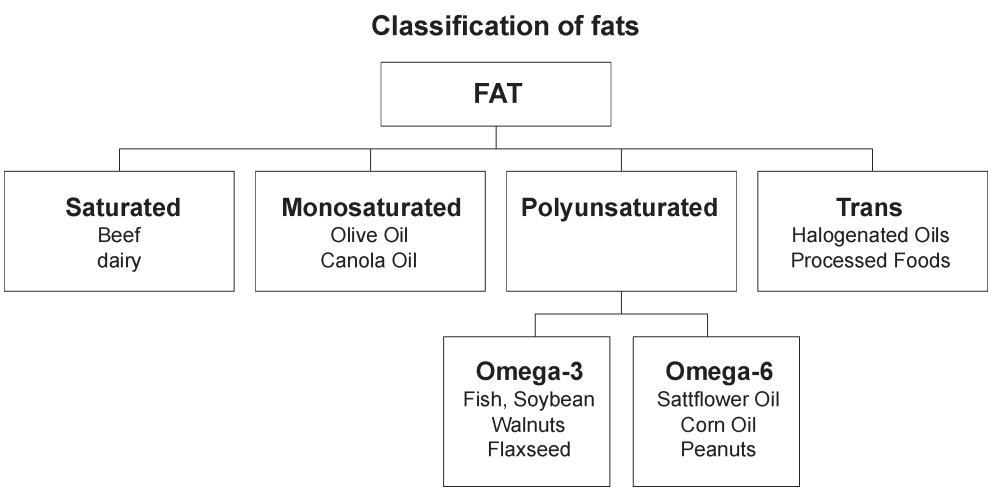

Figure 11.11. Classification of fats

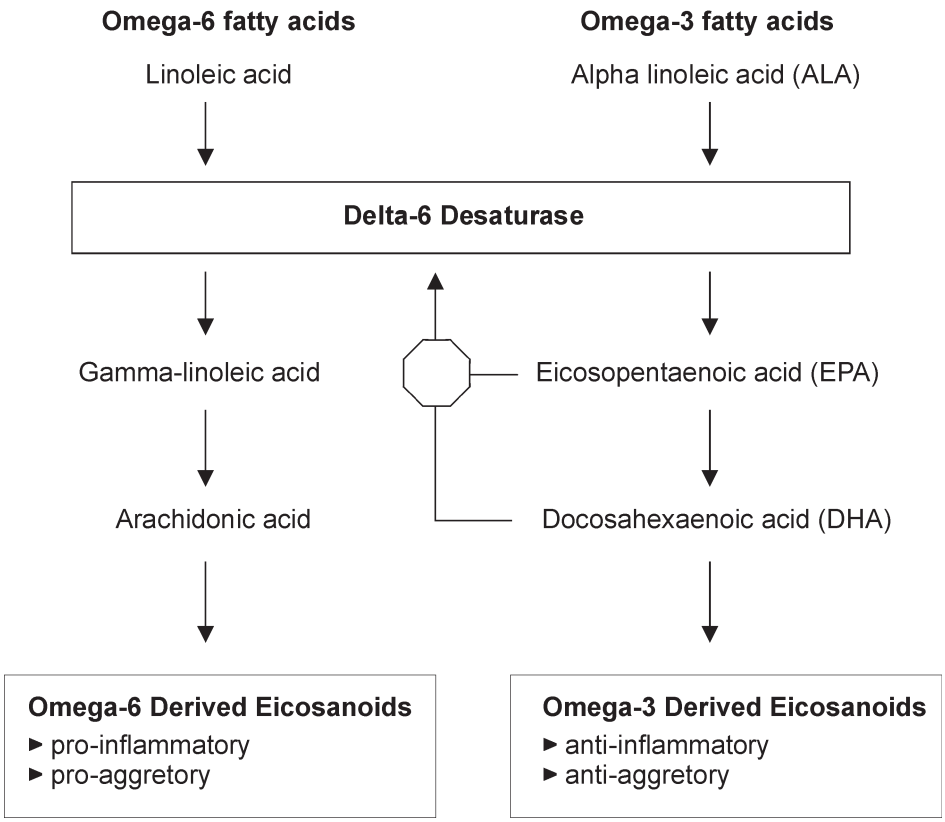

Figure 11.12. Metabolic pathway of omega-6 and omega-3 fatty acids

controls (0.68 vs. 0.65) but the difference was of border level significance ($p = 0.099$). Fishscore (average mean number of servings of fried and processed fish) was significantly lower in cases than in controls (0.17 vs. 0.19, $t = 2.706$, $p = 0.007$). Mean number of fish servings per day in controls and cases were presented in Figure 11.13 and for meat intake in Figure 11.14. The consumption of various meat and fish servings was significantly correlated with each other). While there was very strong correlation between red meat and stewed or cooked meat intakes ($r = 0.768$, $p < 0.0001$), the total fish consumption moderately interrelated with meat consumption ($r = 0.171$, $p < 0.0001$).

Table 11.23 shows the adjusted estimates of risk for colorectal cancer meat- and fishscore based on the unconditional multivariable logistic regression model. Adjusted odds ratio for colorectal cancer was inversely related to fishscore (OR = 0.46; 95% CI: 0.23–0.93) but increased with meatscore (OR = 1.48; 95% CI: 1.07–2.05). Pattern of the relationship between colorectal cancer risk and fish consumption measured by number of servings or amount of fish consumed in g/day was very similar. In Figure 11.15 we present predicted ORs of colorectal cancer related to fish consumption (in g/day).

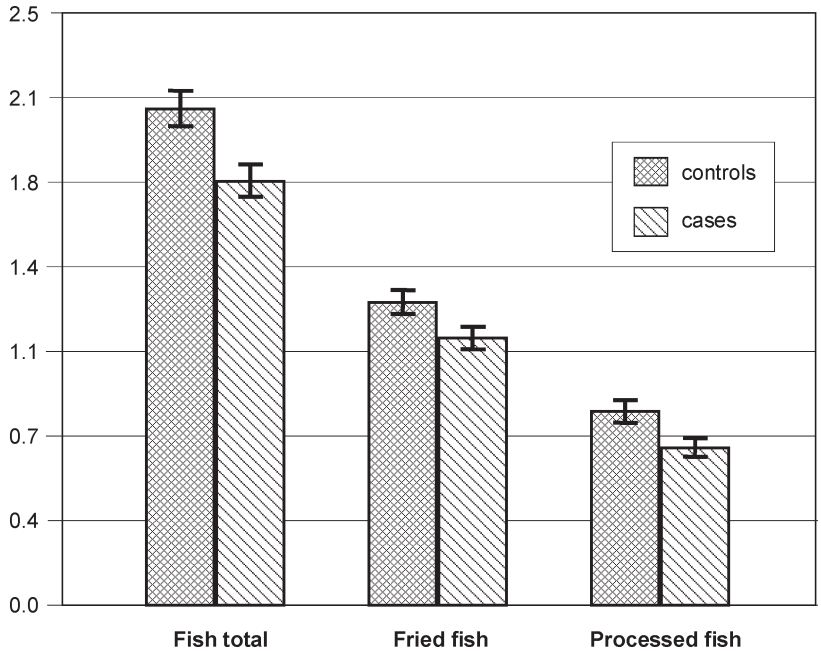

Figure 11.13. Mean and SE of weekly number of fish servings consumed by controls and cases. Data collected over the period 2000–2008 using FFQ in the hospital-based case-control study in Krakow

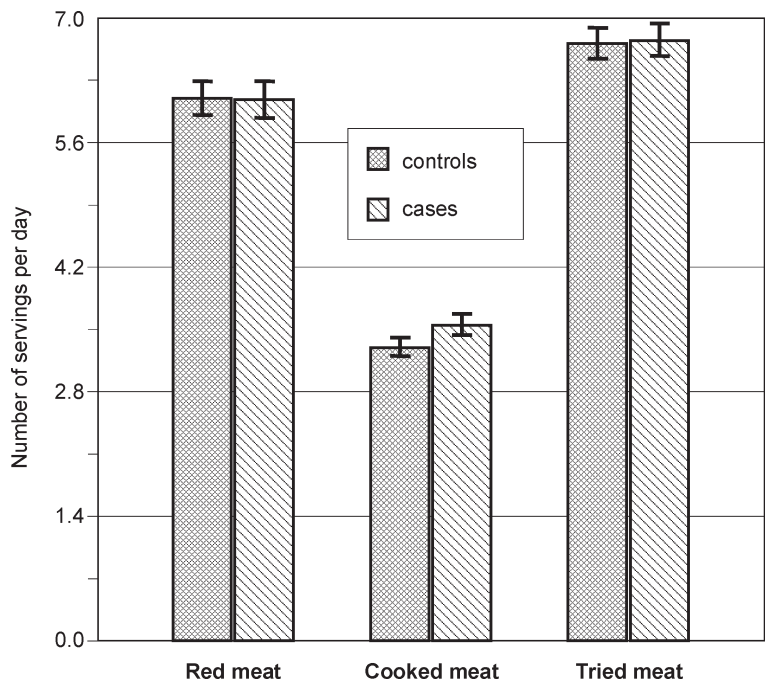

Figure 11.14. Mean and SE of weekly number of meat servings consumed by controls and cases. Data collected over the period 2000–2008 using FFQ in the hospital-based case-control study in Krakow

Table 11.23. Relative risk (OR) of colorectal cancer and dietary components (meat score and fish servings a day) adjusted for potential confounders (estimated from multivariable logistic regression). N = 1329

Predictors	Odds Ratio	Std. Err.	z	P > z	[95% Conf. Interval]	
Gender	0.86	0.11	–1.16	0.245	0.66	1.11
Age (years)	1.02	0.01	2.97	0.003	1.01	1.03
Residence	1.90	0.22	5.52	0.000	1.52	2.39
Marital status	1.80	0.26	4.00	0.000	1.35	2.40
Smoking status	1.08	0.08	1.01	0.313	0.93	1.24
BMI (tertiles)	1.03	0.07	0.38	0.703	0.89	1.18
Energy intake (tertiles)	0.82	0.07	–2.44	0.015	0.70	0.96
Meatscore	1.48	0.25	2.34	0.019	1.07	2.05
Fishscore	0.46	0.16	–2.31	0.021	0.23	0.93

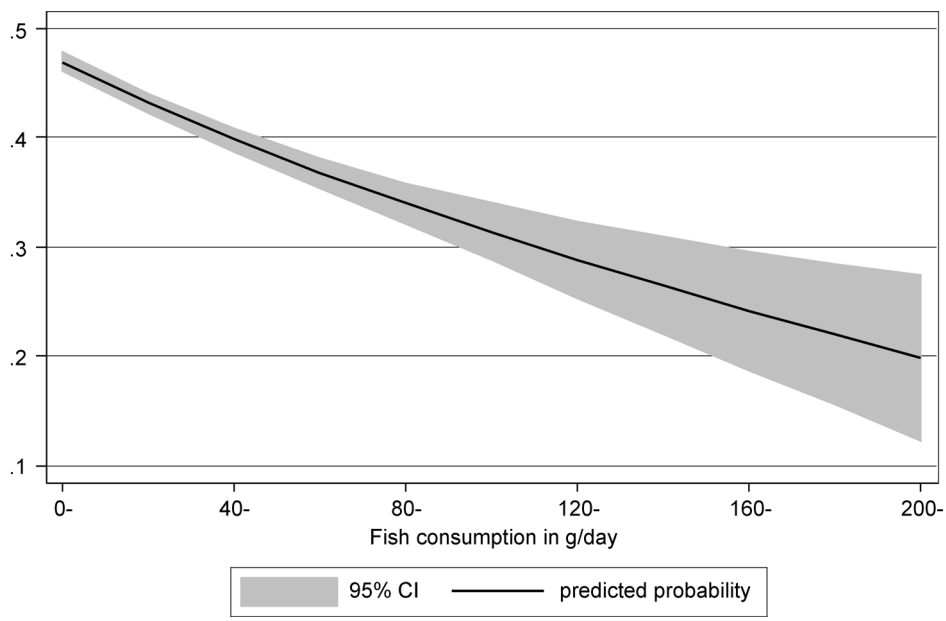

Figure 11.15. Predicted ORs of colorectal cancer related to intake of fish (g/day)

Table 11.24 demonstrates the estimates of colorectal cancer risk after recalculation of number of daily fish servings to number of portions consumed per week. As before, the reduction of colorectal cancer was already seen at the moderate fish intake of one or two servings per week (OR = 0.70, 95% CI: 0.51–0.94) but it was yet lower at higher fish intake (OR = 0.56; 95% CI: 0.39–0.86).

Table 11.24. Effect estimates of fish intake (number of servings per week) adjusted for covariables (gender, age, residence, body mass index, marital status education, and meat consumption)

Case	Odds Ratio	z	P > z	[95% Conf. Interval]	
Less than once a week	1.00				
1–2 times a week	0.70	–2.34	0.019	0.51	0.94
3–4 times a week	0.75	–1.96	0.050	0.56	1.00
More than 4 times a week	0.56	–2.66	0.008	0.39	0.86

Figure 11.16 presents the different impact of meat- and fishscore on colorectal cancer risk. Estimated ORs of colorectal cancer related to meatscore broken down by levels of fish consumption were presented in Tables 11.25 and 11.26. While the effect of meatscore (model without interaction term) was significant at low level of fish consumption (OR = 1.82; 95% CI: 1.09–3.06), the impact became insignificant at higher level of fish consumption (OR = 1.23; 95% CI: 0.81–1.87). In the subsequent analysis (Table 11.27) we documented that the interaction between meat and fish intake was statistically significant (OR = 0.62; 95% CI: 0.40–0.98). The presentation of the interaction effect on the estimated risk ratios was shown in Figure 11.17. All multivariable statistical models employed in the latter analysis considered the set of standard potential confounding variables such as demographic characteristics of subjects (age, gender, place of residency, marital status) BMI and energy intake.

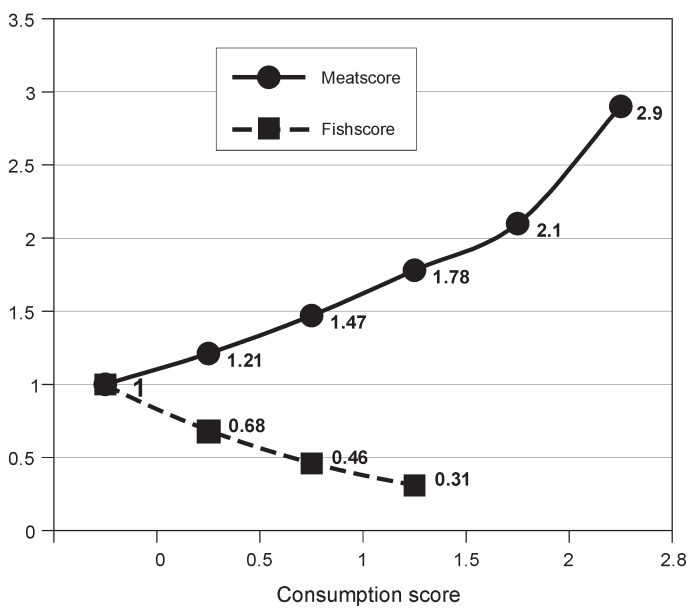

Figure 11.16. ORs of colorectal cancer due to meat and fish consumption level

Table 11.25. Relative risk (OR) of colorectal cancer and meat score in the study sample strata with low fish consumption (below median number of fish servings a day; median = 0.224) adjusted for potential confounders (estimated from multivariable logistic regression). N = 641

Predictors	Odds Ratio	Std. Err.	z	P > z	[95% Conf. Interval]	
Gender	0.81	0.15	–1.11	0.266	0.56	1.17
Age (years)	1.01	0.01	1.47	0.141	0.99	1.03
Residence	2.07	0.35	4.34	0.000	1.49	2.87
Marital status	2.04	0.41	3.52	0.000	1.37	3.03
Smoking status	1.07	0.11	0.64	0.520	0.87	1.31
BMI (tertiles)	0.99	0.15	–0.04	0.972	0.81	1.22
Energy intake (tertiles)	0.83	0.10	–1.52	0.128	0.65	1.06
Meatscore	1.82	0.48	2.30	0.022	1.09	3.06

Table 11.26. Relative risk (OR) of colorectal cancer and meat score in the study sample strata with higher fish consumption (above median number of fish servings a day; median = 0.224) adjusted for potential confounders (estimated from multivariable logistic regression). N = 688

Predictors	Odds Ratio	Std. Err.	z	P > z	[95% Conf. Interval]	
Gender	0.93	0.17	–0.37	0.711	0.65	1.34
Age (years)	1.02	0.01	2.71	0.007	1.01	1.04
Residence	1.81	0.30	3.60	0.000	1.31	2.49
Marital status	1.47	0.32	1.80	0.072	0.97	2.24
Smokin Smoking status	1.09	0.11	0.87	0.384	0.90	1.33
BMI (tertiles)	1.05	0.11	0.51	0.610	0.86	1.28
Energy intake (tertiles)	0.79	0.09	–2.05	0.040	0.63	0.99
Meatscore	1.23	0.26	0.96	0.336	0.81	1.87

Table 11.27. Relative risk (OR) of colorectal cancer related to meat and fish score (above median of meat-score and number of fish servings a day) adjusted for potential confounders (estimated from multivariable logistic regression with interaction term). N = 1329

Predictors	Odds Ratio	Std. Err.	z	P>z	[95% Conf. Interval]	
Gender	0.86	0.11	–1.16	0.247	0.66	1.11
Age (years)	1.02	0.01	3.00	0.003	1.01	1.03
Residence	1.93	0.23	5.64	0.000	1.54	2.43
Marital status	1.77	0.26	3.87	0.000	1.32	2.36
Smoking status	1.07	0.08	0.93	0.354	0.93	1.23
BMI (tertiles)	1.02	0.07	0.33	0.744	0.89	1.18
Energy intake kcal (in tertiles)	0.84	0.07	–2.23	0.026	0.71	0.98
Meatscore*	1.51	0.26	2.40	0.016	1.08	2.11
Fishscore**	1.09	0.18	0.49	0.621	0.78	1.51
Interaction term (meatscore * fishscore)	0.62	0.14	–2.03	0.042	0.40	0.98

* categorized by the median value of meat score
** categorized by the median value of fish servings a day

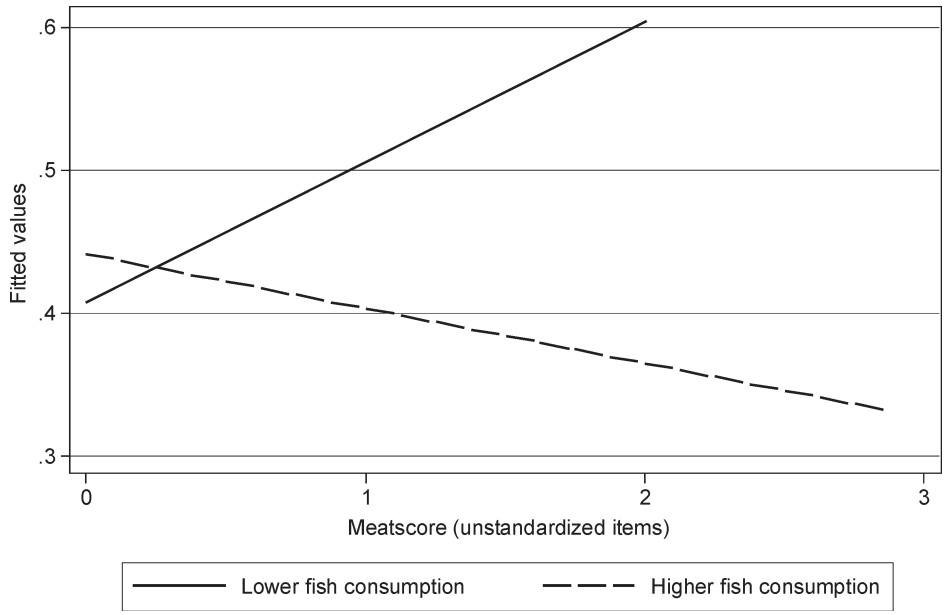

Figure 11.17. Predicted ORs of colorectal cancer related to consumption of meat and fish intake

Tea consumption

The issue of tea consumption and colorectal cancer risk were reported in many studies (146–153) but most of them do not find a significant protective effect on colorectal cancer. It is believed that potential protective effect, if any, is linked with catechins derived from tea (154). In our study we found that controls drank more tea than cases (Fig. 11.18) and that heavy tea drinkers (3 or more cups of tea daily) had much lower risk of colorectal cancer than those with very low tea intake (OR = 0.43, 95% CI: 0.29–0.65) (Table 11.28). The effect of tea consumption on the estimated risk of colorectal cancer was displayed in the Figure 11.19.

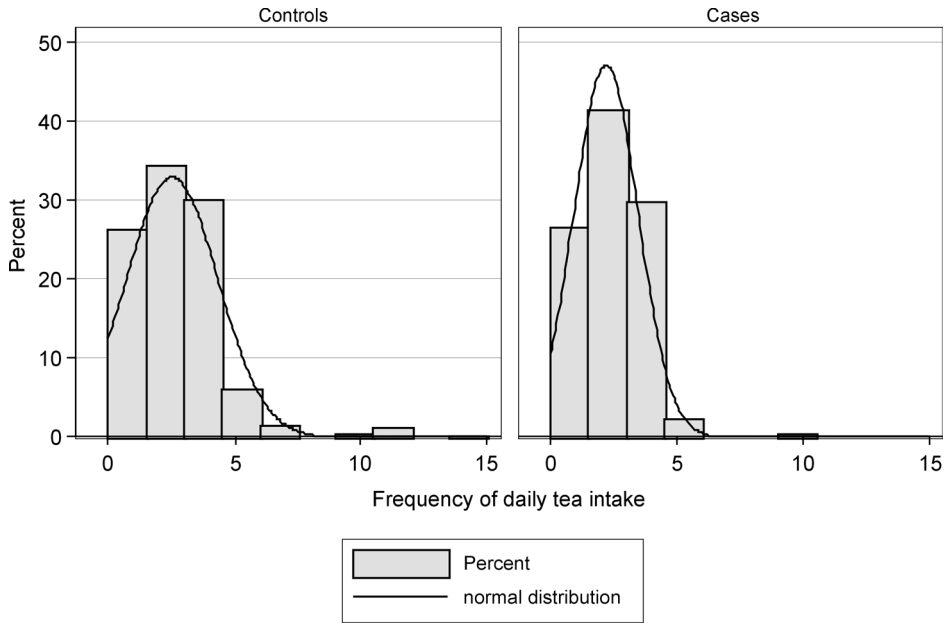

Figure 11.18. Histograms of daily tea portions in controls and cases

Table 11.28. ORs of colorectal cancer related to tea intake daily (number of portions) adjusted for potential confounders (estimated from multivariable logistic regression). N = 1329

Case	Odds Ratio	Std. Err.	z	P > z	[95% Conf.	Interval]
Age (years)	1.02	0.01	3.60	0.000	1.01	1.03
Gender	0.87	0.11	–1.14	0.253	0.68	1.11
Marital status	0.57	0.08	–3.81	0.000	0.43	0.76
Residence	1.95	0.23	5.71	0.000	1.55	2.45
Smoking status						
BMI	1.02	0.07	0.31	0.759	0.89	1.18
Number of tea portions daily						
< 2	1.00					
> 2–3.5	0.88	0.12	–0.98	0.328	0.68	1.14
> 3.5	0.43	0.09	–4.06	0.000	0.29	0.65

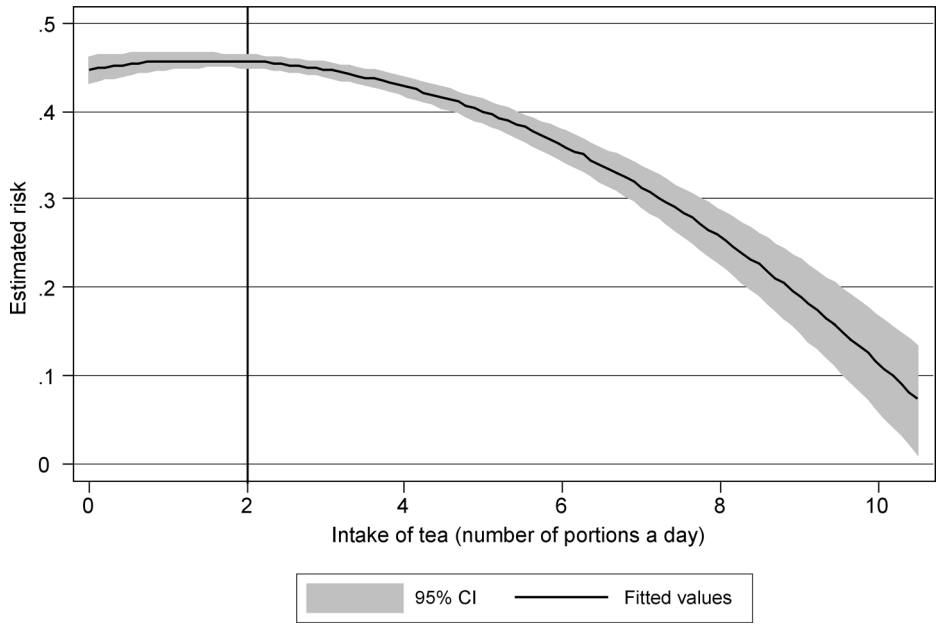

Figure 11.19. Predicted ORs of colorectal cancer related to intake of tea (number of daily portions)

Discussion

The results showed that the risk of colorectal cancer inversely correlated with daily number of apple servings, but significant reduction of OR estimates were observed for an intake of one or more apple servings daily. Colorectal cancer OR was estimated from the multivariable logistic model including a set of potential confounding variables such as demographic characteristics of subjects (age, gender, place of residency, marital status), total energy intake (in tertiles) and intake of vegetables (number of servings per day). Except apples, no other fruits were significantly associated with the reduced risk of colorectal cancer. We think that the reduction of colorectal cancer risk associated with apple consumption was related to rich content of flavonoid and polyphenols in this fruit. As *in vitro* studies shown, the latter phytochemicals can inhibit cancer onset by protecting tissues against free oxygen radicals and inhibiting cell proliferation (31, 32).

The results of this part of our study are in very good agreement with the recently published analysis of several series of case-control studies carried out in Italy on the impact of consumption of apples on cancer occurrence in various sites (56). The Italian study population consisted of 598 patients with incident cancers of the oral cavity and pharynx, 304 with the cancer of oesophagus, 460 of larynx, 1953 of colorectum, 2569 of breast, 1031 of ovary and 1294 of prostate. The authors found a consistent inverse association between apples and risk of cancer in various sites. Multivariate odds ratios (ORs) for each cancer site were obtained with allowance for age, sex, study center, education, body

mass index, tobacco smoking, alcohol drinking, total energy intake, vegetable consumption and physical activity. The results have shown that subjects reporting consumption of one or more apples a day had OR of 0.79 (95% CI: 0.62–1.00) for cancers of the oral cavity and pharynx, 0.75 (95% CI: 0.54–1.03) for esophagus, 0.80 (95% CI: 0.71–0.90) for colorectum, 0.58 (95% CI: 0.44–0.76) for larynx, 0.82 (95% CI: 0.73–0.92) for breast, 0.85 (95% CI: 0.72–1.00) for ovary and 0.91 (95% CI: 0.77–1.07) for prostate.

The relationship of dietary flavonoids (catechins) and epithelial cancer was examined in 728 men (aged 65–84) as part of the Zutphen Elderly Study and apple consumption was associated with decreased epithelial lung cancer incidence (60). Other data from the Zutphen Elderly study showed an inverse association between fruit and vegetable flavonoids and total cancer incidence and tumors of the alimentary and respiratory tract (61). Several other studies have specifically linked apple consumption with a reduced cancer risk, especially lung cancer. In the Nurses' Health Study and the Health Professionals' Follow-up Study, involving over 77 000 women and 47 000 men, fruit and vegetable intake was associated with a 21% reduced risk in lung cancer risk in women, however this association was not seen in men (62). Very few of the individual fruits and vegetables examined had a significant effect on lung cancer risk in women, but apples were one of the individual fruits associated with a decreased risk in lung cancer. In the case control study in Hawaii, it was found that apple and onion intake was associated with a reduced risk of lung cancer in both males and females (63). Smoking history and food intake was assessed for 582 patients with lung cancer and 582 control subjects without lung cancer. There was a 40–50% decreased risk in lung cancer in participants with the highest intake of apples, onions, and white grapefruit when compared to those, who consumed the lowest amount of these fruits. The decreased risk in lung cancer was seen in both men and women and in almost all ethnic groups.

In a Finnish study involving 10 000 men and women and a 24-year follow-up, a strong inverse association was seen between flavonoid intake and lung cancer development (64). In the sampled population, the mean flavonoid intake was 4.0 mg per day, and 95% of the total flavonoid intake was quercetin. Apples and onions together provided 64% of all flavonoid intake. The reduced risk of lung cancer associated with increased flavonoid consumption was especially strong in younger people and in nonsmokers. Apples were the only specific foods that were inversely related to lung cancer risk. Since apples were the main source of flavonoids in the Finnish population, it was concluded that the flavonoids from apples were most likely responsible for the decreased risk in lung cancer.

Up to now, epidemiologic cohort studies on humans that related flavonoid intake to risk of colorectal cancer are sparse and inconclusive. In one cohort study of women, Arts et al. (62) observed an inverse association between certain flavonoid subgroups and risk of rectal cancer. Very big prospective cohort study carried out in USA evaluated the association between intake of flavonoids and colorectal cancer incidence in 71 976 women from the Nurses' Health Study and 35 425 men from the Health Professionals Follow-Up Study. Dietary intake of flavonoids was assessed three times over the period in 1990–1998 by means of a food frequency questionnaire. Between 1990 and 2000, the authors assessed 878 incident cases of colorectal cancer (498 in women and 380 in men) but total flavonoid intake was not inversely associated with colorectal cancer risk among women and men combined (63).

Lack of consistency between case-control and cohort studies in humans raises the question of whether the protective effects of flavonoids demonstrated *in vitro* or in animal studies can be achieved in humans. A central concern in epidemiologic studies on diet and cancer is validity of the dietary assessment and in the debate on shortcomings of studies we have to keep in mind that flavonoid intake in studies was mostly assessed with food frequency questionnaires (FFQ), which may bias the measurement of dietary flavonoids. Since flavonoids are derived from different kinds of foods their total intake varies with many factors, such as processing, storage, or species variety. Different types of apples or other fruits are likely to have different concentrations of flavonoids. Moreover, most flavonoids present in foods are in the form of esters, glycosides, or polymers that cannot be absorbed in their indigenous form (64). They are usually absorbed after being transformed to aglycons in the gastrointestinal tract (65–68). The amount that is bioavailable is usually a small proportion of the ingested amount (69–70) and none of the studies included the correction of the risk estimates for the bioavailability factor. Although recent studies have suggested that the bioavailability of certain flavonoids from food may be higher than expected, it still remains unclear whether the beneficial effects of anti-proliferation and antioxidation from *in vitro* studies would also exist in humans, since the beneficial effects in experimental animal studies were often obtained with much higher concentrations than can be achieved in humans through regular diet (37). Moreover, the colon bacteria flora catalyzes flavonoids into metabolites (71) and the inter-individual variation in the colonic microbial flora and the unpredictable influences of foods on microbial metabolite production complicates the problem concerning the impact of flavoids on health effects in population at large.

This large hospital based case-control study confirmed that besides fruits, also consumption of pickled vegetables was associated with reduced risk of colorectal cancer. In the nested logistic multivariable analysis we were able to confirm that both pickled vegetables (OR = 0.68; 95% CI: 0.51–0.91) and consumption of apples (OR = 0.62; 95% CI: 0.46–0.84) were significantly associated with the lower risk of colorectal cancer. It does mean that an increase in consumption of pickled vegetables by one serving a day may reduce the cancer risk by about 60% and an increase in consumption of one apple daily is to bring about 20% decrease in cancer risk.

The results of case-control studies carried out in other populations have also shown that consumption of vegetables is associated with a lower risk of developing colon cancer, though this was not always statistically significant. Some of these studies indicated that very low consumption of vegetables or fruits may double the risk of colon cancer. In a series of case-control studies conducted in Northern Italy, La Vecchia et al. (72) observed a protective effect of fruit and vegetable consumption against colorectal cancer and estimated that the combined effect of a low intake of beta-carotene and ascorbic acid could account for 43% of all colorectal cancer cases in their target population. Similar conclusions have been drawn from case-control studies in other populations (73–75).

Smith-Warner et al. (76) conducted a case-control study to explore the hypothesis that a high intake of fruits and vegetables may protect against adenomatous polyps and that the protective effects might differ for colon polyps of high compared with low malignant potential. They did observe a protective effect of fruit juice against polyps, which differed for polyps of high compared with low malignant potential. A protective effect

of fruit juice against polyps observed in women showed a significant tendency to be stronger for polyps with moderate or severe dysplasia than for mild dysplastic lesions, but there were neither significant effects of fruit juice in men, nor for various subgroups of fruits and vegetables both in men or women. The authors suggest that fruits and vegetables may reduce the risk of progression from adenomas, rather than of adenoma occurrence.

Epidemiologic cohort studies provide less consistent results on the protective effect of fruits or vegetables on the incident cases of colorectal cancer. Terry et al. (77) observed an increased risk of colorectal cancer amongst the consumers of low amount of fruits and vegetables in a cohort of Swedish women, but Voorrips et al. (78) who had 1000 incident cases of colorectal cancer in 6.3 years of follow-up in the Netherlands Cohort Study on Diet and Cancer found significant association with total vegetable intake or total fruit intake for colon cancer only in men. In women an inverse association was observed for vegetables and fruits combined (RR = 0.66; 95% CI: 0.44–1.01) in the highest quintile of consumption compared with the lowest. Interestingly, certain kind of vegetables (brassica cabbage) and cooked leafy vegetables showed inverse associations for both men and women. For rectal cancer, no statistically significant associations were found for vegetable consumption or fruit consumption or for any particular groups of vegetables and fruits.

Several other large prospective studies in different populations that failed to find any evidence for protective effects of fruit and vegetables against colorectal cancer made the debate on the subject very stormy (79–82). Vegetable consumption was found to be unrelated to risk of incident colon cancer in male health professionals over a 10-year period (RR = 1.24) (79). No association between vegetable consumption and incident colon cancer was seen among male Finnish smokers (RR = 1.2; 95% CI: 0.8–1.9) (81), or men in the Netherlands cohort study (RR= 0.85; 95% CI: 0.57–1.27) (82). Shibata et al. even found a modestly increased risk of colon cancer among older US men with higher vegetable intakes (RR = 1.39; 95% CI: 0.84–2.30) (80).

The results of the epidemiologic studies providing evidence for a protective effect of fruits or vegetables have not been supported by intervention studies with antioxidant supplements using polyp-recurrence as the end-point. For example, McKeown-Eyssen et al. (83) assessed the effect of supplementation for up to 2 years with ascorbic acid (400 mg/day) and alpha-tocopherol (400 mg/day) in 157 patients who had undergone endoscopic polypectomy. Recurrence of polyps was observed in 41.4% of 70 subjects on vitamin supplements and in 50.7% of 67 subjects on placebo. The RR of polyp occurrence was 0.86 (95% confidence 0.51–1.43). The authors concluded that the effect of the intervention with antioxidants was too small to measure under the conditions of their trial. Greenberg (84) randomly assigned 864 patients to four treatment groups – placebo; beta-carotene (25 mg daily); vitamin C (1 g daily) and vitamin E (400 mg daily); or a combined dose of both beta-carotene and vitamins C and E. A total of 751 patients were assessed by colonoscopy repeated after 1 and 4 years but there was no evidence that either beta-carotene or vitamins C and E reduced the incidence of adenomas. Two recent systematic reviews of intervention studies concluded that there was no evidence for protective effects of antioxidant supplements against adenomatous polyps or indeed against any form of gastrointestinal cancer (85–86).

Our case-control study has documented that higher dietary fiber intake (above 75% percentile of the distribution, i.e., 5.56 g/day) is associated with reduced risk of colorectal cancer (OR = 0.67; 95% CI: 0.50–0.89). The term 'dietary fiber' encompasses a complex mix of mostly non-digestible plant cell compounds with variable effects on gut physiology (87, 88). It was already documented that consumption of foods high in beta-carotene and lycopene was associated with trends toward reduced risk of colon cancer. Some meta-analyses (89, 90) of case-control studies on fiber and colorectal cancer that considered methodological similarities among studies found significant inverse association but some do not (91). Our findings for an independent protective role of dietary fiber are contrary to many prospective studies (92–98) and intervention trials of colorectal adenoma recurrence (99–100), but are in agreement with a recent large prospective European EPIC study (101). It is important to mention that the associations seen in age-adjusted models were attenuated after controlling for confounders, especially red meat and beta--carotene. This may suggest that increasing dietary fiber, per se, is not protective but may only be a marker of higher intakes of plant foods. Diets containing a higher amount of vegetables contain a wide range of plant-based antioxidants that may have a possible preventive effect.

Whole grains are high in antioxidants, fiber and certain phytochemicals hypothesized to reduce risk of cancer and nine out of 10 case-control studies reviewed by Jacobs et al. (102) have shown an inverse association between whole grain intake and colorectal cancer (pooled RR = 0.79). Although case-control studies suggest inverse associations between beta-carotene or lycopene from food and colorectal cancer risk, but the prospective studies do not support the findings (103).

Strengths of our study include the ability to control for several important confounders for colon cancer risk. Our food frequency questionnaire included major types of fruits and vegetables. Limitations of this analysis include marginal statistical power to examine associations by colon sub-site, and the limited information on whole grain intake. Apples and pickled vegetables appeared to have the strongest protective effect on colorectal cancer. Moreover, our data suggest that an increase in risk may occur at relatively low intake levels. Since these foods may contain other protective components, the combination of nutrients and non-nutrients may be more important than one specific factor. Our findings warrant further research on specific fruit and vegetable subtypes, and on whether a lower threshold exists for intake of plant foods and colon cancer prevention.

Our results strengthen the evidence that high consumption of meat may increase the risk of cancer of the large intestine, however, higher fish intake has clear opposite effect on colorectal cancer. In this study, the adjusted relative risk of colorectal cancer related to meatscore was 1.48 (95% CI: 1.07–2.05). Instead, the adjusted risk of colorectal cancer was inversely related with the level of fish consumption measured by fishscore (OR = 0.46; 95% CI: 0.23–0.93). The estimates of risk were adjusted for age, gender, place of residence, marital status, smoking and body mass index. The important finding of the study is the fact that adequate fish consumption (at least one serving a week) has the significant modulating effect on the colorectal cancer risk related to meat consumption and this was confirmed by significant interaction term between meat and fish consumption (OR for interaction term = 0.62; 95% CI: 0.40–0.98).

Many previous case-control studies considered the effect of meat consumption on the occurrence of colorectal cancer (5–7, 104–108). Most showed that heavy meat eaters have a higher risk of colorectal cancer although in some studies, the association has been limited to consumption of sausage or other processed meats (117, 121). A meta-analysis of colorectal cancer case-control studies published between 1989 and 2005 (122) found the significant association between meat and colorectal cancer. In the 12 published case-control studies the combined odds ratio (OR) was 1.68 (95% CI: 1.34–2.12) and varied little by types of meat.

Few results are available from prospective studies, which are assumed to have more scientific value than retrospective studies for assessing the relation between diet and cancer since they are supposed to be free from the recall bias (recall of past dietary habits after the cancer has been diagnosed). While prospective study of American women showed no evidence of an association between meat and colorectal cancer (104), the results of the Cancer Prevention Study II Nutrition Cohort including 148 610 adults, aged 50 to 74 years (123) showed that the high intake of red and processed meat was associated with higher risk of colon cancer after adjusting for age and energy intake but not after further adjustment for body mass index, cigarette smoking, and other covariables. When long-term consumption was considered, persons in the highest tertile of consumption had higher risk of distal colon cancer associated with processed meat (RR = 1.50; 95% CI: 1.04–2.17), however, long-term consumption of poultry and fish was inversely associated with risk of both proximal and distal colon cancer. High consumption of red meat was associated with higher risk of rectal cancer (RR = 1.71; 95% CI: 1.15–2.52; $p = 0.007$ for trend).

Our risk estimates regarding the effects of meat and fish consumption on colorectal cancer risk are very close to the conclusions reached in the EPIC study, which prospectively followed 478 040 men and women from 10 Western European countries who were free of cancer at enrollment (6). After a mean follow-up of 4.8 years, 1329 incident colorectal cancers were documented and the relationship between intakes of red and processed meat, poultry, and fish and colorectal cancer risk were assessed. The study showed strong evidence that colorectal cancer risk was positively associated with intake of red and processed meat and inversely associated with intake of fish. The overall association with colorectal cancer risk was stronger for processed than for unprocessed red meat. In the latter study, the estimated absolute risk of developing colorectal cancer within 10 years for a subject aged 50 years was 1.71% for the highest category of red meat intake and 1.28% for the lowest category of intake and was 1.86% for subjects in the lowest category of fish intake and 1.28% for subjects in the highest category of fish intake. The mechanisms underlying the association between colorectal cancer risk and high intake of red and processed meat are uncertain. Controlled human intervention studies have raised the possibility that the endogenous nitrosation that arises from ingestion of heme iron but not of inorganic iron or protein may account for the increased risk associated with red and processed meat consumption. Heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAH) in diet may pose a potential risk of cancer to humans, depending on the extent to which the compounds are activated *in vivo* by metabolic enzymes. HCAs are formed as a byproduct of reactions during the cooking of meat, poultry, and fish at high temperatures, such as pan-frying or grilling with charcoal

or on a gas grill; PAHs are formed in grilled and barbecued meat and in cured, processed foods. The results of studies of the association of polymorphisms of genes encoding for enzymes associated with the metabolism and disposition of HCAs and PAHs and risk of colorectal cancer are inconsistent.

The evidence of an inverse association between colon cancer risk and fish intake has also been observed in other prospective studies (94, 124). A large number of case-control studies did not find any clear association between fish consumption and the risk of colorectal cancer or polyps (125–139). Others have, however, reported a protective effect of fish consumption on colorectal cancer risk (140–144).

The mechanisms underlying the association between colorectal cancer risk and high intake of fish are under debate. Evidence from animal and *in vitro* studies indicates that n-3 fatty acids, especially the long-chain polyunsaturated fatty acids (eicosapentaenoic acid and docosahexaenoic acid), present in fatty fish and fish oils may inhibit carcinogenesis. Several molecular mechanisms whereby n-3 fatty acids may modify the carcinogenic process have been proposed. These include suppression of arachidonic acid--derived eicosanoid biosynthesis; influences on transcription factor activity, gene expression, and signal transduction pathways; alteration of estrogen metabolism or production of free radicals and reactive oxygen species; and mechanisms involving insulin sensitivity and membrane fluidity (145). However, to gain more understanding of the effects of n-3 fatty acid intake on cancer risk further studies are needed to evaluate and verify these mechanisms in humans.

Our estimates of fish consumption in the study sample were very close to those found in the general population. Based on the market data collected in 2005 by the Institute of Farming and Food Economy in Poland, average weight of fishery products (per capita) amounted to 32.4 g/per day (155). In total, sea fish was consumed most frequently (86%), pollock and herrings contributing in 46% to the total amount of fishery products. Pollock fish as a whole was imported and 75% of herrings came from the Baltic sea. Figure 11.20 presents the distribution of different species of fishery products sold in Poland. In our study sample we found – after recalculation of fish servings – that estimated average consumption of fish in controls was 27.4 g/day, 95% CI: 25.5–29.4) and was significantly higher in men (32.3 g/day, 95% CI: 29.2–35.3) than in women (22.1 g/day, 95% CI: 20.0–24.3).

To our knowledge it is the first large epidemiologic study carried out in the Eastern Europe on protective effect of fish intake in the occurrence of colorectal cancer. The study results are in conflict with some case-control studies earlier published. The conflicting results of the epidemiologic studies on the protective effect of fish consumption may arise from many reasons. First, typical limitations for nutritional epidemiology are linked with imprecise estimates of food intake, which could have lead to the various degree of attenuation of the disease risk estimates. To some extent it may be due to the fact that studies do not separate consumption of different fish species having various nutrient and fat content. The proportion of saturated, monounsaturated and polyunsaturated fat varies between species, and the difference in total fat content affects not only the energy content of different fish species, but also the amount of fat-soluble vitamins (A, D, a-tocopherol) that may be important in cancer prevention. Hence, in future studies, the analysis of individual species or of fish subgroups (lean and fatty fish), should be sepa-

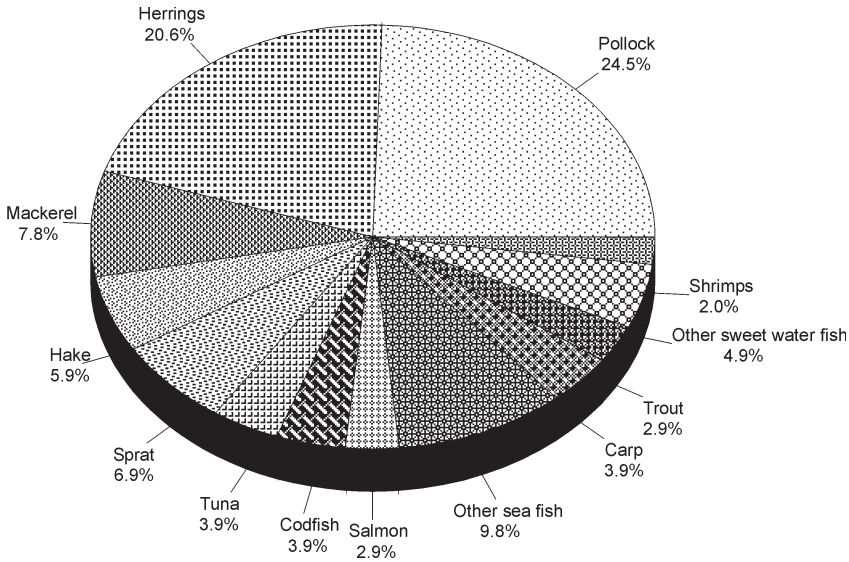

Figure 11.20. Consumption of different species of fishery products in Poland, 2005 (reference 155)

rately considered. Furthermore, it should be avoided to combine different kinds of fish and merge fish consumption with chicken intake. Chicken contains a higher proportion of saturated and monounsaturated fat than fish, and a lower proportion of polyunsaturated fat. Since the association between fish intake and cancer risk greatly depends on a sufficient range of exposure, multicenter studies with a wide range of exposure should be encouraged.

Main conclusions

This is the first large hospital based case-control study in eastern Europe which confirmed that besides fruits, also consumption of pickled vegetables was associated with reduced risk of colorectal cancer. In the nested logistic multivariable analysis we were able to confirm that both pickled vegetables (OR = 0.68; 95% CI: 0.51–0.91) and consumption of apples (OR = 0.62; 95% CI: 0.46–0.84) were significantly associated with the lower risk of colorectal cancer. We think that the reduction of colorectal cancer risk associated with apple consumption may be related to the fact that apples are rich in flavonoid and polyphenols. The latter phytochemicals can inhibit cancer onset by protecting tissues against free oxygen radicals and inhibiting cell proliferation. The protective role of fermented food on the colorectal cancer is not yet clear. However, it is well known that preservation of foods by fermentation ensures not only increased shelf life and microbiological safety of foods but also make many foods more digestible. High on the list of suggested protective factors is lactic acid bacteria because involved in many fermentation processes of milk, meats, cereals and vegetables.

Our results also added an important evidence that high consumption of meat may increase the risk of cancer of the large intestine, however, higher fish intake has clear opposite effect on colorectal cancer. In this study, the adjusted relative risk of colorectal cancer related to meatscore was 1.48 (95% CI: 1.07–2.05). Instead, the adjusted risk of colorectal cancer was inversely related with the level of fish consumption measured by fishscore (OR = 0.46; 95% CI: 0.23–0.93). The estimates of risk were adjusted for age, gender, place of residence, marital status, smoking and body mass index. The important finding of the study is the fact that adequate fish consumption (at least one serving a week) has the significant modulating effect on the colorectal cancer risk related to meat consumption and this was confirmed by significant interaction term between meat and fish consumption (OR for interaction term = 0.62; 95% CI: 0.40–0.98). In the literature, the evidence is still ambiguous, but these findings should prompt interest in the possibility that a high dietary intake of n-3 polyunsaturated fatty acids from oily fish may exert anticarcinogenic effects on the colorectal mucosa, perhaps by reducing the production of proinflammatory eicosanoids and inhibiting the expression and activity of COX-2 in a manner analogous to aspirin and other NSAIDs.

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