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REVIEW

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Vegetables, fruit, antioxidants and cancer: a review of Italian studies

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Summary *Background* Case-control studies have suggested that a diet rich in fresh fruit and vegetables protects from the risk of most common epithelial cancers, including those of the digestive tract, and also several nondigestive neoplasms; however, selections in cohort studies have been generally weaker. *Aim of the study* To review the relation between frequency of consumption of vegetables and fruit, estimated intake of selected antioxidants and the risk of cancer at different sites. *Methods* Systematic overview of data, with specific focus on a network of case-control studies conducted in Italy from 1983 to 1999. *Results* The relative risks (RR) of digestive tract neoplasms were reduced in subjects reporting highest vegetable intake.
A protective effect of vegetables was also observed for hormone-related neoplasms. Fruit was related to a reduced RR of cancers of the upper digestive tract, stomach and urinary tract. With reference to the role of selected antioxidants, beta-carotene, vitamins C and E showed a significant inverse relation with oral and pharyngeal, esophageal and breast cancer risk. Against colorectal cancer, the most consistent protective effects were provided by carotene, riboflavin and vitamin C, but inverse relations were observed also for calcium and vitamin D. *Conclusions* Fruit and vegetable consumption in Mediterranean populations appears to provide protection against several types of neoplasms.

Key words fruit – vegetables – antioxidants – neoplasms – risk factors – diet

Introduction

A diet rich in fruit and vegetables has been associated with a reduced risk of cancer at several sites: the associations tend to be more marked for epithelial cancers, particularly those of the digestive and respiratory tracts [1–6]. Populations consuming low amount of vegetables and fruit have a higher incidence and mortality from cancers of the digestive tract and several other sites [7–9].

Block *et al.* [10] reviewed approximately 300 epidemiological investigations, and found that fruit and vegetables provide a significant protection in most of them. The strongest evidence of a protective effect of vegetable and fruit intake on cancer risk comes, however, from case-control studies. Raw and fresh vegetables showed the most consistent protection, with over 85 % of studies finding an inverse association. Findings were consistent for lettuce, leafy green and cruciferous vegetables, allium, tomatoes, carrots, and citrus fruit, with about 70 % of studies reporting a protective role. More than 60 % of studies on other vegetables and fruit found a protective effect against total cancer risk. Only about 40 % of studies found some protection by legumes and potatoes [2, 10]. However, the effect of these dietary as-

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pects on cancer risk varies according to cancer sites. More than 80% of studies considering vegetable and fruit intake in relation to cancers of the upper respiratory and digestive tracts and lung observed protective effects, as did 80% of studies of cancers of the stomach, pancreas and cervix, and 70% of those of colorectal and ovarian cancers. In a meta-analysis of 26 studies of breast cancer risk and diet, the summary relative risk (RR) was 0.75 (95% CI 0.66–0.85) for high consumption of vegetables, 0.94 (95% CI 0.79–1.11) for fruit, 0.80 (95% CI 0.68–0.95) for vitamin C, and 0.82 (95% CI 0.76–0.91) for beta-carotene [11]. The results were less consistent for bladder and breast cancer, whereas for prostate cancer only about a quarter of studies reported an inverse relation [3, 4, 6].

However the evidence from cohort studies is less consistent [12]. In a prospective study, based on 120,852 men and women from the Netherlands, including 282 stomach cancer cases, no significant association was reported [13]. Data linking vegetable and fruit intake and breast cancer are also not consistent [3, 5, 6]. A pooled analysis of eight prospective studies [14], including more than 7,000 breast cancer cases out of 351,825 women, reported non-significant correlations between fruit and/or vegetable consumption and breast cancer risk. The combined data from the Nurses' Health Study (88,764 women) and Health Professionals' Follow-up Study (47,325 men) [15], including nearly 1,000 cases, reported no clear relation between colorectal cancer and any specific type of fruit and vegetable consumption. Likewise, in the US Health Professionals' Follow-up Study [16], only a weak association was observed between fruit and vegetable intake and bladder cancer, which was significant only for cruciferous vegetables (RR 0.49 95% CI 0.32–0.75).

The association between fruit and vegetable consumption and cancer risk will be critically reviewed in the present paper, with specific focus on data from a series of case-control studies conducted in Italy [2, 5, 17].

Italian case-control studies

The relation between frequency of consumption of vegetables and fruit and cancer risk has been analyzed using data from a series of case-control studies conducted in northern Italy between 1983 and 1999 [17, 18]. The main results of these investigations are reported in Tables 1 and 2.

A consistent pattern of protection against all epithelial cancers was provided by vegetable intake with RRs in the upper tertile of vegetable consumption ranging from 0.3–0.4 for cancers of the esophagus, liver and larynx to 0.8 for breast cancer [18] (Table 1). All trends in risk were in the same direction, and were significant for most carcinomas. In contrast, no association was observed between vegetable consumption and lymphoid neoplasms.

Table 1 Relative risk (RR) of selected cancers according to frequency of vegetable consumption. Milan, Italy, 1983–1999*

Type of cancer	Total number of cases[1]	RR (95% CI) for intake tertiles		
		Low[2]	Medium	High
Oral cavity and pharynx	524	1	0.73 (0.6–0.9)	0.74 (0.6–0.9)
Esophagus	410	1	0.49 (0.4–0.6)	0.33 (0.3–0.4)
Stomach	745	1	0.76 (0.6–0.9)	0.49 (0.4–0.6)
Colon	955	1	0.92 (0.8–1.1)	0.56 (0.5–0.7)
Rectum	625	1	0.99 (0.8–1.2)	0.68 (0.6–0.9)
Liver	435	1	0.74 (0.6–0.9)	0.39 (0.3–0.5)
Galbladder	65	1	0.67 (0.4–1.2)	0.30 (0.2–0.6)
Pancreas	402	1	0.70 (0.6–0.9)	0.39 (0.3–0.5)
Larynx	338	1	0.66 (0.5–0.9)	0.44 (0.3–0.6)
Breast	3,412	1	0.91 (0.8–1.0)	0.76 (0.7–0.9)
Endometrium	750	1	0.89 (0.7–1.1)	0.52 (0.4–0.7)
Ovary	971	1	0.97 (0.8–1.2)	0.70 (0.6–0.8)
Prostate	127	1	0.72 (0.5–1.1)	0.16 (0.1–0.3)
Bladder	431	1	0.78 (0.6–1.0)	0.17 (0.1–0.2)
Kidney	190	1	0.92 (0.7–1.3)	0.24 (0.1–0.4)
Thyroid	428	1	0.68 (0.5–0.9)	0.83 (0.6–1.1)
Hodgkin's disease	201	1	1.06 (0.7–1.6)	0.90 (0.6–1.3)
Non-Hodgkin's lymphomas	529	1	0.99 (0.8–1.3)	1.10 (0.9–1.4)
Multiple myeloma	185	1	0.92 (0.6–1.3)	0.71 (0.5–1.0)

* Modified from La Vecchia et al. (1999) (18). Relative risk (RR) derived from multiple logistic regression equations including terms for age, area of residence, calendar period at interview, education, smoking, alcohol consumption and (when required) sex.

[1] Controls were 10,058 patients admitted to hospital for acute, non-neoplastic conditions, unrelated to long-term dietary modifications.

[2] Reference category

With reference to fruit (Table 2), strong protective effects for cancers of the upper digestive and respiratory tracts were observed with RR estimates around 0.4 and 0.5 for cancers of the oral cavity, pharynx, esophagus and larynx when comparing the highest tertile of fruit intake with the lowest [18]. The more distal the tumor was in the digestive tract, the weaker was the apparent protective effects of fruit. Significant protective effects of fruit were also observed for cancers of the gallbladder, pancreas, prostate and urinary tract, but not for liver, breast, female genitalia, or thyroid. No consistent relation was observed with lymphomas and myelomas.

Substantial geographical differences in the incidence of and mortality from different neoplasms have been observed in Italy, with lower rates being generally registered in southern areas, where fruit and vegetable consumption has long been higher [19]. Thus, even in the absence of a clear biological explanation, these data suggest that, in this population, vegetable intake is associated with a substantial reduction of risk for several common epithelial cancers, and that fruit intake has a favorable effect, too, especially on cancers of the upper digestive and urinary tracts.

Table 2 Relative risk (RR) of selected cancers according to fruit intake. Milan, Italy, 1983–1999*

Type of cancer	Total number of cases[1]	RR (95 % CI) for intake tertile		
		Low[2]	Medium	High
Oral cavity and pharynx	524	1	0.68 (0.5–0.9)	0.45 (0.4–0.6)
Esophagus	410	1	0.62 (0.5–0.8)	0.37 (0.3–0.5)
Stomach	745	1	0.70 (0.6–0.9)	0.44 (0.4–0.6)
Colon	955	1	0.93 (0.5–1.1)	0.63 (0.5–0.8)
Rectum	625	1	1.10 (0.9–1.4)	0.76 (0.6–0.9)
Liver	435	1	1.33 (1.0–1.8)	1.03 (0.8–1.4)
Galbladder	65	1	0.86 (0.4–1.6)	0.42 (0.2–0.8)
Pancreas	402	1	0.83 (0.6–1.1)	0.65 (0.5–0.8)
Larynx	338	1	0.54 (0.4–0.7)	0.51 (0.4–0.7)
Breast	3,412	1	0.93 (0.8–1.1)	1.12 (0.7–1.3)
Endometrium	750	1	1.10 (0.8–1.4)	0.90 (0.7–1.2)
Ovary	971	1	1.17 (0.9–1.5)	1.27 (1.0–1.6)
Prostate	127	1	0.88 (0.6–1.4)	0.48 (0.3–0.8)
Bladder	431	1	1.07 (0.8–1.4)	0.50 (0.4–0.7)
Kidney	190	1	1.05 (0.7–1.6)	0.63 (0.4–0.9)
Thyroid	428	1	1.22 (0.9–1.7)	1.26 (0.9–1.7)
Hodgkin's disease	201	1	0.73 (0.5–1.1)	0.82 (0.6–1.2)
Non-Hodgkin's lymphomas	529	1	0.85 (0.6–1.1)	0.95 (0.8–1.2)
Multiple myeloma	185	1	1.03 (0.7–1.6)	1.14 (0.8–1.7)

* Modified from La Vecchia et al. (1999) (18). Relative risk (RR) derived from multiple logistic regression equations including terms for age, area of residence, calendar period at interview, education, smoking, alcohol consumption and (when required) sex.

[1] Controls were 10,058 patients admitted to hospital for acute, non-neoplastic conditions, unrelated to long-term dietary modifications.

[2] Reference category

Table 3 Population-attributable risk for fruit and vegetable consumption and in association with alcohol and tobacco consumption on selected epithelial cancer in Northern Italy*

Type of cancer	Population attributable risk (%)	
	Vegetables and fruit	Vegetables and fruit + tobacco + alcohol
Oral cavity and pharynx		
men	25	94
women	17	57
Esophagus		
men	40	90
women	29	58
Larynx		
men	18	86
women	15	86
Stomach	60	–
Colorectal	43	–
Breast	21	–

* Modified from Negri et al., 1992, 1993; Tavani et al., 1994; Franceschi et al., 1995; La Vecchia et al., 1995, 1996 (21–26)

The attributable risks, based on multivariate RR estimates [20] for low intakes of vegetables and fruit, combined with tobacco smoking and alcohol drinking were over 90 % for oral and pharyngeal and esophageal cancers, and over 85 % for laryngeal cancers in men [21–23]. The risks attributable to low fruit and vegetable intake were 43 % for colorectal and 60 % for stomach cancer in both sexes combined, and 21 % for breast cancer (Table 3) [24–26]. Since alcohol and tobacco are less strongly related to these neoplasms [27], no estimate is given for the attributable risk of tobacco and alcohol combined with low fruit and vegetable consumption.

A significant inverse relation was also observed between measures of diet diversity (i. e., variety in food intake computed as the total number of foods consumed at least once per week) and colorectal and stomach cancer risk, with RRs around 0.6 for the highest diversity levels [28]. A diet rich in fruit and vegetables provided on apparently stronger protection. This adds epidemiological support to the dietary guidelines recommending a more varied diet – particularly with reference to fruit and vegetables – and would therefore have relevant public health implications.

When the relationship between selected antioxidants and various cancers was considered [29, 30], beta-carotene, vitamin E and calcium showed a significant inverse relation with breast cancer risk [30]. Vitamin C, beta-carotene and lutein/zeaxanthin were inversely related to ovarian cancer risk [31]. For colorectal cancer, the most consistent protective effects were provided by beta-carotene, riboflavin and vitamin C. Inverse relations were also observed for calcium and vitamin D. The RR was 0.46 in subjects reporting a high calcium/vitamin D ratio and selected antioxidant intake, as compared to those reporting low intake of both micronutrients [29].

Olive oil has been inversely related to breast, ovarian, colorectal, oral and esophageal cancer in studies on the Mediterranean populations [32–35]. Part of the apparent benefit may be due to the positive correlation between olive oil and vegetable intake. Olive oil is high in mono-unsaturated fats (mainly oleic acid), but also has antioxidant properties due to its fatty acid composition or its content of antioxidants (mainly related to its vitamin E content) [36, 37].

In view of the persisting uncertainty concerning possible mechanisms by which high vegetable and fruit intake reduces cancer risk, foods with different contents of potentially important micronutrients remain a priority for investigation. Tomatoes are relatively low in beta-carotene, but high in lycopene, an active antioxidant agent with no vitamin A activity [38], and are one of the key constituents of the Mediterranean diet. Therefore, the relation of tomatoes to cancer risk has been considered in the integrated network of Italian case-control studies mentioned above, including 324 oral and pharyngeal cancers, 85 esophageal, 723 gastric, 955 colon and 629 rectal cancers, and a total of 1,819 controls [39, 40]. There was a consistent pattern of protection for all sites, with RRs in the upper quartile of tomato con-

sumption ranging between 0.4 and 0.7, most notably for gastrointestinal neoplasms. Lycopene was inversely related to oral, pharyngeal [41], esophageal [42] and breast cancer [43], but not colorectal [29] and ovary [31]. Easy to prepare to grow and transport, tomatoes may, thus, constitute a privileged single focal issue for diet and cancer prevention campaigns, together perhaps with oranges and carrots [38, 44].

We considered the interaction between selected antioxidants and the major recognized risk factors for oral and pharyngeal cancer, i. e., alcohol and tobacco. Compared to never/ex smokers in the highest intake tertile, the RR for current smokers of ≥25 cigarettes/day in the lowest intake tertile were 12.09 for vitamin C, 10.69 for carotene, and 7.36 for vitamin E (Table 4) [41]. With reference to alcohol, subjects who drank eight or more drinks/day and reported a low nutrient intake compared to subjects who drank less than four drinks/day and reported a high intake of each micronutrient, had a RR of 21.03 for vitamin C, 18.68 for carotene and 14.90 for vitamin E (Table 5) [41]. When we looked at the joint effect of these three nutrients, they showed negative synergism, i. e., the effect of one was most evident at low levels of intake of the others. This suggests that these nutrients may well be "markers" of something else, which remains elusive. The favorable effect may be due to other still unidentified compound(s) in fruit and vegetables, or may be caused by a complex action of several different compounds [45].

Similar findings were observed in other studies on oral and pharyngeal [46] and esophageal cancer, where the strongest inverse associations were reported for carotene (RR 0.3), lutein/zeaxanthin (RR 0.4) and vitamin C (RR 0.4) [47, 48], as well as in studies conducted in women only [42, 49].

Table 4 Relative risk (RR), and corresponding 95 % confidence intervals (CI) of oral and pharyngeal cancer according to the combined effects of tobacco smoking and intake of selected antioxidants (vitamin C, carotene and vitamin E). Italy and Switzerland, 1992–1997*

Intake tertiles	Tobacco smoking, RR[1] (95 % CI)		
	Never/ex smoker	< 25 cigarettes/day	≥ 25 cigarettes/day
Vitamin C			
3	1[2]	2.88 (1.78–4.67)	7.05 (3.42–14.52)
2	1.29 (0.82–2.02)	3.03 (1.85–4.95)	6.46 (3.31–12.61)
1	2.38 (1.55–3.65)	8.42 (5.38–13.18)	12.09 (6.87–21.30)
Carotene			
3	1[2]	2.68 (1.68–4.27)	6.19 (2.77–13.80)
2	1.21 (0.80–1.85)	3.35 (2.14–5.24)	5.34 (2.69–10.60)
1	1.97 (1.28–3.02)	6.48 (4.16–10.11)	10.69 (6.18–18.48)
Vitamin E			
3	1[2]	3.41 (2.19–5.30)	6.44 (3.21–12.94)
2	1.37 (0.89–2.10)	3.30 (2.09–5.21)	8.84 (4.76–16.40)
1	1.73 (1.09–2.74)	5.82 (3.60–9.39)	7.36 (4.04–13.42)

* Modified from Negri et al., 2000 (41).
[1] Estimates from multiple logistic regression models including terms for age, sex, study center, education, occupation, body mass index, alcohol drinking and non-alcohol energy.
[2] Reference category

Table 5 Relative risk (RR), and corresponding 95 % confidence intervals (CI) of oral and pharyngeal cancer according to the combined effects of alcohol drinking and intake of selected antioxidants (vitamin C, carotene and vitamin E). Italy and Switzerland, 1992–1997*

Intake tertiles	Alcohol drinking (drinks/day), RR[1] (95 % CI)		
	< 4	4 – < 8	≥ 8
Vitamin C			
3	1[2]	2.47 (1.39–4.38)	9.58 (5.51–16.65)
2	0.73 (0.43–1.25)	3.08 (1.81–5.24)	16.28 (9.45–28.05)
1	2.52 (1.61–3.94)	6.57 (4.08–10.59)	21.03 (12.84–34.44)
Carotene			
3	1[2]	2.40 (1.34–4.29)	10.95 (6.33–18.94)
2	1.01 (0.62–1.67)	2.79 (1.65–4.73)	15.59 (9.07–26.80)
1	1.95 (1.21–3.14)	6.68 (4.02–11.09)	18.68 (11.06–31.55)
Vitamin E			
3	1[2]	2.45 (1.42–4.21)	11.91 (7.12–19.92)
2	1.20 (0.73–1.96)	2.99 (1.77–5.07)	15.72 (9.19–26.90)
1	1.50 (0.91–2.48)	5.80 (3.39–9.90)	14.90 (8.51–26.11)

* Modified from Negri et al., 2000 (41).
[1] Estimates from multiple logistic regression models including terms for age, sex, study center, education, occupation, body mass index, tobacco smoking and non-alcohol energy.
[2] Reference category

Possible biological mechanisms

The protective effect of vegetables and fruit against (epithelial) cancer has been related to multiple constituent substances and mechanisms, including antioxidants, dietary fibers, micronutrients and other phytochemicals [50, 51] Potentially anticarcinogenic agents found in fruit and vegetables include numerous micronutrients such as carotenoids, vitamins C and E, dietary fiber, selenium, glucosinolates and indoles, isothiocyanates, flavonoids, phenols, protease inhibitors and plant sterols. These and other agents display both complementary and overlapping mechanisms of action, including induction of detoxification enzymes [52, 53], antioxidant effects, inhibition of the formation of nitrosamines, binding and dilution of carcinogens in the digestive tract, and alteration of hormone metabolism [50, 51, 54].

In particular, beta-carotene has been associated with a reduced risk of cancer at several sites [55–58]. Moreover, observational epidemiology cannot reveal whether the protective effects of fruit and vegetables are due principally to beta-carotene itself or to other carotenoids [59–61]. The recent results of large-scale intervention trials, however, did not support such a protective effect and indicated that in well-nourished populations no material benefit on cancer risk comes from beta-carotene supplementation [62–64].

Other micronutrients investigated include lycopene, ascorbic acid and alpha-tocopherol – which also have an antioxidant effect – weakly estrogenic isoflavones in soy food and other vegetables, and precursors of lignans. Vegetables and fruit also contain glucosinolates and indoles, thiocyanates and isothiocyanates, phenols and coumarins, which may induce various phase I and phase II metabolizing enzymes. Carotenoids and sterols may also affect wall membrane structure and integrity [51, 65, 66]. Low folic acid causes chromosome breaks in rodents and humans, and has been associated with several neoplasms, particularly colorectal, breast, and cervical intraepithelial cancer [12, 66, 67].

None of these mechanisms, however, seems by itself able to totally explain the apparent protection of fruit and vegetables on several cancer sites. It is possible that only the combined effect of several concurrent mechanisms can explain the favorable effect of fruit and vegetables on cancer risk observed in epidemiological studies. The high intake of fruit and vegetables often accompanies lower intakes of fats, proteins, refined cereals (starches) and other nutrients that may increase the risk of cancer at several sites. Therefore, frequent consumption of fruit and vegetables may also be an indicator of a more generally healthie diet and lifestyle [45].

Social status is a potential confounding factor in epidemiological studies on diet and disease. Lower socioeconomic status has been associated with cigarette smoking and alcohol drinking, which are major risk factors for several cancers, as well as with generally poor diet and other unfavorable lifestyle habits [68]. In addition, in several areas of the world (although not necessarily in Mediterranean countries), fresh fruit and vegetables may be comparably expensive and difficult to obtain, and members of lower socioeconomic groups may be less able to include them in their diet.

Conclusions

Case-control studies suggest that a diet rich in vegetables and fruit provide protection against epithelial cancers at several common sites. The evidence is more convincing and consistent for vegetables than for fruit, and in regard to epithelial cancers, mainly those of the upper respiratory and digestive tracts. In contrast, no consistent protective effects have been observed of vegetable and fruit consumption against non-epithelial, mainly lymphoid, neoplasms. Results from cohort studies, mainly from North America, are less supportive of these protective effects, leaving the issue open to discussion and further investigation.

The possible mechanism of action of micronutrients and other constituents of vegetables and fruit, including antioxidants, and their interactions with other risk factors, such as alcohol, cigarette smoking and other aspects of diet also require further elucidation.

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