Fruit and vegetables and cancer risk: a review of southern European studies

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Abstract

High intakes of fruit and vegetables may reduce the risk of cancer at several sites. Evidence has been derived mainly from case–control studies. We reviewed the relationship between consumption of vegetables and fruit and the risk of several common cancers in a network of Italian and Swiss case–control studies including over 10 000 cases of fourteen different cancers and about 17 000 controls. Data were suggestive of a protective role of vegetable intake on the risk of several common epithelial cancers. OR for the highest compared with the lowest levels of consumption ranged from 0.2 (larynx, oral cavity and pharynx) to 0.9 (prostate). Inverse associations were found for both raw and cooked vegetables, although for upper digestive tract cancers the former were somewhat stronger. Similar inverse associations were found for cruciferous vegetables. Frequent consumption of allium vegetables was also associated with reduced risk of several cancers. Fruit was a favourable correlate of the risk of several cancers, particularly of the upper digestive tract, with associations generally weaker than those reported for vegetables. A reduced risk of cancers of the digestive tract and larynx was found for high consumption of citrus fruit. Suggestive protections against several forms of cancer, mainly digestive tract cancers, were found for high consumption of apples and tomatoes. High intakes of fibres, flavonoids and proanthocyanidins were inversely related to various forms of cancer. In conclusion, data from our series of case–control studies suggested a favourable role of high intakes of fruit and vegetables in the risk of many common cancers, particularly of the digestive tract. This adds evidence to the indication that aspects of the Mediterranean diet may have a favourable impact not only on CVD, but also on several common (epithelial) cancers, particularly of the digestive tract.

Key words: Cancer risk: Diet: Fruit: Vegetables

The Mediterranean diet is a collection of eating patterns with different components, traditionally followed by populations from countries bordering the Mediterranean Sea, and is generally characterised by frequent consumption of fruit, vegetables, complex carbohydrates, pulses and fish; low consumption of meat and cheese; low-to-moderate amount of wine intake during meals; and use of olive oil for seasoning

Abbreviations: FRAP, ferric reducing–antioxidant power; TEAC, Trolox equivalent antioxidant capacity; TRAP, total radical-trapping antioxidant parameter.

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fruit consumption and cancer risk from an integrated series of multi-centric case–control studies conducted in Italy and Switzerland.

Methods

Since the early 1990s, a series of case–control studies of various neoplasms were conducted in Italy and Switzerland. These included 768 cases of oral and pharyngeal cancer (10), 198 cases of nasopharyngeal cancer (11), 304 cases of oesophageal cancer (12), 230 cases of stomach cancer (13), 1953 cases of colorectal cancer (14), 185 cases of liver cancer (15), 526 cases of pancreatic cancer (16), 527 cases of laryngeal cancer (17), 2569 cases of breast cancer (18), 454 cases of endometrial cancer (19), 1031 cases of ovarian cancer (20), 1294 cases of prostate cancer (21) and 767 cases of kidney cancer (22), 190 cases of non-Hodgkin’s lymphomas (23) (Table 1); and a total of over 17000 controls. Cases were individuals admitted to major teaching and general hospitals with incident, histologically confirmed cancers. Controls were patients with no history of their corresponding cancer site or dietary modification. The study protocols were revised and approved by the ethical committees of the hospitals involved, according to the regulations at the time of study conduction. All participants gave informed consent.

<table>
<thead>
<tr>
<th>Cancer sites</th>
<th>Cruciferous vegetables (≥ 1 v. &lt; 1 portion/week)</th>
<th>Allium vegetables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>OR</td>
</tr>
<tr>
<td>Oral cavity and pharynx</td>
<td>768</td>
<td>0·83</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>198</td>
<td>–</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>304</td>
<td>0·72</td>
</tr>
<tr>
<td>Stomach†</td>
<td>230</td>
<td>0·90</td>
</tr>
<tr>
<td>Colorectum</td>
<td>1953</td>
<td>0·83</td>
</tr>
<tr>
<td>Liver</td>
<td>185</td>
<td>0·72</td>
</tr>
<tr>
<td>Pancreas</td>
<td>326</td>
<td>0·90</td>
</tr>
<tr>
<td>Larynx</td>
<td>527</td>
<td>0·84</td>
</tr>
<tr>
<td>Breast</td>
<td>2569</td>
<td>0·83</td>
</tr>
<tr>
<td>Endometrium†</td>
<td>454</td>
<td>0·93</td>
</tr>
<tr>
<td>Ovary</td>
<td>1031</td>
<td>0·91</td>
</tr>
<tr>
<td>Prostate</td>
<td>1294</td>
<td>0·87</td>
</tr>
<tr>
<td>Kidney</td>
<td>767</td>
<td>0·68</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphomas</td>
<td>190</td>
<td>–</td>
</tr>
</tbody>
</table>

* Qualitative variable scored as 1 for ‘non-use or low use’, 2 for ‘intermediate use’, and 3 for ‘high use’.
† For endometrial and stomach cancer only, the OR is for consuming ≥ 2 v. 0 portions/week of onion.

Trained personnel interviewed cases and controls during their hospital stay using a structured questionnaire, including information on sociodemographic characteristics, anthropometric measures, lifestyle habits (e.g. tobacco smoking and alcohol drinking), dietary habits, personal medical history, family history of cancer, and, for women, menstrual and reproductive factors, use of oral contraceptives and hormone replacement therapy. The usual diet of the subjects 2 years before diagnosis (or hospital admission, for controls) was investigated using a reproducible and valid FFQ (24, 25), including seventy-eight food items and beverages. Subjects were asked to indicate the average weekly frequency of consumption for each dietary item, and the seasonal consumption for a few vegetables and fruit, with the corresponding duration.

OR, and the corresponding 95% CI, for quintiles (computed among controls) of vegetable or fruit intake were estimated by multiple logistic regression models. For nasopharyngeal and liver cancers and non-Hodgkin’s lymphomas, subjects were grouped according to quartiles of intake. Although models were derived independently for each cancer site, according to their potential confounding factors, all of them included terms for age, sex (when appropriate), study centre or area of residence, education and energy intake. Models for liver and breast cancers were also adjusted for alcohol drinking; models for stomach cancer were adjusted for tobacco smoking; and models for cancers of oral cavity and pharynx, nasopharynx, oesophagus, pancreas, larynx and kidney were adjusted for both alcohol drinking and tobacco smoking. Allowance for BMI or physical activity was performed for cancers of oral cavity and pharynx, pancreas, kidney and colorectum. A term for hepatitis was included in the models for liver cancer (B and/or C viruses) and non-Hodgkin’s lymphomas (C virus). Concerning female hormone-related cancers, OR for breast cancer were also adjusted for parity.
those for ovarian cancer were adjusted for parity and oral contraceptive use, and those for endometrial cancer were adjusted for parity, oral contraceptive use, hormone replacement therapy, age at menarche, menopausal status and history of diabetes.

In the present review, we also provided results on selected vegetables or fruit of specific interest, i.e. those that are cheap and easy to store and transport, and thus the most frequently consumed.

Vegetables

The present data supported a protective role of high intake of vegetables in the risk of several common epithelial cancers (Fig. 1). In particular, the OR for the highest compared with the lowest levels of vegetable intake were 0.19 (95% CI 0.13, 0.29) for oral and pharyngeal cancer, 0.51 (95% CI 0.29, 0.90) for nasopharyngeal cancer, 0.32 (95% CI 0.19, 0.55) for oesophageal cancer, 0.47 (95% CI 0.27, 0.81) for stomach cancer, 0.57 (95% CI 0.47, 0.69) for colorectal cancer, 0.72 (95% CI 0.31, 1.64) for liver cancer, 0.66 (95% CI 0.39, 1.12) for pancreatic cancer and 0.27 (95% CI 0.11, 0.62) for laryngeal cancer. Among hormone-related cancers, breast, endometrial and ovarian cancers were inversely related to vegetable consumption, with OR of 0.73 (95% CI 0.60, 0.88), 0.59 (95% CI 0.37, 0.94) and 0.47 (95% CI 0.34, 0.64), respectively, whereas the estimate for prostate cancer was below unity (i.e. 0.87), but not significant. A favourable role of vegetable intake was also observed for kidney cancer (OR 0.65, 95% CI 0.47, 0.90), as well as for non-Hodgkin’s lymphomas (OR 0.49, 95% CI 0.28, 0.87).

Cooking food may destroy selected nutrients and enzymes, alter the structure and thus digestibility of the food, and create by-products. However, for some foods and food components (e.g. lycopene), cooking not only kills potentially harmful organisms, but also actually improves the bioavailability of certain nutrients and digestibility. Findings from our case–control studies supported inverse relationships between consumption of both raw and cooked vegetables and the risk of cancers, with the exception of breast cancer, for which an inverse association was found essentially for raw vegetables. In general, these relationships appeared somewhat stronger for raw than cooked vegetables for upper digestive tract cancers. OR for the highest quartiles of raw and cooked vegetables were respectively, 0.25 and 0.50 for oral and pharyngeal cancer, 0.54 and 0.67 for nasopharyngeal cancer, 0.32 and 0.79 for oesophageal cancer, 0.59 and 0.57 for colorectal cancer, 0.77 and 0.57 for pancreatic cancer, 0.22 and 0.32 for laryngeal cancer, 0.73 and 0.96 for breast cancer, 0.47 and 0.65 for ovarian cancer, 0.87 and 0.74 for prostate cancer, and 0.74 and 0.68 for kidney cancer.

Cruciferous vegetables (cabbages, cauliflowers, broccoli, brussels sprouts and turnip greens) are important sources of sulphur-containing compounds (glucosinolates), whose major breakdown products (isothiocyanates and indoles) have anti-carcinogenic properties in vitro and animal studies. Our data showed significantly reduced OR for regular (≥1 portion/week) compared with no/occasional intake for cancers of the oral cavity and pharynx, oesophagus, colorectum, breast and kidney (Table 1).

Frequent consumption of allium vegetables, particularly onion, represents a peculiar feature of the Mediterranean diet. Garlic and onion are a source of several organosulphur compounds in addition to amino acids, vitamins and micronutrients, and have anti-inflammatory, anti-thrombotic, anti-coagulant and anti-mutagenic properties. For instance, garlic is known to contain a number of organosulphur compounds, including diallyl sulfoxides, which are thought to be responsible for its anti-tumour activities. These compounds are also believed to play a role in the prevention of cancer, possibly by inhibiting the activation of pro-carcinogens and by modulating the expression of genes involved in cell growth and survival. In addition, garlic and onion are known to contain a number of vitamins and minerals, including vitamin C, vitamin E, zinc, selenium and copper, which are all important for a healthy immune system.

In conclusion, the present review suggests that a diet rich in vegetables and fruits is associated with a lower risk of cancer, particularly of the upper digestive tract. The protective effects of vegetables and fruits are likely to be mediated by a number of anti-carcinogenic compounds, including vitamins, minerals, fibre, antioxidants and bioactive compounds.

Fig. 1. OR and 95% CI of selected cancers for the highest quintile v. the lowest quintile of vegetable consumption for all cancer sites, except for nasopharyngeal and liver cancers, and non-Hodgkin’s lymphomas (quartiles). Italy and Switzerland, 1991–2009. *Raw vegetables.

Fig. 2. OR and 95% CI of selected cancers for the highest quintile v. the lowest quintile of fruit consumption for all cancer sites, except for nasopharyngeal and liver cancers, and non-Hodgkin’s lymphomas (quartiles). Italy and Switzerland, 1991–2009. *Non-citrus fruits.
cholesterol-lowering and antioxidant effects. Data from the present series of case–control studies support a favourable role of allium vegetable intake in cancer risk in Italy and Switzerland (Table 1). In particular, a significantly decreased risk for high intakes of onion and garlic was found for cancers of oral cavity and pharynx, oesophagus, colorectum, larynx, endometrium, ovary and kidney (only garlic).

Fruit

Fruit was a favourable correlate of the risk of several cancers, particularly of the digestive tract; however, associations were generally weaker than for vegetables. The OR for the highest compared with the lowest levels of intake were 0·39 (95 % CI 0·26, 0·59) for oral and pharyngeal cancer, 0·52 (95 % CI 0·31, 0·87) for oesophageal cancer, 0·53 (95 % CI 0·30, 0·93) for stomach cancer, 0·72 (95 % CI 0·60, 0·87) for colorectal cancer, 0·60 (95 % CI 0·39, 0·98) for pancreatic cancer and 0·52 (95 % CI 0·35, 0·77) for laryngeal cancer (Fig. 2). A strong association with fruit was also found for non-Hodgkin’s lymphomas (OR 0·51, 95 % CI 0·30, 0·85). The OR for liver cancer was around 0·5; however, it did not reach statistical significance. No appreciable association was observed for hormone-related and kidney cancers, with OR ranging from 0·83 (endometrial cancer) to 1·02 (kidney cancer).

A reduced risk of cancers of the digestive tract and larynx was observed in our data for increasing intakes of citrus fruit, rich in vitamin C, flavanones and other compounds with antioxidant, anti-mutagenic and anti-proliferative properties. Compared with subjects consuming less than 1 portion of citrus fruit per week, the OR for those consuming 4 or more portions per week were 0·47 (95 % CI 0·36, 0·61) for oral cavity and pharyngeal cancer, 0·42 (95 % CI 0·25, 0·70) for oesophageal cancer, 0·69 (95 % CI 0·52, 0·92) for stomach cancer, 0·82 (95 % CI 0·72, 0·93) for colorectal cancer and 0·55 (95 % CI 0·37, 0·83) for laryngeal cancer. For other neoplasms, including cancers of breast, ovary, endometrium, prostate and kidney, no evidence of a beneficial effect of citrus fruit was found.

Apples contain several phytochemicals, including flavonoids and phenolic acids, and, when compared with other fruits, they had the second highest level of antioxidant activity (after cranberries) and phenolic compounds, and the highest level of free phenolic compounds. Subjects eating at least one apple a day had a reduced risk of cancers of oral cavity and pharynx (OR 0·79, 95 % CI 0·62, 1·00), colorectum (OR 0·80, 95 % CI 0·71, 0·90), larynx (OR 0·58, 95 % CI 0·44, 0·76), breast (OR 0·82, 95 % CI 0·73, 0·92) and ovary (OR 0·85, 95 % CI 0·72, 1·00). OR for oesophageal and prostate cancers were 0·75 (95 % CI 0·54, 1·03) and 0·91 (95 % CI 0·77, 1·07), respectively (Fig. 3). Tomatoes are a typical aspect of the Italian diet and, in general, of the Mediterranean diet, and are the main source of lycopene, a carotenoid with strong antioxidant properties that is not converted to vitamin A. Compared with the lowest quintile of tomato intake, the OR of colorectal cancer for the highest quintile was 0·8 (95 % CI 0·6, 0·9). We estimated an OR of 0·65 (95 % CI 0·4, 1·0) for cancer of oral cavity, pharynx and oesophagus, and one of 0·43 (95 % CI 0·3, 0·6) for cancer of the stomach, for the highest compared with the lowest quartile of intake.

Fibres, flavonoids and proanthocyanidins

With regard to specific components of vegetables and fruit, dietary fibre intake was inversely associated with most cancers considered, particularly with those of the digestive tract (Fig. 4). The OR for an increment of intake equal to the difference between the 80th and 20th percentile were 0·51 (95 % CI 0·40, 0·65) for colorectal cancer, 0·42 (95 % CI 0·25, 0·70) for oesophageal cancer, 0·59 (95 % CI 0·35, 0·97) for laryngeal cancer, 0·46 (95 % CI 0·28, 0·76) for breast cancer, 0·42 (95 % CI 0·24, 0·74) for ovary cancer and 0·42 (95 % CI 0·25, 0·70) for prostate cancer. For other neoplasms, including cancers of the digestive tract and larynx, no evidence of a beneficial effect of fibre was found.
Potential limitations include selection and information bias. However, participation of cases and controls was high and similar, and attention was paid in excluding from the control group subjects who were admitted for any condition that might have affected dietary habits. Furthermore, cases and controls came from comparable catchment areas and were interviewed by the same trained personnel in a hospital setting. Among the strengths are the large sample size, the use of a reproducible and valid FFQ, and the ability to adjust for a number of potential confounding factors for the cancers investigated, as well as energy intake.

In terms of population-attributable risks, 20–60% of digestive tract cancers in Italy could be attributable to low consumption of vegetables and fruit. In particular, the risks attributable to low consumption of vegetables and fruit in men and women were 25 and 17% for oral and pharyngeal cancer, 40 and 29% for oesophageal cancer, and 18 and 15% for laryngeal cancer, respectively. In both sexes combined, the attributable risks were 60% for stomach cancer and 43% for colorectal cancer. For breast cancer, the attributable risk was 21%.

The favourable effect of vegetables and fruit against most forms of cancers has been related to several of their constituents, in the absence, however, of a clear understanding of which of these may be the key relevant ones. Indeed, vegetables and fruit are sources of a wide variety of micronutrients and other bioactive compounds, including carotenoids, folate, vitamins C, D and E as well as vitamin B9, flavonoids, dietary fibre and selenium. These may act against cancer through their antioxidant activities, free radical-trapping capacity, modulation of detoxification enzymes, anti-mutagenic and anti-proliferative properties, stimulation of the immune system, as well as modulation of hormone concentration and hormone metabolism. Given the high correlation between several micronutrients, it is difficult to disentangle their role and detect which specific component or group of components is responsible for a protective role against cancer. Since several antioxidants may influence cancer risk and act to prevent carcinogenesis, examining overall antioxidant exposure rather than individual antioxidants has recently been proposed. Inverse relationships of the Non-Enzymatic Antioxidant Capacity

Discussion

Data from this integrated network of studies support a favourable role of vegetable intake on the risk of several common cancers, particularly of the digestive tract. Fruit intake was inversely related to the risk of digestive tract cancers as well, with associations generally less stronger than those for vegetable intake.

Potential associations were found for cancers of the stomach, colorectum, pancreas, endometrium and prostate, with OR for the highest quintiles of intake equal to the difference between the 80th and 20th percentile of 0·58 (95% CI 0·34, 0·96) for nasopharyngeal cancer, 0·47 (95% CI 0·28, 0·79) for stomach cancer, 0·4 (95% CI 0·2, 0·7) for pancreatic cancer, 0·3 (95% CI 0·2, 0·4) for laryngeal cancer and 0·68 (95% CI 0·53, 0·88) for ovarian cancer. Conversely, a lack of association was observed for cancers of breast, endometrium, prostate and kidney.

Results on flavonoids from the present series of Italian and Swiss case–control studies showed a significant protective role of flavanones on upper aero-digestive tract cancers (OR for the highest v. the lowest quintiles of intake 0·51, 95% CI 0·37, 0·71 for oral cavity and pharyngeal cancer; 0·38, 95% CI 0·23, 0·66 for oesophageal cancer; 0·60, 95% CI 0·41, 0·89 for laryngeal cancer), flavonols (OR 0·64, 95% CI 0·54, 0·77) and anthocyanidins (OR 0·67, 95% CI 0·54, 0·82) on colorectal cancer, flavonols (OR 0·80, 95% CI 0·66, 0·98) and flavones (OR 0·81, 95% CI 0·66, 0·98) on breast cancer, and flavonoids (OR 0·63, 95% CI 0·47, 0·84) and isoflavones (OR 0·51, 95% CI 0·37, 0·69) on ovarian cancer. Specific results on proanthocyanidins are shown in Fig. 5. Significant inverse associations were found for cancers of the stomach, colorectum, pancreas, endometrium and prostate, with OR for an increment of intake equal to the difference between the 20th and the 80th percentile of 0·58 (95% CI 0·44, 0·77) for stomach cancer, 0·88 (95% CI 0·81, 0·95) for colorectal cancer, 0·62 (95% CI 0·49, 0·79) for pancreatic cancer, 0·81 for endometrial cancer (95% CI 0·66, 0·98) and 0·87 (95% CI 0·76, 0·99) for prostate cancer (unpublished results).
(NEAC) from diet, measured in terms of ferric reducing–antioxidant power (FRAP), trolox equivalent antioxidant capacity (TEAC) and total radical-trapping antioxidant parameter (TRAP), were reported in our studies for colorectal and stomach cancer. The OR of colorectal cancer for the highest v. the lowest quintiles were 0.68 (95% CI 0.57, 0.82) for FRAP, 0.69 (95% CI 0.57, 0.85) for TEAC and 0.69 (95% CI 0.57, 0.83) for TRAP. The corresponding OR for stomach cancer were 0.54 (95% CI 0.33, 0.88) for FRAP, 0.67 (95% CI 0.42, 1.07) for TEAC and 0.57 (95% CI 0.39, 0.90) for TRAP, respectively (submitted).

The beneficial effect of high intakes of vegetables and fruit in these studies may be also due, at least in part, to the fact that their high consumption often accompanies lower intakes of foods that may be positively related to the risk of cancer. They may, therefore, represent a general indicator of healthy diet and lifestyle habits. Indeed, high intakes of fruit and vegetables are key features of the Mediterranean diet, which has been inversely related to overall mortality as well as to specific health outcomes including CVD and cerebrovascular diseases, as well as cancer. A beneficial role of vegetable and fruit consumption in the risk of cancer has been reported either from a number of case–control studies or from large cohort investigations. However, also a number of prospective studies, which generally have a higher level of evidence than case–control studies, have reported null associations, casting some doubts about the possible benefits of high vegetable and fruit consumption. Findings from the European Prospective Investigation into Cancer and Nutrition (EPIC) study, across ten countries, have supported significant inverse associations between fruit consumption and upper aero-digestive tract cancers (mouth, pharynx, larynx and oesophagus) and lung cancer (in smokers), as well as between fruit and vegetable consumptions and colorectal cancer. For the other cancer sites considered (i.e. stomach, pancreas, breast, cervix, prostate, bladder and lymphoma), no significant association was reported for both fruit and vegetables consumption. A large number of studies conducted in Mediterranean countries, indicate a beneficial effect of vegetable and fruit intake on the risk of several cancer sites, and this may well be due to the relative abundance of vegetables and fruit in the Mediterranean diet.

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**References**


