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Cruciferous vegetables and cancer risk in a network of case–control studies

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Background: Cruciferous vegetables have been suggested to protect against various cancers, though the issue is open to discussion. To further understand their role, we analyzed data from a network of case–control studies conducted in Italy and Switzerland.

Patients and methods: The studies included a total of 1468 cancers of the oral cavity/pharynx, 505 of the esophagus, 230 of the stomach, 2390 of the colorectum, 185 of the liver, 326 of the pancreas, 852 of the larynx, 3034 of the breast, 367 of the endometrium, 1031 of the ovary, 1294 of the prostate, 767 of the kidney, and 11 492 controls. All cancers were incident, histologically confirmed; controls were subjects admitted to the same network of hospitals as cases for a wide spectrum of acute nonneoplastic conditions.

Results: The multivariate odds ratio (OR) for consumption of cruciferous vegetables at least once a week as compared with no/occasional consumption was significantly reduced for cancer of the oral cavity/pharynx (OR = 0.83), esophagus (OR = 0.72), colorectum (OR = 0.83), breast (OR = 0.83), and kidney (OR = 0.68). The OR was below unity, but not significant, for stomach (OR = 0.90), liver (OR = 0.72), pancreatic (OR = 0.90), laryngeal (OR = 0.84), endometrial (OR = 0.93), ovarian (OR = 0.91), and prostate (OR = 0.87) cancer.

Conclusion: This large series of studies provides additional evidence of a favorable effect of cruciferous vegetables on several common cancers.

Key words: brassicaceae, cancer, case–control study, cruciferous vegetables, risk factor, vegetables

introduction

The issue of vegetables and cancer risk has long been considered in the absence, however, of definite quantification [1, 2].

Cruciferous vegetables have been of specific interest due to their content in glucosinolates, whose major breakdown products [isothiocyanates (ITCs) and indoles] have anticarcinogenic properties in *in vitro* and animal studies [3–5]. Glucosinolates are converted to ITCs and indoles through myrosinase activity, a β -thioglucosidase enzyme found in vacuoles and activated following mastication or cutting of plant tissue [6]. Most of the ITCs are metabolized *in vivo* through the mercapturic acid pathway; indole compounds can react

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with ascorbic acid producing ascorbigen and, at the low pH of the stomach, a series of condensed products that may act as further bioactive compounds [6].

Relatively few epidemiological studies have evaluated the specific role of cruciferous vegetables on cancer risk [4, 7]. Inverse associations have been reported in case-control studies on cancers of the stomach, colon, lung, and breast [4, 7–12], although the evidence from cohort studies has been less convincing [4, 13]. Data are scanty and inconclusive for other selected neoplasms [1, 4, 7, 14–18].

In order to add further information on this issue, we considered the association between cruciferous vegetables and the risk of several common cancers using data from a network of case-control studies conducted in Italy and Switzerland.

materials and methods

Between 1991 and 2009, we conducted an integrated series of case-control studies on various neoplasms in different areas of Northern (the greater Milan area; the provinces of Pordenone, Padua, Udine, Gorizia and Forlì; the urban area of Genoa), Central (the provinces of Rome and Latina), and Southern (the urban area of Naples) Italy. We also conducted companion studies on cancers of the oral cavity and pharynx, esophagus, colorectum, larynx, and breast in the canton of Vaud, Switzerland. The studies included a total of 1468 cases of cancer of the oral cavity and pharynx [19–21], 505 of the esophagus [22, 23], 230 of the stomach [24], 2390 of the colorectum [25, 26], 185 of the liver [27], 326 of the pancreas [28], 852 of the larynx [29], 3034 of the breast [30, 31], 367 of the endometrium [32], 1031 of the ovary [33], 1294 of the prostate [34], 767 of the kidney [35], and a total of 11 492 controls (Table 1).

Cases were incident histologically confirmed cancers, identified in the major teaching and general hospitals of the study areas. Controls were subjects admitted to the same network of hospitals as cases for a wide spectrum of acute nonneoplastic conditions unrelated to known risk factors for the corresponding cancer site. Overall, 7.2% of controls were admitted for traumatic conditions, 23.1% for nontraumatic orthopedic conditions, 32.7% for acute surgical conditions, and 37.1% for miscellaneous other illnesses. The proportion of refusal of subjects approached was <5% in Italy

Table 1. Distribution of cases with selected cancers and corresponding controls by sex and median age

Cancer site, references	Cases (men/women)	Median age (years)	Controls (men/women)	Median age (years)
Oral cavity and pharynx	1190/278	58	2553/1208	58
Esophagus	438/67	60	919/340	60
Stomach	143/87	63	286/261	63
Colorectum	1401/989	62	2586/2357	58
Liver	149/36	66	278/126	65
Pancreas	174/152	63	348/304	63
Larynx	770/82	62	1564/406	61
Breast	–/3034	55	–/3392	56
Endometrium	–/367	60	–/798	61
Ovary	–/1031	56	–/2411	57
Prostate	1294/–	66	1451/–	63
Kidney	494/273	62	988/546	62

Italy and Switzerland, 1991–2009.

and ~15% in Switzerland. 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, and all participants gave informed consent.

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, alcohol drinking), dietary habits, personal medical history, family history of cancer, and, for women, menstrual and reproductive factors, use of oral contraceptives (OCs), and hormone replacement therapy (HRT). Subjects' usual diet 2 years before diagnosis (or hospital admission, for controls) was investigated using a reproducible and valid 78-item food frequency questionnaire (FFQ), which included a specific question on weekly consumption of cruciferous vegetables (cabbages, cauliflowers, broccoli, brussels sprouts, and turnip greens) [36, 37]. Seasonal consumption of cruciferous vegetables and the corresponding duration was also considered.

Odds ratios (ORs) for each cancer site according to the consumption of cruciferous vegetables and the corresponding 95% confidence intervals (CIs) were estimated by unconditional multiple logistic regression models [38]. The models included terms for sex, age, study center, year of interview, education, alcohol drinking, tobacco smoking, body mass index, and total energy intake. For breast, ovarian, and endometrial cancer, models further included parity, menopausal status, age at menopause, and OC and HRT use, and, for breast only, age at first birth. ORs were computed comparing the consumption of at least one portion of cruciferous vegetables (~125 g) per week to no or occasional consumption. Continuous ORs for an increment of one portion per week were also estimated. All statistical analyses were performed with SAS 9.1 statistical software (SAS Institute, Cary, NC).

results

Table 2 gives the distribution of cancer cases and controls according to the consumption of cruciferous vegetables and the corresponding ORs (also shown in Figure 1A). The ORs for subjects consuming of at least one portion of cruciferous vegetables per week as compared with those with no or occasional consumption were significantly below unity for cancers of the oral cavity and pharynx (OR = 0.83), esophagus (OR = 0.72), colorectum (OR = 0.83), breast (OR = 0.83), and kidney (OR = 0.68). The point estimates were also below unity in the absence, however, of significant associations for stomach (OR = 0.90), liver (OR = 0.72), pancreatic (OR = 0.90), laryngeal (OR = 0.84), endometrial (OR = 0.93), ovarian (OR = 0.91), and prostatic (OR = 0.87) cancer. The continuous ORs for one portion per week were 0.82 for oral and pharyngeal, 0.78 for esophageal, 0.84 for stomach, 0.88 for colorectal, 0.94 for liver, 0.84 for pancreatic, 0.87 for laryngeal, 0.94 for breast, 0.98 for endometrial, 0.87 for ovarian, 0.87 for prostate, and 0.78 for kidney cancer, but significant only for cancers of the oral cavity and pharynx, colorectum, and kidney (Figure 1B). The estimates did not meaningfully change after adjustment for fruit or meat, while they were slightly reduced after allowance for noncruciferous vegetables. This is due to the colinearity between various types of vegetables.

Table 3 gives the ORs in strata of sex, age (<60, ≥60 years), tobacco smoking (nonsmokers and current smokers), and alcohol consumption (<3 drinks/day and ≥3 drinks/day) for

Table 2. Distribution of cases with selected cancers and controls and corresponding OR and 95% CI, according to consumption of cruciferous vegetables

Cancer site	Weekly consumption of cruciferous vegetables		Continuous OR ^a for one portion/week (95% CI)
	<1 portion	≥1 portion	
Oral cavity and pharynx			
Cases:controls	1096/2397	372/1364	
OR ^a (95% CI)	1 ^b	0.83 (0.70–0.98)	0.82 (0.72–0.93)
Esophagus			
Cases:controls	409/874	96/385	
OR ^a (95% CI)	1 ^b	0.72 (0.52–0.99)	0.78 (0.60–1.01)
Stomach			
Cases:controls	172/400	58/147	
OR ^a (95% CI)	1 ^b	0.90 (0.61–1.30)	0.84 (0.62–1.14)
Colorectum			
Cases:controls	1784/3595	606/1348	
OR ^a (95% CI)	1 ^b	0.83 (0.74–0.94)	0.88 (0.80–0.97)
Liver			
Cases:controls	122/267	63/137	
OR ^a (95% CI)	1 ^b	0.72 (0.47–1.11)	0.94 (0.65–1.37)
Pancreas			
Cases:controls ^c	257/510	69/141	
OR ^a (95% CI)	1 ^b	0.90 (0.63–1.30)	0.84 (0.61–1.14)
Larynx			
Cases:controls ^c	634/1352	217/617	
OR ^a (95% CI)	1 ^b	0.84 (0.67–1.05)	0.87 (0.74–1.03)
Breast			
Cases:controls	2293/2384	741/1008	
OR ^{a,d} (95% CI)	1 ^b	0.83 (0.74–0.94)	0.94 (0.86–1.03)
Endometrium			
Cases:controls	248/562	119/236	
OR ^{a,e} (95% CI)	1 ^b	0.93 (0.68–1.27)	0.98 (0.75–1.28)
Ovary			
Cases:controls	744/1816	287/595	
OR ^{a,e} (95% CI)	1 ^b	0.91 (0.76–1.11)	0.87 (0.74–1.03)
Prostate			
Cases:controls ^c	1048/1159	246/291	
OR ^a (95% CI)	1 ^b	0.87 (0.70–1.09)	0.87 (0.72–1.06)
Kidney			
Cases:controls	598/1129	169/405	
OR ^a (95% CI)	1 ^b	0.68 (0.54–0.84)	0.78 (0.65–0.94)

Italy and Switzerland, 1991–2009.

^aEstimates from logistic regression model adjusted for sex (when appropriate), age, study center, year of interview, education, body mass index, alcohol drinking, tobacco smoking, and total energy intake.

^bReference category.

^cThe sum does not add up to the total because of some missing values.

^dFurther adjusted for age at first birth, parity, oral contraceptive and hormone replacement therapy use, and age at menopause.

^eFurther adjusted for parity, oral contraceptive and hormone replacement therapy use, and age at menopause.

OR, odds ratio; CI, confidence interval.

cancer sites significantly associated with cruciferous vegetables. No inverse relation with oral and pharyngeal cancer was found in women and in moderate drinkers, possibly on account of the limited number of cases in these strata; for colorectal cancer, no protection was found for subjects below age 60 years and for heavy drinkers; for kidney cancer, the inverse association was stronger in younger as compared with older subjects. However, no significant heterogeneity in risk estimates was observed across any of the other strata considered.

discussion

The present analysis confirms that cruciferous vegetables have a beneficial role on the risk of various common cancers, in particular, those of the upper digestive tract, colorectum, breast, and kidney.

Our results for colorectum are consistent with the conclusions of a International Agency for Research on Cancer working group and the results from a few subsequent publications showing that the intestine is among the cancer

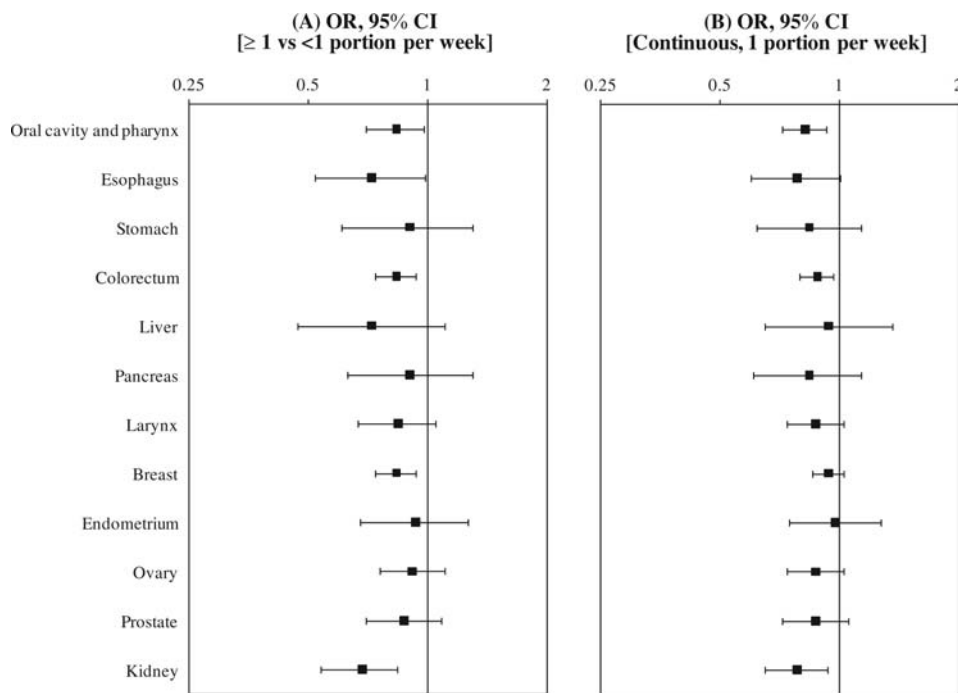


Figure 1. Odds ratios (OR) of selected cancers and corresponding 95% confidence intervals (CI) according to: (A) regular (≥ 1 portion/week) consumption of cruciferous vegetables versus no/occasional consumption (< 1 portion/week) and (B) for an increment of one portion of cruciferous vegetables per week. Italy and Switzerland, 1991–2009. ORs are the estimates from logistic regression model adjusted for sex (when appropriate), age, study center, year of interview, education, body mass index, alcohol drinking, tobacco smoking, and total energy intake. OR for breast cancer was further adjusted for age at first birth, parity, oral contraceptive and hormone replacement therapy use, and age at menopause; those for ovarian and endometrial cancer were further adjusted for parity, oral contraceptive and hormone replacement therapy use, and age at menopause.

Table 3. OR^a of selected cancers and 95% CI, according to regular (≥ 1 portion/week) consumption of cruciferous vegetables versus no/occasional consumption (< 1 portion/week), in strata of sex, age, tobacco smoking, and alcohol consumption

Covariate	Cancer site				
	Oral cavity and pharynx	Esophagus	Colorectum	Breast ^b	Kidney
Sex					
Men	0.70 (0.57–0.85) ^c	0.68 (0.48–0.98)	0.82 (0.70–0.96)	–	0.81 (0.61–1.07)
Women	1.05 (0.76–1.44) ^c	0.81 (0.38–1.73)	0.85 (0.70–1.04)	0.83 (0.74–0.94)	0.52 (0.36–0.75)
Age (years)					
<60	0.75 (0.60–0.95)	0.59 (0.36–0.97)	1.08 (0.90–1.29) ^d	0.92 (0.79–1.07)	0.52 (0.37–0.73) ^c
≥ 60	0.81 (0.63–1.04)	0.78 (0.51–1.20)	0.71 (0.61–0.83) ^d	0.73 (0.60–0.88)	0.80 (0.60–1.07) ^c
Tobacco smoking					
Non smokers	0.89 (0.71–1.12)	0.69 (0.44–1.06)	0.82 (0.72–0.94)	0.84 (0.73–0.96)	0.67 (0.51–0.87)
Current smokers	0.68 (0.53–0.88)	0.59 (0.37–0.95)	0.84 (0.67–1.07)	0.78 (0.61–1.01)	0.68 (0.45–1.04)
Alcohol consumption					
<3 drinks/day	1.20 (0.83–1.74) ^d	0.94 (0.33–2.66)	0.66 (0.52–0.83) ^c	0.91 (0.77–1.07)	0.53 (0.35–0.80)
≥ 3 drinks/day	0.60 (0.50–0.72) ^d	0.60 (0.43–0.83)	0.92 (0.80–1.06) ^c	0.76 (0.64–0.91)	0.74 (0.57–0.96)

Italy and Switzerland, 1991–2009.

^aEstimates from logistic regression model adjusted for sex (when appropriate), age, study center, year of interview, education, alcohol drinking, tobacco smoking, body mass index, and total energy intake.

^bFurther adjusted for age at first birth, parity, age at menopause, oral contraceptives use, and hormone replacement therapy use.

^cP value for interaction < 0.05 .

^dP value for interaction < 0.005 .

OR, odds ratio; CI, confidence interval.

sites for which the evidence of a beneficial effect of cruciferous vegetables is more convincing [4, 7, 11]. Breast cancer has also been reported to be inversely related to cruciferous vegetables

[7–9, 39]. Inverse relations for cancers of the oral cavity and esophagus have been reported in a few other (case–control) studies, although data for these neoplasms are limited [1, 4,

40]; these cancers, however, have been consistently related to low vegetables consumption [1]. Data are even scantier for kidney cancer [4, 41]. The absence of an inverse relation with gastric cancer in our data is somewhat in contrast with the results of previous studies suggesting a beneficial effect of cruciferous vegetables, although the issue remains open to discussion [4, 7].

The beneficial effect of cruciferous vegetables on various common cancers may be due to their high content of several antioxidants and vitamins, including carotenoids, polyphenols, vitamin C, and folate [3, 4, 42]. Moreover, they contain high levels of glucosinolates, whose major breakdown products (indoles and ITCs) have been shown—in *in vitro* and animal studies—to have high anticarcinogenic properties, particularly on cancers of the digestive tract, liver, lung, and breast [4, 43]. In cultured human cancer cells, ITCs can induce apoptosis and arrest of cell cycle that are critical processes in the prevention of tumor growth [3]. Moreover, ITCs seem to inhibit histone deacetylase activity, which removes acetyl groups from histones, thus enabling transcription of tumor suppressor proteins that promote differentiation and apoptosis in precancerous cells [44]. ITCs can also affect xenobiotic-metabolizing enzymes that are able to modulate the access of chemical carcinogens to DNA in target tissues [4, 43, 45]. In particular, ITCs can modulate expression of phase II enzymes, while indoles act as bifunctional inducers of both phase I and phase II enzymes. This mechanism of action can explain the protection against numerous xenobiotics and carcinogens (e.g. those produced through tobacco smoke or cooked food mutagens), and it was demonstrated also in human colon cancer cell lines following the supplementation with ITCs and indoles where the induction of phase I and phase II enzymes was able to protect cells against benzo[*a*]pyrene-induced DNA damage [43]. Indoles can also decrease estrogen receptor- α expression [46]. Through this mechanism, estrogen-dependent signal transduction that results in breast cancer cell proliferation would be decreased, thus providing a molecular basis for the chemopreventive activity against breast cancer.

In the present study, the inverse association with cruciferous vegetables was stronger in smokers than in nonsmokers in the absence, however, of significant heterogeneity. In a recent intervention study, smokers had a reduction in both endogenous and *ex vivo*-induced DNA damage following the regular intake of 250 g of steamed broccoli for 10 days, and this effect was particularly evident in subjects with glutathione-S-transferase (GST) M1-null genotype [44]. GSTs are involved in the metabolism of ITCs and may modulate the effect of cruciferous vegetables on cancer risk [7]. However, we could not determine the impact of GST M1 polymorphism on our results.

It is difficult to extrapolate the contribution of a specific class of vegetables on cancer risk, and in particular, it is not possible to disentangle the specific role of cruciferous vegetables from that of all vegetables because of their high correlation.

Our FFQ was not specifically designed to investigate the consumption of cruciferous vegetables and did not allow us to investigate single items of the Brassicaceae family. The intake of cruciferous vegetables is highly variable in different

populations [4]. Asian and Middle Eastern populations have relatively high intakes (40–80 g/day) as compared with European ones (5.7–32.7 g/day) with an estimate in the Italian population of ~11.5 g/day [46]. Thus, the low consumption of cruciferous vegetables in our study population—as in other European countries [47]—did not allow us to study specific levels of consumption. Apart from differences in the total amount of cruciferous vegetables, the levels of specific glucosinolate derived ITCs can vary depending on the vegetable consumed. As ITCs can have different strength of activity depending on chemical structure, this may in part explain discrepant results in the literature.

Our studies have the inherent limitations of case-control studies, including potential recall and selection bias. However, cases and controls in our studies came from comparable catchment areas, were interviewed by uniformly trained interviewers in the hospital setting, and their participation was high, thus reducing any such bias. Moreover, we took great care in excluding from the control group of all diagnoses that might have led to long-term modifications of diet and other risk factors for the neoplasms considered. Among the strengths of the study, there are the large sample size, the use of a reproducible and valid FFQ [36, 37], and the ability to adjust for total energy intake, as well as for other major potential confounding factors for the cancers investigated.

In conclusion, this large integrated series of studies provides additional evidence of a favorable effect of cruciferous vegetables on several common cancer sites. Promoting the intake of cruciferous vegetables in populations where consumption is comparably low should be considered [46].

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disclosure

The authors declare no conflict of interest.

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