Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk[1–4]

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ABSTRACT

Background: Diets rich in fruit and vegetables have been recommended for preventing cancer. The evidence supporting this recommendation is based on observational studies, although results of several prospective studies have cast some doubts on whether fruit and vegetables are associated with cancer risk reduction.

Objective: We sought to summarize evidence from case-control and prospective studies on fruit and vegetable intake and cancer risk with a meta-analytic approach.

Design: Published case-control and cohort studies that reported on total vegetable and fruit intake and risk of cancer of several sites were included. Relative risks were estimated by using linear logistic regression models.

Results: Case-control studies overall support a significant reduction in the risks of cancers of the esophagus, lung, stomach, and colorectum associated with both fruit and vegetables; breast cancer is associated with vegetables but not with fruit; and bladder cancer is associated with fruit but not with vegetables. The overall relative risk estimates from cohort studies suggest a protective effect of both fruit and vegetables for most cancer sites considered, but the risk reduction is significant only for cancers of the lung and bladder and only for fruit.

Conclusions: Prospective studies provide weaker evidence than do case-control studies of the association of fruit and vegetable consumption with reduced cancer risk. The discrepancies may be related to recall and selection biases in case-control studies. In contrast, the association may have been underestimated in prospective studies because of the combined effects of imprecise dietary measurements and limited variability of dietary intakes within each cohort. *Am J Clin Nutr* 2003;78(suppl):559S–69S.

KEY WORDS Fruit, vegetables, cancer risk, odds ratio, case-control study, cohort study

INTRODUCTION

Diet and physical activity together with smoking are the most important modifiable determinants of cancer risk. Apart from overweight and obesity, the most abundant evidence for an effect of diet on cancer incidence has been related to a lower risk with greater intake of fruit and vegetables. In 1997, an international review panel (World Cancer Research Fund–American Institute for Cancer Research) (1) concluded that there was convincing evidence that high intake of vegetables decreases the risk of cancers of the mouth and pharynx, esophagus, lung, stomach, colon, and rectum; that it probably decreases the risk of cancers of the larynx, pancreas, breast, and bladder; and that it possibly decreases the risk of cancers of the liver, ovary, endometrium, cervix, prostate, thyroid, and kidney. High fruit intake was considered to decrease the risk of most of the cancers previously mentioned, with the exception of cancers of the liver, prostate, kidney, colon, and rectum, for which the data were considered limited or inconsistent. In 1998, the expert group commissioned by the Chief Medical Officer's Committee on Medical Aspects of Food and Nutrition Policy of the United Kingdom (COMA) (2) reached similar conclusions (**Table 1**).

However, some recent results of epidemiologic studies do not support the hypothesis of the protective role of fruit and vegetables in the etiology of cancer. For colorectal cancer, while recent case-control studies have reported a protective effect of vegetables and to a lesser extent of fruit (3–9), cohort studies have almost unanimously reported null associations (10–14), with one exception (15). The Polyp Prevention Trial did not provide evidence that increasing fruit and vegetable consumption for 4 y lowers the risk of recurrent adenomas (16). Regarding gastric cancer, only 2 out of the 5 case-control studies (17, 18) and 2 out of 4 cohort studies (19, 20) found significant protection for fruit. For breast cancer, 2 case-control studies reported a protective effect for vegetables and fruit (21, 22), but the pooled analysis of 8 cohort studies did not find any protection from vegetables or fruit (23). Regarding bladder cancer risk, the Health Professionals Follow-up Study (24) found a nonsignificant modest protection for vegetables and no association for fruit, and a Japanese cohort study (25) found a significant protective effect of fruit and vegetables, but the dietary questionnaire was very limited. For lung, 2 case-control studies out of 6, both in nonsmoking females (26, 27), reported significant protective effects of vegetables and 3 studies found significant protective effect of fruit (27–29). Three prospective studies (30–32) reported significant protective effects for fruit and vegetables, but they were statistically significant in

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TABLE 1
Summary of main conclusions of the WCRF-AICR and COMA reports on the possible effect of high fruit and vegetable consumption on cancer risk[1]

Cancer site	WCRF-AICR	COMA
Mouth and pharynx	Convincing	Weakly consistent for fruit, inconsistent for vegetables
Larynx	Probably	Moderately consistent, limited data
Esophagus	Convincing	Strongly consistent
Lung	Convincing, particularly for green vegetables and carrots	Moderately consistent for fruit, weakly consistent for vegetables
Stomach	Convincing, in particular for raw vegetables, allium vegetables, and citrus fruit	Moderately consistent
Pancreas	Probable	Strongly consistent, limited data
Liver	Possible for vegetables, not fruit	Not included in the review
Colon and rectum	Convincing for vegetables, limited and inconsistent data for fruit	Moderately consistent for vegetables, inconsistent and limited data for fruit
Breast	Probable, in particular for green vegetables	Moderately consistent for vegetables, weakly consistent for fruit
Ovary	Possible	Insufficient
Endometrium	Possible	Insufficient
Cervix	Possible	Strongly consistent, limited data
Prostate	Possible for vegetables, inconsistent for fruit	Moderately consistent, especially raw and salad type for vegetables, inconsistent for fruit
Kidney	Possible for vegetables, limited evidence for fruit	Not included in the review
Thyroid	Possible	Not included in the review
Bladder	Probable	Moderately consistent, limited data

[1] WCRF-AICR, World Cancer Research Fund–American Institute for Cancer Research; COMA, Chief Medical Officer's Committee on Medical Aspects of Food and Nutrition Policy of the United Kingdom.

the Nurses' cohort (31) for only vegetables. The Health Professionals Cohort Study (31) failed to find evidence of a protective effect of fruit or vegetables.

The results of prospective studies have cast some doubts about the possible benefits of high vegetable and fruit consumption in relation to cancer and whether the recommendations of increasing fruit and vegetable intake for reducing cancer risk are still valid. The purpose of this review is to examine the epidemiologic evidence from case-control and cohort studies on total fruit and vegetable intake for different cancer sites by summarizing it quantitatively with a meta-analytic approach.

METHODS

The criteria for inclusion of epidemiologic studies were as follows: case-control or cohort studies evaluating the relationship between total vegetable and/or total fruit consumption and risk of cancer (esophagus, larynx, stomach, colon and rectum, breast, lung, and bladder); in males, females, or in both sexes; with incidence or mortality as the endpoint; providing the information required for the statistical analysis; published in English between January 1973 and June 2001; and referenced in the MEDLINE database (National Library of Medicine, Washington, DC). We identified articles by the key words vegetables, fruit, diet, and lifestyle, and the cancer sites. Besides the MEDLINE search, we systematically examined the list of references in the identified articles.

Definition of exposure

We included in the analyses the food groups defined in the articles as "all vegetables," "total vegetables," or "vegetables" and "all fruit," "total fruit," or "fruit." The variables raw vegetables, cooked vegetables, green salads, green-yellow vegetables, citrus fruit, and other fruit were not considered equivalent to "all vegetables" or "all fruit" and were not included in the meta-analysis. Studies that included potatoes or pulses in the vegetable group were included in the analyses.

In Asian studies that reported fresh vegetables and pickled vegetables separately, we considered the variable "fresh vegetables" equivalent to the food group "total vegetables" of studies conducted in populations where pickled vegetables are not or are very rarely consumed. Studies that reported "fresh fruit" were included under the hypothesis that fresh fruit accounted for a very high proportion of the total fruit consumption.

Statistical methods

The method used is described in detail in a published meta-analysis of red and processed meat and colorectal cancer (33). Briefly, we computed the summary estimate of the relative risk (RR) as the pooled coefficient b in the linear logistic regression model $\ln RR = bX$, where X is the difference between each level of intake and the reference category. The individual slopes of each study were combined, weighting by the inverse of their variances. Random effect models were assumed when there was evidence of heterogeneity. All the analyses were done in SAS version 8.02 (SAS Institute Inc, Cary, NC).

We extracted from the studies the risk estimates that reflected the greatest degree of controlling for confounders (ie, risk factors and/or energy) and all risk estimates by subgroups (eg, by sex, cancer site). The statistical method required that the number of case subjects, the number of control subjects, the adjusted logarithm of the RR, and its variance estimate for 3 or more exposure levels be known. Some extra computations were performed to complete the required data, provided that the paper gave the information to do so. If this was not possible, the article was not included in the analysis.

Subgroup analyses were performed to explore the sources of heterogeneity by study design (case control or cohort) and geographical

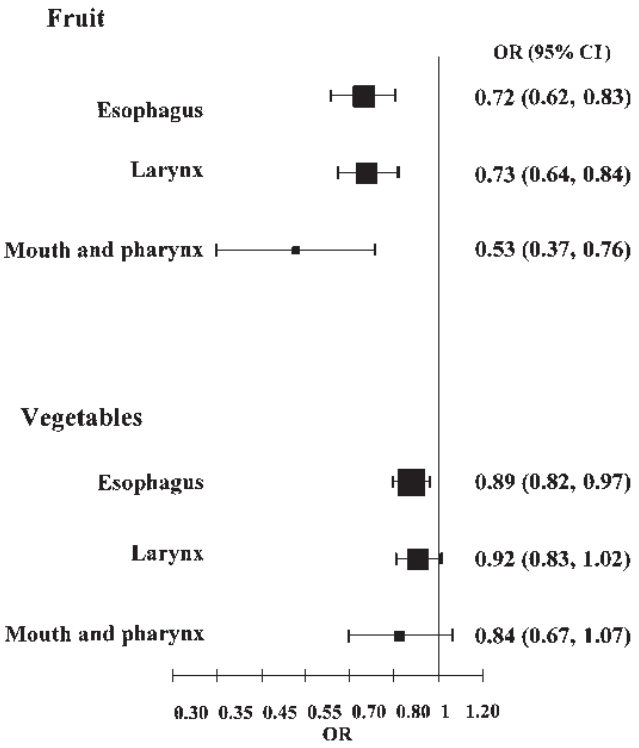

FIGURE 1. Meta-analysis of case-control studies on fruit and vegetable intake. Estimated odds ratios (ORs) for the development of cancers of the upper aerodigestive tract with an increase in fruit or vegetable intake of 100 g/d.

area (North America, Europe, Asia, South America), depending on the number of studies. In all analyses, the unit of intake was grams per day. When the exposures were expressed on a qualitative scale (eg, high, medium, low), we used the mean consumption and the variance given in the original article to estimate midpercentiles for each level of intake, assuming a log-normal distribution. When exposure was expressed in frequency of consumption and no mean intake was reported, we used 80 g as the approximate average "portion size" for vegetables and 100 g for fruit. These values were derived from preliminary results of the European Prospective Investigation into Cancer and Nutrition (EPIC) (E Riboli, unpublished observations, 2001). When the highest category was open ended, the upper boundary of the open-ended interval was calculated using as interval length the width of the closest interval. When the lowest category was open ended, the lowest boundary was assumed to be zero. The exposure value for each category was then calculated as the midpoint of the logarithm of the boundaries, retransformed to grams per day.

RESULTS

Oral and pharyngeal cancer

Published studies on cancers of the mouth and pharynx include a variety of cancer sites that were not always clearly defined in the articles. We extracted information from 12 case-control studies (34–45) that reported results on oral and pharyngeal cancer. Three studies were excluded because they did not provide the number of cases and controls by category of consumption or we could not compute it from the publications (35, 36, 40). The excluded studies found significant protective effect of fruit, with the exception of the Indian study (36), in which fruit consumption was lower than the values reported in other studies. Five studies were excluded from the analysis on vegetables (35, 36, 40, 41, 43). All the excluded studies found that high consumption of vegetables, raw or cooked, was a significant protective factor. One study in tongue cancer (46) not included in the analysis found significant protective effects of fruit and vegetables.

The overall results indicate that fruit intake consistently decreases the risk of oral and pharyngeal cancer (**Figure 1**). The protective effect is statistically significant for fruit but not for vegetables. We could not perform analysis according to smoking status, but we used odds ratios adjusted by smoking. In individual studies that did the analysis by smoking status, the protective effect was present in those who chewed and/or smoked tobacco and in nonusers as well. Smoking and alcohol consumption remained the most important risk factors for these cancer sites.

Laryngeal cancer

Eight case-control studies were identified (36, 39, 47–52). One study was not included because the study subjects were classified into only 2 categories of consumption (36). This study reported that there is a significant protective effect of vegetables and no association with fruit intake. Two other studies were not included in the analysis on fruit: one that did not find an association (51) and one that reported a significant protective effect (48).

On average, case-control studies provide evidence of a significant protective effect of fruit against the risk of laryngeal cancer (39, 47, 49, 50, 52), but the association with vegetable intake was not significant (39, 49, 50, 52) (Figure 1). The results are limited by the absence of prospective studies.

Esophageal cancer

Thirteen studies—1 cohort (53) and 12 case control (54–65)—were included in the meta-analysis. Four studies were excluded (36, 66–68), all supportive of a protective effect of green vegetables and fruit.

On average, there is a significant protective effect of fruit and vegetables (**Table 2**) that seems to be more important for fruit than for vegetables. The results were statistically heterogeneous. Subgroups analyses showed that the protective effect was not statistically different by geographical area ($P > 0.05$). European and North American studies, however, have more consistent results, while the heterogeneity persisted in Asian and South American studies.

The results of the meta-analysis are limited by the lack of prospective studies, with the exception of the case-control study (53) nested in a cohort of subjects participating in a randomized nutrition intervention trial in Linxian, a rural county in north central China that has one of the world's highest incidence rates of esophageal and gastric cancer. In this study, there was a 2-fold risk increase among long-term smokers, while alcohol consumption was uncommon and not related to risk. High consumption of eggs or fresh vegetables was associated with 20% reductions in risk, and risk significantly declined as pretrial body mass index, an indicator of long-term nutritional status, increased.

Gastric cancer

We identified 31 case-control studies (17, 18, 39, 69–95) and 11 cohort studies (19, 20, 53, 96–103). Seventeen studies, 5 cohort (19, 20, 98, 101, 103) and 12 case control (17, 69, 70, 75, 77–79, 82, 83, 85, 89, 92), were excluded from the meta-analysis on vegetables. Of

TABLE 2
Estimated relative risks (RRs) of esophageal and gastric cancer for an increase in fruit or vegetable intake of 100 g/d[1]

	Vegetables			Fruit		
	RR (95% CI)	n^2	P^3	RR (95% CI)	n^2	P^3
Esophageal cancer						
All studies	0.89 (0.82, 0.97)	13	0.002	0.72 (0.62, 0.83)	15	<0.01
Europe	0.79 (0.68, 0.92)	4	0.16	0.82 (0.66, 1.01)	4	<0.01
United States	0.81 (0.67, 0.98)	2	0.83	0.80 (0.67, 0.96)	2	0.52
Asia	0.98 (0.91, 1.05)	5	0.02	0.68 (0.43, 1.06)	5	0.03
South America	0.68 (0.32, 1.43)	2	0.04	0.56 (0.38, 0.82)	4	<0.01
Gastric cancer						
All studies	0.81 (0.75, 0.87)	22	<0.01	0.74 (0.69, 0.81)	31	<0.01
Case-control	0.78 (0.71, 0.86)	17	<0.01	0.69 (0.62, 0.77)	24	<0.01
Cohort	0.89 (0.75, 1.05)	5	<0.01	0.89 (0.73, 1.09)	7	<0.01
Europe	0.75 (0.66, 0.84)	9	<0.01	0.84 (0.76, 0.93)	11	<0.01
United States	0.80 (0.63, 1.00)	2	0.22	0.83 (0.64, 1.08)	4	0.03
Asia	0.92 (0.86, 0.98)	7	<0.01	0.56 (0.40, 0.79)	7	<0.01
Asian case-control	0.92 (0.86, 0.98)	5	<0.01	0.51 (0.30, 0.88)	5	<0.01
Asian cohort	0.90 (0.69, 1.18)	2	<0.01	0.67 (0.36, 1.22)	2	<0.01

[1] *P* values of publication bias tests for all studies were as follows: esophagus, $P = 0.14$ and 0.40 for vegetables and fruit, respectively; gastric, $P = 0.35$ and 0.86 for vegetables and fruit, respectively.
[2] No. of studies.
[3] Heterogeneity test.

these, 10 case-control (17, 70, 75, 77-79, 82, 83, 85, 89) and 1 cohort study (19) did not report on vegetables; 2 case-control (69, 92) and 1 cohort study (20) reported protective effects based only on 2 categories of intake; and 3 cohort studies (98, 101, 103) reported for vegetable intake other than "all vegetables," with no statistically significant results. For the meta-analysis on fruit, 7 case-control studies (17, 69, 78, 82, 85, 89, 91) were excluded, mainly because data were grouped in only 2 categories of intake. In 3 of them there was a significant protective effect (17, 82, 85), in 2 studies (78, 89) no significant protective association was found, and in another 2 (69, 91) no data were provided. Five cohort studies were excluded (19, 20, 53, 96, 103) because they did not provide the required data. One reported significant protective effects (20), one did not analyze fruit (96), and the remaining found no significant protective effects.

We found a significant protective effect of fruit in case-control but not in cohort studies (Table 2). Overall results were heterogeneous, within both case-control and cohort studies and in all the geographical subgroups, with the exception of North America. The pooled RR estimates were significant between case-control and cohort studies and between geographical areas for fruit ($P < 0.05$) but not for vegetables. As was the case for esophageal cancer, the heterogeneity of results consisted mostly in differences of the magnitude of the protective effect and not in the directionality of the association. Only 3 studies found RR estimates higher than 1. The protective effect from fruit was higher than that from vegetables, particularly in Asian studies (Table 2), but this difference was not confirmed by European and North American studies.

Colorectal cancer

We identified 28 case-control (3, 5–9, 39, 104–124) and 12 cohort studies (10–15, 125–129) on colorectal cancer. In the meta-analysis on vegetables 13 studies were excluded—2 cohort (125, 126) and 11 case-control studies (6–8, 39, 107, 108, 110, 112, 114, 116, 123)—out of which 3 case-control studies (6, 8, 108) found a significant protective effect of high vegetable intake and the remaining reported no association. For fruit, 3 cohort studies (125–127) and 18 case-control studies (3, 6–8, 104–108, 110, 112–114, 116, 118, 119, 123, 124) were excluded, because they did not provide data on total fruit or because data were in only 2 categories of intake. Two of the case-control studies (3, 8) reported significant protective effects of citrus fruit, 8 studies (105–108, 110, 112, 114, 123) did not find any association, and the remaining 8 case-control (6, 7, 104, 113, 116, 118, 119) and the 3 cohort studies did not report results on fruit. A cohort study in American women (130) published after we finalized the meta-analysis did not find an association between fruit and vegetable intake with colon cancer. This study used a dietary questionnaire with only 5 items for fruit and 14 for vegetables.

The pooled RR indicates that there is a moderate but significantly decreased risk of colorectal cancer with high intake of vegetables and fruit for all studies combined. This protective effect was significantly stronger in case-control than in cohort studies for vegetables ($P < 0.05$), while there was no statistically significant difference for fruit. The overall results were heterogeneous. Subgroups by study design, sex, geographical area, and subsite remained heterogeneous, with the exception of cohort studies on vegetables, which reported more homogeneous results. In the analyses by cancer site and by study design, cohort studies found a statistically significant protective effect of vegetables on colon cancer but not on rectal cancer ($P < 0.05$), while for fruit the protection was stronger for rectal cancer than for colon cancer. There were no differences by sex, except for cohort studies on fruit, in which the protective effect was significantly stronger for women than for men ($P < 0.05$). We found no significant differences between studies from Europe and North America (**Table 3**).

Breast cancer

We identified 15 case-control (21, 22, 131–143) and 10 cohort studies that evaluated the association between breast cancer and fruit and vegetable intake (23, 128). Nine of the 10 cohort studies were included in a pooled analysis recently published (23).

One study (143) was excluded from the meta-analysis of fruit because odds ratios were not reported for all categories of

TABLE 3
Estimated relative risks (RRs) of colorectal cancer for an increase in fruit or vegetable intake of 100 g/d[1]

	Vegetables			Fruit		
	RR (95% CI)	n^2	P^3	RR (95% CI)	n^2	P^3
All studies	0.91 (0.86, 0.97)	46	<0.01	0.94 (0.90, 0.98)	31	<0.01
Case-control	0.87 (0.80, 0.95)	29	<0.01	0.93 (0.87, 0.99)	15	0.003
Cohort	0.96 (0.90, 1.05)	17	0.13	0.96 (0.90, 1.01)	16	0.001
Colon	0.91 (0.83, 1.00)	27	<0.01	0.94 (0.89, 1.00)	19	<0.01
Case-control	0.90 (0.78, 1.03)	17	<0.01	0.90 (0.82, 0.99)	10	0.002
Cohort	0.91 (0.86, 0.96)	11	0.59	0.97 (0.91, 1.04)	9	0.003
Rectum	0.95 (0.80, 1.11)	9	0.01	—		
Case-control	0.75 (0.51, 1.08)	4	<0.01	—		
Cohort	1.06 (0.90, 1.25)	5	0.32	0.88 (0.81, 0.96)	5	0.30
Men	0.97 (0.89, 1.05)	15	<0.01	0.96 (0.87, 1.03)	12	<0.01
Case-control	0.91 (0.83, 1.00)	8	<0.01	0.91 (0.77, 1.08)	5	0.006
Cohort	0.97 (0.89, 1.05)	7	0.37	1.03 (0.95, 1.11)	5	0.72
Females	0.96 (0.86, 1.07)	18	<0.01	0.92 (0.87, 0.97)	15	0.10
Case-control	0.95 (0.76, 1.17)	8	<0.01	0.90 (0.83, 0.98)	6	0.50
Cohort	0.96 (0.86, 1.07)	10	0.05	0.92 (0.87, 0.97)	9	0.15
Europe	0.93 (0.83, 1.04)	17	<0.01	0.93 (0.85, 1.02)	4	0.10
Case-control	0.91 (0.78, 1.07)	10	<0.01	0.95 (0.87, 1.04)	8	0.04
Cohort	0.97 (0.87, 1.07)	7	0.52	0.94 (0.86, 1.02)	6	0.10
United States	0.92 (0.83, 1.00)	18	0.002	0.98 (0.90, 1.06)	9	<0.01
Case-control	0.79 (0.65, 0.96)	8	0.03	0.78 (0.68, 0.90)	4	0.57
Cohort	0.97 (0.88, 1.08)	10	0.03	0.98 (0.90, 1.06)	9	<0.01

[1] P values of publication bias tests for all studies were as follows: $P = 0.46$ and 0.39 for vegetables and fruit, respectively.
[2] No. of RR estimates used.
[3] Heterogeneity test.

consumption. This study found a nonsignificant protective role of fruit in women younger than 50 y and a risk increase in women older than 50. Three studies (136, 140, 143) were excluded in the meta-analysis of vegetables because they did not provide odds ratios or number of cases and control by category of intake.

There is a significant protective effect of vegetables against breast cancer when all studies are considered together. The protective effect is found in a separate analysis of case-control studies and is significantly different from the pooled estimate from cohort studies ($P < 0.05$), which consistently failed to find any association (**Table 4**). Neither the case-control nor the cohort studies found a significant protective effect of fruit against breast cancer.

Lung cancer

Twenty-five case-control studies (26–29, 92, 144–163) and 11 cohort studies (30–32, 128, 164–170) investigated the association between fruit and vegetable intake with lung cancer risk. In the meta-analysis of vegetables, 7 case-control studies were not included because they did not provided the required data (27, 29, 144, 146, 147, 151, 160) and 5 because they did not report results on total vegetables (28, 150, 152, 153, 157). All the excluded case-control studies except one (29) reported a significant protective effect of vegetable consumption. One cohort study conducted in Finland (169) that did not find significant associations was excluded. In the meta-analysis of fruit, 4 case-control studies were excluded (27, 29, 146, 151), out of which 2 (27, 146) reported significant protective effects and the other 2 no association.

Case-control and cohort studies on fruit found on average similar significant protective effects, but the results are heterogeneous within each subgroup (Table 4). Case-control and cohort studies on vegetables found different results, which are of borderline statistical significance ($P = 0.05$), with significant protective effect on case-control but not on cohort studies. When analysis by sex is performed, fruit seem to have a significant protective effect in men that is not found in women ($P < 0.05$). The results for vegetables do not differ by sex.

In all the studies included in the meta-analysis, the statistical analyses were adjusted for smoking. There are only a few studies in nonsmoking populations. In the Netherlands Cohort Study (32), the authors estimated RRs by smoking condition. They reported a nonsignificant protective effect of fruit and vegetables in only current and former smokers, while in nonsmokers RR estimates were higher than 1. On the other hand, 2 case-control studies in nonsmoking women reported protective effects of fruit and vegetables (151, 155).

Bladder cancer

Epidemiologic studies of fruit and vegetable intake and bladder cancer risk have yielded inconsistent results. Six case-control studies (25, 39, 171–174) and 3 cohort studies (128, 175, 176) have investigated the role of fruit and vegetables as risk factors of bladder cancer. We found that both case-control and cohort studies are supportive of a protective effect of fruit consumption on bladder cancer risk, while no significant association was found for vegetables in either case-control or cohort studies (**Figures 2** and **3**).

DISCUSSION

In our meta-analysis we find that there are discrepancies between the overall results of case-control and cohort studies regarding the effect of fruit and vegetables on cancer risk. Prospective studies provide weaker evidence than case-control

TABLE 4
Estimated relative risks (RRs) of cancer of breast, lung, and bladder for an increase in fruit or vegetable intake of 100 g/d[1]

	Vegetables			Fruit		
	RR (95% CI)	n^2	P^3	RR (95% CI)	n^2	P^3
Breast						
All studies	0.96 (0.94, 0.98)	20	0.89	0.99 (0.98, 1.00)	18	0.88
Case-control	0.86 (0.78, 0.94)	10	<0.01	0.92 (0.84, 1.01)	8	<0.01
Cohort	1.00 (0.97, 1.02)	10	0.99	0.99 (0.98, 1.00)	10	0.99
Lung						
All studies	0.89 (0.82, 0.93)	25	0.003	0.85 (0.78, 0.92)	35	<0.01
Case-control	0.85 (0.77, 0.92)	14	0.006	0.83 (0.74, 0.94)	22	<0.01
Cohort	0.92 (0.84, 1.07)	11	0.14	0.86 (0.78, 0.94)	13	<0.01
Men	0.84 (0.67, 1.06)	7	0.01	0.65 (0.51, 0.83)	12	<0.01
Women	0.87 (0.77, 0.97)	9	0.06	0.93 (0.82, 1.06)	11	0.005
Bladder						
All studies	0.91 (0.82, 1.00)	6	0.12	0.81 (0.73, 0.91)	8	0.007
Case-control	0.90 (0.78, 1.03)	4	0.06	0.82 (0.70, 0.94)	5	0.004
Cohort	0.92 (0.75, 1.14)	2	0.24	0.80 (0.65, 0.99)	3	0.13

[1] *P* values of publication bias tests for all studies were as follows: breast, $P = 0.48$ and 0.40 for vegetables and fruit, respectively; lung, $P = 0.18$ and 0.12 for vegetables and fruit, respectively; bladder, $P = 0.44$ and 0.46 for vegetables and fruit, respectively.
[2] No. of RR estimates used.
[3] Heterogeneity test.

studies of the association of fruit and vegetable consumption with reduced cancer risk. Case-control and cohort studies are in agreement with respect to the protective effect of fruit on the risk of lung and bladder cancers. The 2 types of studies also concur in not finding a significant protection of fruit on breast cancer and vegetables on bladder cancer. As for the other results summarized in **Table 5**, the meta-analyses of case-control studies find a significant risk reduction associated with vegetables for cancers of the breast, esophagus, lung, stomach, and colorectum, and with fruit for cancers of the lung, bladder, stomach, colorectum, mouth and pharynx, larynx, and esophagus, while only the protective effect of fruit on lung and bladder

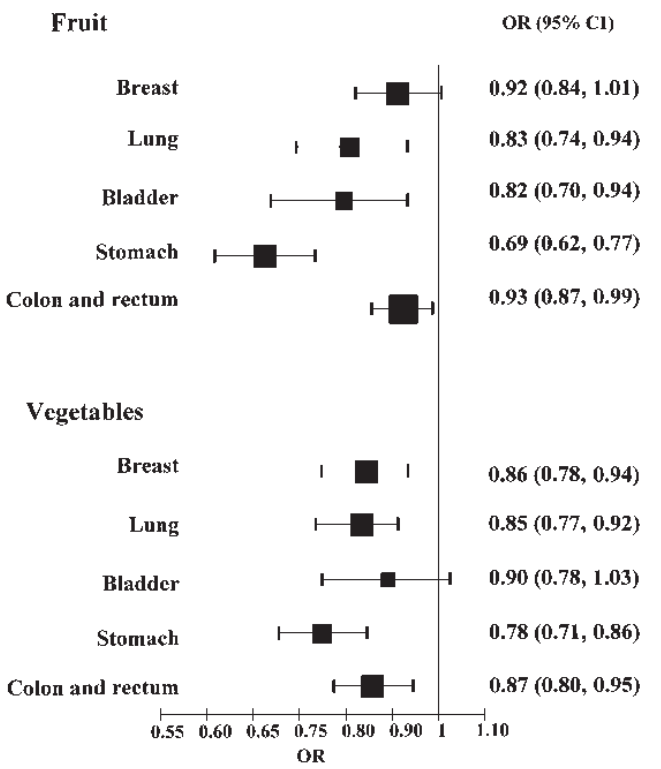

FIGURE 2. Meta-analysis of case-control studies on fruit and vegetable intake. Estimated odds ratios (ORs) for the development of cancers of the breast, lung, bladder, stomach, colon, and rectum with an increase in fruit or vegetable intake of 100 g/d.

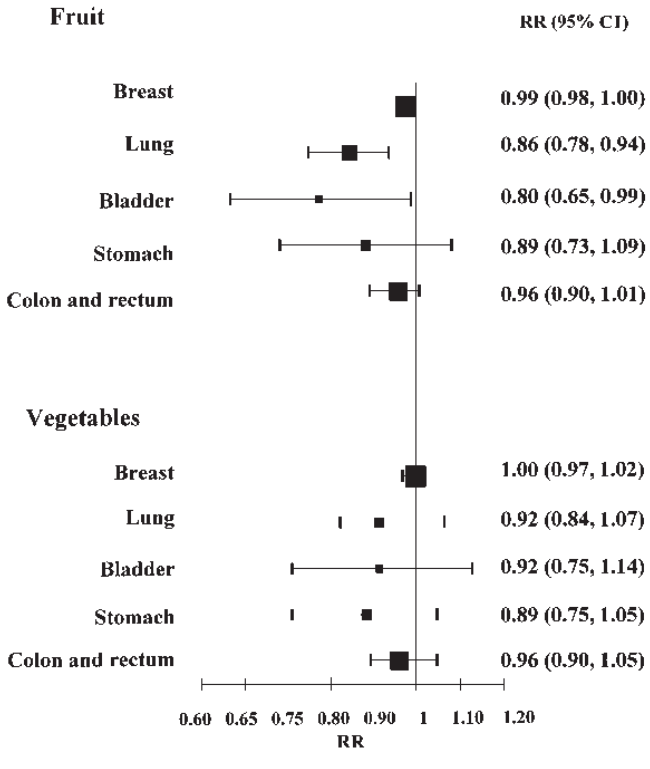

FIGURE 3. Meta-analysis of cohort studies on fruit and vegetable intake. Estimated relative risks (RRs) of developing cancers of the breast, lung, bladder, stomach, colon, and rectum with an increase in fruit or vegetable intake of 100 g/d.

TABLE 5
Summary results of the meta-analyses on fruit and vegetables and the risk of some cancers in case-control and cohort studies[1]

	Vegetables		Fruit	
	Case-control	Cohort	Case-control	Cohort
Mouth and pharynx	NS	?	↓	?
Larynx	NS	?	↓	?
Esophagus	↓	?	↓	?
Breast	↓	NS	NS	NS
Lung	↓	NS	↓	↓
Bladder	NS	NS	↓	↓
Stomach	↓	NS	↓	NS
Colorectum	↓	NS	↓	NS

[1] ↓, significant protective effect; NS, nonsignificant protective effect.

cancer comes out as statistically significant in the meta-analyses of cohort studies.

There may be several reasons why case-control and cohort studies provide different results. The difference may result from recall bias in retrospective studies. In a prospective study, data collected retrospectively showed an association of dietary fat intake and breast cancer while the prospective analysis did not (177). In case-control studies, changes of dietary habits in cases could have occurred some months or a few years before the baseline measurement because of preclinical symptoms. In the Netherlands Cohort Study it was observed that in the 1 or 2 y before the diagnosis, subjects who were subsequently diagnosed with gastric cancer consumed fewer vegetables but not less fruit than did those who were diagnosed in later years (14).

The estimation of portion size and frequency of consumption of a wide range of vegetables is rather difficult, and the nondifferential misclassification may result in bias of the RR estimate toward the null value. In a situation in which the association between any single dietary component and cancer might be relatively weak, the empirical RR estimates will be even weaker because of random measurement error, and the failure of a cohort study to show an association with disease may not negate an important relation (178). It should be considered that, even when the meta-analyses of cohort studies do not provide statistically significant values, the estimates for both fruit and vegetables are always lower than 1, with the exception of vegetables and rectal and breast cancers. Therefore, one cannot discard the possibility that the lack of significance could be indicative of a lack of statistical power of the published prospective studies because of random error in the measurement of diet and not because of a lack of biological association.

An important issue in the interpretation of the meta-analysis is whether the results are homogeneous and the identification of factors eventually explaining heterogeneity. In our meta-analysis, the results are heterogeneous and the heterogeneity persists for case-control and cohort studies separately, with the exception of the cohort studies on vegetables and colorectal cancer. Subgroup analysis of case-control studies by sex, anatomical subsite, or geographical region did not result in the identification of any homogeneous group (data not presented). Similar results were found in a previous meta-analysis of meat and colorectal cancer (33).

It was possible to do meta-analyses by sex for only colorectal and lung cancer. For colorectal cancer, the protection conferred by vegetables and fruit was significant in cohort studies in women but not in men. For lung cancer, the protection for vegetables was statistically significant for women but not for men, while for fruit it was the other way around. These discrepancies in statistical significance may be due to the limited number of studies rather than to real differences in the underlying associations. Some cohort studies reported a protective effect of fruit and vegetables more pronounced for women than for men (14, 127, 128). The difference was attributed to greater accuracy of female food intake data, but this interpretation was not supported by the validation study of one of the cohorts (14). Colon cancer incidence rates are similar in men and women, but it is possible that diet is not associated with colon cancer in the same way in both sexes. Hormonal influences appear to reduce risk, especially the use of estrogen replacement therapy by women. Differences in gut function between men and women have been reported in relation to metabolic and physiologic responses to fiber (179).

Cohort studies do not support the hypothesis of a protective effect of vegetable and fruit consumption on colorectal cancer risk. Because no single risk factor has a particularly high attributable risk for colorectal cancer, a comprehensive approach to lifestyle modification seems most promising as a general recommendation, particularly increasing physical activity and avoiding overweight.

Tobacco and alcohol are by far the main risk factors of esophageal cancer in Europe, Oceania, and North America, which explains why the incidence is so much higher in men than in women. In developing countries of Asia, dietary deficiencies seem to play a major role in the pathogenesis of esophageal cancer. In many of the case-control studies, the protective effect for vegetables and fruit remained after controlling for smoking and alcohol. Two case-control studies reported a protective role of fruit and vegetables in never-smokers and never-drinkers (180, 181). For now, however, most of the evidence in esophageal cancer is based on case-control studies.

In gastric cancer, excessive salt intake is implicated in the development of superficial gastritis and chronic atrophic gastritis, in the pathway to carcinogenesis. Salt may also exert a promoting effect at later stages. Carotenoids and other dietary components with antioxidant capacity may suppress the progression from atrophic gastritis to carcinoma. It has been proposed that protection against gastric cancer may be afforded by dietary intake of foods rich in vitamin C and E and polyphenols; these compounds have been shown to inhibit the production of carcinogenic *N*-nitroso compounds in humans. In the Nutrition Intervention Trial in Linxian (182), reductions in cancer mortality and incidence, especially for gastric cancer, were observed for individuals who received daily supplements containing β-carotene, vitamin E, and selenium. A reduction in esophageal cancer was also suggested among those receiving riboflavin and niacin.

Because the estimates presented in this article are based on observational studies, they represent the overall effect of possible beneficial and adverse properties of fruit and vegetables in the amounts and varieties prepared by and consumed in the different study populations, but it cannot be ruled out that some other factor associated with high fruit and vegetable consumption could be the true protective agent, such as physical activity or avoidance of smoking. Although this cannot be ruled out, it should be noted that many studies included in the meta-analyses have controlled for other risk factors and that the association with fruit and vegetables, when present, persisted after adjustment. Apart from fruit and vegetables, other major risk factors of cancer require attention. It is unlikely that any major cancer prevention effect can be achieved in practice by varying only one of the risk factors, but

there is a substantial potential for preventing cancer through diet. The modification of dietary habits could have an impact on the risk of other diseases, particularly cardiovascular disease.

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