

## Diet and Bladder Cancer: A Meta-analysis of Six Dietary Variables

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In 1996, more than 300,000 new cases of bladder cancer were diagnosed worldwide. Besides tobacco smoking, occupation, and other factors, diet may play a role in causation of this illness. The authors performed a meta-analytical review of epidemiologic studies linking six dietary factors to bladder cancer. These factors include retinol, beta-carotene, fruits, vegetables, meat, and fat. Increased risks of bladder cancer were associated with diets low in fruit intake (relative risk (RR) = 1.40, 95% confidence interval (CI): 1.08, 1.83), and slightly increased risks were associated with diets low in vegetable intake (RR = 1.16, 95% CI: 1.01, 1.34). Elevated risks were identified for diets high in fat intake (RR = 1.37, 95% CI: 1.16, 1.62) but not for diets high in meat intake (RR = 1.08, 95% CI: 0.82, 1.42). No increased risks were found for diets low in retinol (RR = 1.01, 95% CI: 0.83, 1.23) or beta-carotene (RR = 1.10, 95% CI: 0.93, 1.30) intake. These results suggest that a diet high in fruits and vegetables and low in fat intake may help prevent bladder cancer, but the individual dietary constituents that reduce the risks remain unknown. *Am J Epidemiol* 2000;151:693–702.

bladder neoplasms; carotene; diet; fats; fruit; meat; vegetables; vitamin A

The World Health Organization has estimated that 310,000 people developed bladder cancer in 1996 (1). Risk factors such as smoking, occupation, and arsenic have been well documented (2–4). Several studies have suggested that various dietary constituents may have causal and protective roles in bladder cancer as well. The idea that diet may play a role in cancer of the bladder is not surprising, considering that many ingested substances, including dietary carcinogens and antioxidants, are excreted through the urinary tract and come into direct contact with the bladder epithelium.

Although the carcinogenic potential of many food items has been studied, our analysis was limited to the following six factors: retinol, beta-carotene, fruits, vegetables, meat, and fat. These items were chosen because a relatively large number of epidemiologic studies have evaluated them, yet some controversy remains despite this research. For example, several of the earliest studies of diet and bladder cancer suggested that vitamin A may have anticarcinogenic properties (5–7). Unfortunately, many of these investiga-

tions did not distinguish between preformed vitamin A (retinol) and carotenoids. This distinction is important since these two compounds may have different effects in cancer causation or prevention and are found in markedly different foods. Recently, most research has distinguished between the two, and although retinol appears to have little effect on bladder cancer risk, research findings regarding beta-carotene have been equivocal (8, 9). This equivocation may be related to the fact that many of these studies estimated beta-carotene levels from intake of foods containing other potentially anticarcinogenic compounds. Consequently, investigators could not rule out the possibility that any effect ascribed to beta-carotene was actually due to another factor found in the same foods.

Meanwhile, studies involving broad categories of fruits and vegetables have identified protective associations much more consistently than have those studies focusing solely on beta-carotene. Thus, some factor or combination of factors in fruits and vegetables other than beta-carotene may be responsible for the chemoprotective effects of these foods (10, 11). One goal in performing this analysis was to establish whether fruits and vegetables are associated with decreased risks of bladder cancer and whether beta-carotene might be responsible for some portion of this effect.

Controversy also exists surrounding the association between bladder cancer and diets high in meat or fat intake. For example, in a cohort study of almost 8,000 Japanese-American men living in Hawaii, Chyou et al. found elevated rates of bladder cancer for men who ate

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Abbreviations: CI, confidence interval; RR, relative risk; SE, standard error.

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five or more servings of meat per week compared with those who ate one or fewer servings per week (relative risk (RR) = 1.57, 95 percent confidence interval (CI): 0.78, 3.15) (12). In contrast, in a case-control study involving 432 cases in Spain, Riboli et al. reported low risks of bladder cancer for those with the highest intakes of meat (RR = 0.67, 95 percent CI: 0.46, 0.96) (13).

To evaluate these controversies, we used a meta-analytical approach to objectively assess the relative importance of six dietary factors in the risk of bladder cancer. To our knowledge, this is the first report to pool epidemiologic data on multiple dietary variables and to present estimates of the relative risk of bladder cancer for each variable. Our goal was not to quantify the exact cancer risk associated with a particular quantity of each food. Doing so would have been difficult since very few articles presented exposure variables in comparable, quantifiable terms. Instead, our intent was to identify and rank those factors most commonly associated with bladder cancer. This information may be useful in establishing general dietary recommendations. It also may provide some guidance for future research by identifying those items that may or may not warrant further investigation. In addition, this information may help address the possibility of confounding with diet in studies of other factors that cause bladder cancer.

## MATERIALS AND METHODS

Databases such as MEDLINE and CancerLit were searched for epidemiologic literature regarding bladder cancer and each of the six dietary factors of interest. Review articles on nutrition and cancer or on bladder cancer etiology were searched for relevant references. Case-control and cohort studies that presented data in terms of a relative risk were included. Several studies included cancers of the renal pelvis, ureter, and urethra with those of the bladder. In these studies, cancer of the bladder accounted for approximately 90 percent of the cases (12, 14–16). These studies were therefore included in this analysis, whereas studies involving cancers of the kidney parenchyma and prostate were not.

Studies were excluded from our analysis for the following reasons. First, ecologic investigations comparing national bladder cancer mortality rates with national food consumption patterns were excluded; these studies do not reflect the tremendous range of diets that may exist in a particular country or differences in detection and treatment rates between countries. Second, studies in which the exposure variable was defined as “vitamin A” and there was no distinction between retinol and beta-carotene (5–7, 17) were excluded. Two clinical trials on beta-carotene supple-

ments (18, 19) were excluded because of questions regarding the length of the follow-up period and the timing of supplementation relative to the natural history of the cancer process (20). Third, three studies in which serum micronutrients were collected after the diagnosis of cancer (21–23) were excluded since this diagnosis may alter a patient’s diet. Finally, a few studies did not provide data that could be used to estimate a standard error. These studies are discussed in the following sections; however, because they could not be assigned an accurate weight, they were not included in our meta-analysis.

We followed the general principles presented by Greenland (24). For each article, an effect measure and its 95 percent confidence interval were extracted. Many articles presented data on several similar food items, each of which could have been classified as one of our dietary factors. For example, Shibata et al. presented separate relative risk estimates for “dark green vegetables,” “yellow vegetables,” and “all vegetables” (25). In these instances, the item that provided the broadest representation of the particular dietary item was chosen. In the example just described, “all vegetables” was selected. When relative risks for several levels of exposure were provided, we used the relative risk comparing the highest with the lowest exposure level. Also, several articles reported relative risks for males separately from females or for subjects aged more than 65 years separately from subjects aged less than 65 years. In these instances, both relative risk estimates were included. When available, relative risks adjusted for tobacco smoking were used, since smoking may be associated with both diet and bladder cancer (2, 26).

Sometimes more than one article presented data from the same study population. In these instances, we chose the most recently published article unless an earlier study fit our inclusion criteria more precisely. For example, both Chyou et al. and Wilkens et al. studied bladder cancer patients in Oahu, Hawaii (12, 15). Although the Wilkens et al. article was published last, data from Chyou et al. were used because this article reported relative risks for the broad category of “fruits,” whereas Wilkens et al. reported relative risks for “fruit drinks” only.

Each relative risk extracted was assigned a weight ( $W_i$ ) based on the inverse square of its standard error (SE) ( $W_i = 1/SE^2$ ). Standard errors were calculated by dividing the natural log of the ratio of the upper and lower 95 percent confidence intervals by 3.92 ( $SE = \ln(CI_{upper}/CI_{lower})/3.92$ ). Missing confidence intervals were estimated by using Byar’s approximation (27) for cohort studies or were calculated by using unadjusted data for case-control studies. For each study, the

weight was multiplied by the natural log of the risk ratio ( $b_i$ ) to give a summary measure ( $W_i b_i$ ). A pooled summary was calculated by dividing the sum of the summary measures by the sum of the weights ( $b = \Sigma W_i b_i / \Sigma W_i$ ). A summary relative risk was produced by taking the exponential of the pooled summary ( $RR_{sum} = \exp^b$ ).

Heterogeneity among studies was assessed by using the chi-square statistic ( $\chi^2 = \Sigma W_i (b - b_i)^2$ ). When evidence of heterogeneity was present, the 95 percent confidence interval of the summary relative risk was adjusted by using the method described by Shore et al. (28). That is, for the pooled relative risks in which the

chi-square test statistic was greater than the number of degrees of freedom, the variance of the log of the pooled relative risk was multiplied by the ratio of the heterogeneity chi-square statistic to its degrees of freedom. This adjusted variance was then used to adjust the 95 percent confidence interval.

**RESULTS**

We identified 38 articles reporting data on diet and bladder cancer that met our inclusion criteria. As shown in table 1, elevated relative risks were found for diets high in fat intake (RR = 1.37, 95 percent CI:

**TABLE 1. Summary of pooled relative risks for intake of six dietary variables and separate analysis based on adjustment for smoking and type of diet and bladder cancer study**

	RR*	95% CI*	No. of studies	$\chi^2$ †	df	Adjusted 95% CI‡
<i>Low retinol</i>						
All studies	1.01	0.90, 1.14	8	24.9	9	0.83, 1.23
Case-control	0.99	0.88, 1.12	6	22.4	6	0.79, 1.26
Cohort	1.27	0.82, 1.97	2	1.44	2	NA*
<i>Low carotenoids</i>						
All studies	1.10	0.99, 1.22	9	24.8	10	0.93, 1.30
Case-control	1.11	1.00, 1.24	7	22.8	8	0.92, 1.33
Cohort	0.88	0.52, 1.50	2	1.24	1	0.49, 1.59
<i>High meat</i>						
All studies	1.08	0.90, 1.30	7	15.5	7	0.82, 1.42
Smoking adjusted	0.96	0.73, 1.27	4	9.2	3	0.59, 1.58
Smoking unadjusted§	1.28	1.03, 1.60	5	8.4	5	0.96, 1.71
Case-control	0.95	0.77, 1.16	4	6.8	4	0.72, 1.24
Cohort	1.86	1.23, 2.81	3	0.5	2	NA
<i>High fat</i>						
All studies	1.37	1.16, 1.62	7	5.1	7	NA
Smoking adjusted	1.39	1.17, 1.64	6	4.9	5	NA
Smoking unadjusted§	1.51	1.23, 1.85	3	1.8	4	NA
Case-control	1.45	1.22, 1.72	6	1.4	6	NA
Cohort	0.85	0.51, 1.43	1	NA	NA	NA
<i>Low vegetables</i>						
All studies	1.16	1.01, 1.34	10	11.1	11	1.01, 1.34
Smoking adjusted	1.15	0.98, 1.35	8	10.2	7	0.95, 1.40
Smoking unadjusted§	1.38	1.17, 1.64	7	8.3	8	1.16, 1.64
Case-control	1.18	1.01, 1.38	7	8.6	8	1.01, 1.38
Cohort	1.09	0.78, 1.51	3	2.3	2	0.76, 1.54
<i>Low fruit</i>						
All studies	1.40	1.20, 1.64	9	26.4	9	1.08, 1.83
Smoking adjusted	1.47	1.25, 1.74	8	23.9	7	1.08, 2.00
Smoking unadjusted§	1.18	0.95, 1.48	5	7.2	5	0.91, 1.55
Case-control	1.40	1.17, 1.67	5	22.0	5	0.96, 2.04
Cohort	1.42	1.04, 1.93	4	4.3	3	0.98, 2.06

\* RR, relative risk; CI, confidence interval; NA, not adjusted if  $\chi^2 < df$ .

†  $\chi^2$ , chi-square heterogeneity test statistic.

‡ Adjusted for the heterogeneity statistic.

§ Includes unadjusted data from all studies reviewed that either matched on or adjusted for age and gender.

1.16, 1.62) and low in fruit intake (RR = 1.40, 95 percent CI: 1.08, 1.83) but not for diets low in retinol intake (RR = 1.01, 95 percent CI: 0.83, 1.23) or high in meat intake (RR = 1.08, 95 percent CI: 0.82, 1.42). The relative risk estimate for diets low in vegetable intake (RR = 1.16, 95 percent CI: 1.01, 1.34) was only slightly higher than the relative risk estimate for diets low in beta-carotene intake (RR = 1.10, 95 percent CI: 0.93, 1.30). However, the heterogeneity statistic for beta-carotene was 24.8 ( $p = 0.003$ ), while that for vegetables was only 11.1 ( $p = 0.27$ ). Thus, studies were statistically consistent in supporting a small protective role for vegetables, whereas the association with low beta-carotene intake was both weaker and inconsistent.

Table 1 also shows the results of separate analyses based on study type and adjustment for smoking. Except for meat and fat, study type appears to have had little impact on these results. A relative risk of 1.86 (95 percent CI: 1.23, 2.81) was calculated from the three cohort studies for high-meat diets. The impact of study type on the pooled analysis of fat is difficult to interpret since only one cohort study was available. To assess the effect of smoking, pooled relative risk estimates were calculated by using only smoking-adjusted data and were compared with those

calculated by using only unadjusted data. In those studies reporting adjusted as well as unadjusted data, both results were used. For retinol and beta-carotene, all but one of the studies adjusted for smoking, and we did not attempt to extract unadjusted data from these articles. For each dietary factor except fruit, the relative risks from adjusted data were lower than the relative risks from unadjusted data. For all factors, however, the relative risk estimate produced by using only adjusted data was always within 12 percent of the original estimate.

Tables 2–4 summarize the studies included in our meta-analysis and display the weights applied to each study result. For fruits, vegetables, meats, and fats, no individual study contributed more than 32 percent of the total weight. For retinol and carotenoids, however, the Risch et al. study contributed 62 percent of the total weight (29). Removal of this study from the analysis resulted in a pooled relative risk of 1.24 (95 percent CI: 0.95, 1.61;  $\chi^2 = 23.7$ ) for diets low in carotenoid intake and a relative risk of 1.13 (95 percent CI: 0.81, 1.59;  $\chi^2 = 26.6$ ) for diets low in retinol intake. Thus, removal of this study resulted in only modest increases in the pooled relative risks, wider confidence intervals, and little change in the heterogeneity statistics.

TABLE 2. Diet and bladder cancer studies included in the meta-analysis of carotenoid and retinol intake

Authors (reference no.) (gender or age (years) studied)	Study type	Assessment method	Smoking adjusted	Location	No. of cases	RR*	95% CI*	$W_i^*$
<i>Low carotenoids</i>								
Nomura et al. (16) (male)	CC*	FFQ*	Yes	Hawaii	195	1.4	0.8, 2.5	12.6
Nomura et al. (16) (female)	CC	FFQ	Yes	Hawaii	66	2.0	0.8, 5.0	4.4
Steineck et al. (47)	CC	FFQ	Yes	Stockholm	323	1.11	0.67, 1.67	18.4
Riboli et al. (13)	CC	FFQ	Yes	Spain	432	0.76	0.52, 1.12	26.1
Vena et al. (48) (>65)	CC	FFQ	Yes	New York	180	1.39	0.79, 2.44	12.1
Vena et al. (48) (<65)	CC	FFQ	Yes	New York	171	2.22	1.28, 3.85	12.7
Breumner et al. (49)	CC	FFQ	Yes	Washington State	262	0.93	0.55, 1.56	14.1
Risch et al. (29)	CC	FFQ	Yes	Canada	826	1.03	0.90, 1.18	209.4
La Vecchia et al. (50)	CC	FFQ	Yes	Italy	163	2.44	1.58, 4.57	13.6
Shibata et al. (25)	COH*	FFQ	Yes	California	71	0.76	0.42, 1.37	11.0
Helzlsouer et al. (30)	COH	Serum	Yes	Maryland	35	1.6	0.5, 5.2	2.8
<i>Low retinol</i>								
Steineck et al. (47)	CC	FFQ	Yes	Stockholm	323	0.83	0.50, 1.43	13.9
Risch et al. (29)	CC	FFQ	Yes	Canada	826	0.96	0.83, 1.11	181.9
Riboli et al. (13)	CC	FFQ	Yes	Spain	432	0.78	0.52, 1.18	22.9
Breumner et al. (49)	CC	FFQ	Yes	Washington State	262	1.92	1.04, 3.45	10.7
Nomura et al. (16) (male)	CC	FFQ	Yes	Hawaii	195	0.63	0.37, 1.11	12.7
Nomura et al. (16) (female)	CC	FFQ	Yes	Hawaii	66	1.0	0.4, 2.5	4.1
Helzlsouer et al. (30)	COH	Serum	Yes	Maryland	35	0.77	0.18, 3.28	1.8
Paganini-Hill et al. (51) (male)	COH	FFQ	No	California	31	1.21	0.71, 1.94	15.2
Paganini-Hill et al. (51) (female)	COH	FFQ	No	California	6	2.22	0.60, 5.68	3.0
La Vecchia et al. (50)	CC	FFQ	Yes	Italy	163	2.63	1.26, 3.63	13.7

\* RR, relative risk; CI, confidence interval;  $W_i$ , weight of each relative risk based on the inverse square of its standard error; CC, case-control; FFQ, food frequency questionnaire; COH, cohort.

TABLE 3. Diet and bladder cancer studies included in the meta-analysis of fat and meat intake

Authors (reference no.) (gender or age (years) studied)	Study type	Assessment method	Smoking adjusted	Location	No. of cases	RR*	95% CI*	W <sub>i</sub> *
<i>High fat</i>								
Claude et al. (14)	CC*	FFQ*	No	Germany	431	1.18	0.62, 2.24	9.3
Steineck et al. (47)	CC	FFQ	Yes	Stockholm	323	1.70	1.00, 2.80	14.5
Riboli et al. (13)	CC	FFQ	Yes	Spain	432	1.43	0.91, 2.22	19.3
Bruemmer et al. (49)	CC	FFQ	Yes	Washington State	262	1.75	0.74, 4.13	5.2
Vena et al. (48) (<65)	CC	FFQ	Yes	New York	171	1.59	0.93, 2.17	21.4
Vena et al. (48) (>65)	CC	FFQ	Yes	New York	180	1.27	0.74, 2.19	13.1
Kunze et al. (52)	CC	FFQ	Yes	Germany	675	1.40	1.00, 1.80	44.5
Chyou et al. (12)	COH*	FFQ	Yes	Hawaii	96	0.85	0.51, 1.43	14.5
<i>High meat</i>								
Claude et al. (14) (male)	CC	FFQ	No	Germany	431	0.97	0.70, 1.35	35.6
Claude et al. (14) (female)	CC	FFQ	No	Germany	431	1.53	0.80, 2.92	9.2
Steineck et al. (47)	CC	FFQ	Yes	Stockholm	323	1.4	0.6, 3.3	5.3
La Vecchia et al. (50)	CC	FFQ	No	Italy	163	1.15	0.59, 1.83	12.0
Riboli et al. (13)	CC	FFQ	Yes	Spain	432	0.67	0.46, 0.96	28.4
Steineck et al. (53)	COH	FFQ	No	Sweden	80	2.2	1.1, 4.4	8.0
Chyou et al. (12)	COH	FFQ	Yes	Hawaii	96	1.57	0.78, 3.15	7.9
Mills et al. (54)	COH	FFQ	Yes	United States	52	1.85	0.87, 3.95	6.7

\* RR, relative risk; CI, confidence interval; W<sub>i</sub>, weight of each relative risk based on the inverse square of its standard error; CC, case-control; FFQ, food frequency questionnaire; COH, cohort.

Tables 2–4 also present the method used to collect nutrition data in each study. As shown, all studies except the one by Helzlsouer et al. used food frequency questionnaires (30). Exclusion of the Helzlsouer et al. study

TABLE 4. Diet and bladder cancer studies included in the meta-analysis of fruit and vegetable intake

Authors (reference no.) (gender studied)	Study type	Assessment method	Smoking adjusted	Location	No. of cases	RR*	95% CI*	W <sub>i</sub> *
<i>Low fruit</i>								
Claude et al. (14) (male)	CC*	FFQ*	Yes	Germany	340	1.4	1.1, 2.7	17.2
Claude et al. (14) (female)	CC	FFQ	No	Germany	91	1.1	0.5, 2.7	4.8
Slattery et al. (55)	CC	FFQ	Yes	Utah	419	0.79	0.52, 1.20	22.0
Riboli et al. (13)	CC	FFQ	Yes	Spain	432	1.05	0.74, 1.49	31.4
Bruemmer et al. (49)	CC	FFQ	Yes	Washington State	262	1.89	1.07, 3.33	11.9
Negri et al. (56)	CC	FFQ	Yes	Italy	365	2.5	1.7, 3.3	32.3
Chyou et al. (12)	COH*	FFQ	Yes	Hawaii	96	1.59	0.92, 2.70	13.3
Shibata et al. (25)	COH	FFQ	Yes	California	71	1.79	0.90, 3.57	8.1
Mills et al. (54)	COH	FFQ	Yes	United States	52	3.22	1.00, 11.11	2.7
Steineck et al. (53)	COH	FFQ	No	Sweden	80	1.0	0.6, 1.6	16.0
<i>Low vegetables</i>								
Claude et al. (14) (male)	CC	FFQ	Yes	Germany	340	1.4	1.0, 2.7	17.2
Claude et al. (14) (female)	CC	FFQ	No	Germany	91	1.1	0.5, 2.7	4.8
Mettlin and Graham (7) (female)	CC	FFQ	No	New York	140	1.37	0.69, 2.75	8.0
Mettlin and Graham (7) (male)	CC	FFQ	No	New York	429	1.32	0.87, 2.02	21.7
Riboli et al. (13)	CC	FFQ	Yes	Spain	432	0.96	0.68, 1.37	31.3
D'Avanzo et al. (57)	CC	FFQ	Yes	Italy	431	1.3	0.9, 1.9	27.5
Momas et al. (58)	CC	FFQ	Yes	France	219	1.7	1.1, 2.8	17.6
Bruemmer et al. (49)	CC	FFQ	Yes	Washington State	262	1.15	0.69, 1.92	14.7
Slattery et al. (55)	CC	FFQ	Yes	Utah	419	0.79	0.52, 1.20	22.0
Steineck et al. (53)	COH	FFQ	No	Sweden	80	1.0	0.6, 1.6	16.0
Shibata et al. (25)	COH	FFQ	Yes	California	71	0.91	0.52, 1.56	12.7
Mills et al. (54)	COH	FFQ	Yes	United States	52	1.80	0.88, 3.85	7.1

\* RR, relative risk; CI, confidence interval; W<sub>i</sub>, weight of each relative risk based on the inverse square of its standard error; CC, case-control; FFQ, food frequency questionnaire; COH, cohort.

had little impact on either low carotenoids (RR = 1.10, adjusted 95 percent CI: 0.93, 1.22) or low retinol (RR = 1.01, adjusted 95 percent CI: 0.83, 1.23).

As mentioned previously, three studies were excluded from our meta-analysis because serum beta-carotene or vitamin A levels were collected after cancer was diagnosed (21–23). Table 5 summarizes the other studies that were excluded and the reasons for

exclusion. Three studies were excluded because they did not define vitamin A adequately. In the majority of the remainder, we were able to extract a relative risk and confidence interval from other articles reporting on the same study population. In the 10 studies involving study populations not represented in the meta-analysis, all reported results generally were consistent with our conclusions.

**TABLE 5. Diet and bladder cancer studies excluded from the meta-analysis of intake of six dietary variables**

Authors (reference no.)	Study type	No. of cases	Variable	Result	Reason not used
<i>Retinol</i>					
Vena et al. (48)	CC*	351	Dietary retinol	No evident effect after adjustment for calories and other confounders	RR* not given
Criqui et al. (59)	COH*	14	Mean serum retinol	8% greater in cases ( $p = 0.079$ )†	RR not given
Middleton et al. (6)	CC	410	Low dietary vitamin A	RR = 1.35–1.61	Vitamin A not defined
Smith and Jick (17)	CC	37	Use of vitamin A preparations	Regular use in 8% of cases, 14% of controls	Vitamin A not defined
Mettlin and Graham (7)	CC	569	Low dietary vitamin A	RR = 2.07 ( $p = 0.009$ )	Vitamin A not defined
Kolonel et al. (5)	CC	164	Mean dietary vitamin A	5–21% lower in cases ( $p > 0.05$ )	Vitamin A includes retinol and carotene; same population as Nomura et al. (16)
Paganini-Hill et al. (51)	COH	59	Low dietary vitamin A	RR = 1.21	Same population as Shibata et al. (25)
Nomura et al. (60)	COH	27	Median serum retinol	4% lower in cases ( $p > 0.50$ )	RR not given; same population as Nomura et al. (16)
Knecht et al. (61)	COH	15	Mean serum retinol	12% lower in cases ( $p = 0.08$ )	Gives RR for increase per one standard unit only
<i>Carotenoids</i>					
Shekelle et al. (62)	COH	19	Mean dietary carotene	No significant difference	RR not given; graphic display only
Wald et al. (63)	COH	15	Mean serum carotene	9% lower in cases (SE,* 20%)	RR not given
Connett et al. (64)	COH	7	Mean serum carotene	23% higher in cases ( $p = 0.51$ )	RR not given
Hennekens et al. (18)	CT*	103	Beta-carotene supplements vs. placebo	34% more cases in the supplement group; not statistically significant after adjustment for multiple comparisons	Supplement trial
Alpha-tocopherol (19)	CT	155	Beta-carotene supplements vs. placebo	4% more cases in the supplement group	Supplement trial
Knecht et al. (61)	COH	15	Mean serum carotene	13% higher in cases ( $p = 0.35$ )	Gives RR for increase per one standard unit only
Paganini-Hill et al. (51)	COH	58	Low dietary carotene	Estimated RR = 1.61 and 6.55 for males and females, respectively	Same population as Shibata et al. (25)
Comstock et al. (65)	COH	35	Low serum beta-carotene	OR* = 1.6 ( $p$ for trend = 0.35)	SE not given; same population as Helzlsouer et al. (30)
Nomura et al. (60)	COH	27	Median serum beta-carotene	Equal levels in cases and controls ( $p > 0.50$ )	RR not given; same population as Nomura et al. (16)
<i>Vegetables</i>					
Nomura et al. (16)	CC	261	Low intake of dark green vegetables	OR = 1.25 and 1.67 for males and females, respectively ( $p$ for trend = 0.02 and 0.41 for males and females, respectively)	SE not given
Hirayama (66)	COH	UNK*	Low intake of yellow-green vegetables	RR = 1.47	SE not given
Tavani and La Vecchia (67)	CC	365	Low intake of green vegetables	RR = 3.33	SE not given; same data as D'Avanzo et al. (57)
La Vecchia et al. (50)	CC	163	Low intake of green vegetables	RR = 1.72 ( $p$ for trend <0.10)	Same population as D'Avanzo et al. (57)
Negri et al. (56)	CC	365	Low intake of green vegetables	RR = 3.33 (CI*: 2.5, 5.0)	Same population as D'Avanzo et al. (57)
Kunze et al. (52)	CC	675	Consumption of fruits and vegetables	No relation found	RR not given; same population as Claude et al. (14)

Table continues

Table 5. Continued

Authors or study (reference no.)	Study type	No. of cases	Variable	Result	Reason not used
<i>Fruits</i>					
Kunze et al. (52)	CC	675	Consumption of fruits and vegetables	No relation found	RR not given; same population as Claude et al. (14)
Tavani and La Vecchia (67)	CC	365	Low intake of fruit	RR = 2.5	SE not given; same population as Negri et al. (56)
La Vecchia et al. (50)	CC	163	Low intake of fresh fruit	RR = 0.99 ( $p$ for trend > 0.10)	Same population as Negri et al. (56)
Nomura et al. (16)	CC	262	Low intake of papayas and tomatoes	RR = 0.83 and 1.43 for papayas and tomatoes, respectively ( $p$ for trend = 0.62 and 0.27, respectively)	SE not given; same population as Chyou et al. (12)
Wilkins et al. (15)	CC	261	Low intake of fruit drinks	RR = 1.11 for males (CI: 0.71, 1.67); RR = 1.67 for females (CI: 0.83, 3.33)	Broader exposure category in Chyou et al. (12)
<i>Fat and meat</i>					
Claude et al. (14)	CC	431	Meals with high fat content (males)	RR = 1.56 (CI: 1.13, 2.14)	Same population as Kunze et al. (52)
Wilkins et al. (15)	CC	261	Intake of specific types of meats	RR = 0.6–2.8	Broader exposure category in Chyou et al. (12)
Kunze et al. (52)	CC	675	Frequent eating of meat	No relation found	RR not given; same population as Claude et al. (14)

\* CC, case-control; RR, relative risk; COH, cohort; SE, standard error; CT, clinical trial; OR, odds ratio; UNK, unknown; CI, confidence interval.

†  $p$  value for the conditional logistic regression coefficient.

## DISCUSSION

The results of this meta-analysis support the hypothesis that diets high in vegetable and fruit intake and low in fat intake reduce the risk of bladder cancer, whereas dietary retinol, beta-carotene, and meat play a minimum role in this disease. Considering the relatively low risks identified, the results presented here cannot be interpreted as straightforward associations unless the impacts of certain biases are assessed. Most likely to have the greatest impact on pooled analyses of this type are confounding, publication bias, and exposure misclassification.

For several reasons, potential confounding factors do not appear to have caused substantial bias in our report. First, with regard to smoking, most of the studies we used adjusted for smoking, and exclusion of unadjusted data resulted in only small changes from the original estimates. For example, in the analysis of low-fruit diets, exclusion of the two studies that did not adjust for smoking only lowered the risk estimate from 1.47 to 1.40 (table 1). Second, many of the occupational or other exposures associated with bladder cancer involve relatively small populations. Although the risks associated with these exposures can be quite high, the chances are remote that a meta-analysis involving thousands of people from many different populations would be biased by a relatively rare exposure. Third, several of the factors related to diet and associated with other types of cancer, such as alcohol and exercise (31), have not been shown to affect blad-

der cancer risks (2). Even so, many of these factors are correlated with smoking (32–34); therefore, most of the studies involved in our analysis probably adjusted for these other factors indirectly when they adjusted for smoking.

We also considered the possibility that the positive association identified for dietary fat might have been due to a confounding bias from fruit and vegetable intake. That is, if people who consume diets high in fats also tend to consume diets low in fruits and vegetables, a protective effect of fruits and vegetables may lead to a false causal effect ascribed to fat. In fact, previous research has shown that intake of fruits and vegetables is inversely correlated with fat intake. However, this association is only moderate (correlation coefficient ( $r$ ) = -0.25) (35) and thus generally not of sufficient magnitude to be solely responsible for the elevated risk that we identified for fat.

Another potential problem with pooled analyses is the possibility of publication bias—the tendency of journals to publish only those studies reporting significant associations. There are two indications that our results were not biased by this tendency. First, large studies are generally published regardless of the associations they report (36), and all of the studies used in our analysis of those factors for which positive associations were found were large. That is, for fats, fruits, and vegetables, the smallest case-control study included over 200 cases, and the smallest cohort study included over 34,000 people. Second, publication bias

typically excludes those studies failing to report "positive" associations (37). In this analysis, however, the 95 percent confidence intervals for 49 of the 59 individual relative risk estimates included unity. This tendency to publish statistically nonsignificant results may be due to the relative popularity of research on diet and cancer. Alternatively, it may be related to the fact that most of the articles from which relative risk estimates were extracted reported data on other exposure variables that were significantly associated with bladder cancer. Regardless, these findings suggest that exclusion of "negative" studies is not likely to have impacted this report.

Another factor that may have influenced our analysis was the large proportion of case-control studies and the susceptibility of this study design to various forms of exposure misclassification. Forty-three of the 59 individual relative risk estimates included in this report were from case-control studies. In nutritional case-control studies, cases are asked to recall their typical diets before the participants were diagnosed. These studies rely on the ability to remember past details about relatively insignificant events and therefore can be somewhat inaccurate, at least on an individual basis. Additionally, several of these studies asked about only a few selected "indicator foods" and consequently may have missed important food items. Finally, inaccuracies in assessing dietary intakes may also result if errors are made in calculating the nutritional content of foods.

In most instances, these problems would have had little effect on the results of our analysis, since accurate individual exposure quantification is not needed to generate unbiased relative risk estimates. Rather, cases and controls need only to be accurately ranked with regard to an exposure variable. Although few of the studies in our analysis apparently validated their questionnaires, several food frequency questionnaires have been shown to rank subjects accurately on various dietary factors, even for diets recalled from the distant past (38–41). In addition, most of the studies in our analysis used a similar method to collect data from both cases and controls, so most inaccuracies in data collection would have led to nondifferential rather than differential errors in dietary classifications. This nondifferential misclassification would have caused substantial bias only if the degree of misclassification was large and would only have biased the results toward the null value, not produced false associations.

A type of exposure misclassification that could produce differential effects is recall bias. In general, little evidence exists that recall bias is more than just a theoretical concern (42, 43). However, considering the widespread publicity received by studies of diet and

cancer (44), and because the relative risks identified in our analysis were small and therefore susceptible even to small differential errors, the potential for recall bias should be evaluated.

Several pieces of evidence suggest that differential recall was not responsible for the positive associations identified in this report. If recall bias had played a role, the risk estimates derived from the cohort studies, where recall bias is not a possibility, should have been substantially lower than those found in the combined analysis. This occurred only for fats, a variable for which only one cohort study was available.

Another method of assessing recall bias is to compare the main exposure findings with those for another exposure for which recall bias is equally likely but is unrelated to the disease. Our results suggest that beta-carotene can be used as this unrelated exposure variable; although beta-carotene is found in several fruits and vegetables, not all fruits and vegetables contain high levels of this micronutrient (45). Since we found no evidence that fruits and vegetables high in beta-carotene are recalled any differently from those low in beta-carotene, differential recall, if it exists, should affect the analysis of vegetables, fruits, and beta-carotene equally. The fact that we did not find significant associations between bladder cancer and beta-carotene provides additional evidence that recall bias did not play a substantial role.

Research that assesses the impact of diet on bladder cancer risks has important public health implications. Several hundred thousand people are diagnosed with this disease each year, and diet may play a role in its development. Previous research regarding many nutritional factors and bladder cancer has been inconsistent and controversial; however, the results of our analysis support the hypothesis that diets high in fruit and vegetable intake and low in fat intake decrease the risk of bladder cancer. Although the relative risks identified in our analysis were small, the results are important considering the large numbers of people who consume unhealthy diets. In a 1991 survey, for example, only 23 percent of people in the United States reported meeting the vegetable and fruit intake guidelines recommended by the National Cancer Institute (46). Consequently, public health interventions aimed at increasing fruit and vegetable intake and lowering fat intake could have an impact on reducing the number of incident bladder cancer cases.

These results also suggest that beta-carotene and retinol are not responsible for the chemoprotective effects reported in early studies of vitamin A. Rather, it appears that some other component, or combination of components, in fruits and vegetables may truly protect against cancer. In fact, laboratory testing has found

that a variety of different compounds commonly found in fruits and vegetables, including vitamin C, folate, isoflavones, and D-limonene, have some anticarcinogenic effects (11). Future research on these and other potentially anticarcinogenic compounds should be encouraged.

Finally, the relatively small magnitude of the effects identified in our analysis suggests that these dietary variables would rarely confound studies of other potential causes of bladder cancer. Investigations of potential bladder carcinogens identifying relative risks greater than those observed in our analysis are unlikely to be substantially biased by confounding from the dietary variables studied here.

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