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FRUITS AND VEGETABLES AND PROSTATE CANCER: NO ASSOCIATION AMONG 1,104 CASES IN A PROSPECTIVE STUDY OF 130,544 MEN IN THE EUROPEAN PROSPECTIVE INVESTIGATION INTO CANCER AND NUTRITION (EPIC)

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We examined the association between self-reported consumption of fruits and vegetables and prostate cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Data on food consumption and complete follow-up for cancer incidence were available for 130,544 men in 7 countries recruited into EPIC between 1993 and 1999. After an average of 4.8 years of follow-up, there were 1,104 incident cases of prostate cancer. The associations of consumption of total fruits, total vegetables, cruciferous vegetables and combined total fruits and vegetables with prostate cancer risk were examined using Cox regression, stratified for recruitment center and adjusted for height, weight and energy intake. There was a wide range in consumption of fruits and vegetables: mean intakes (g/day) in the bottom and top fifths of the distribution, as estimated from 24-hr recalls in a subsample of participants, were 53.2 and 410.7 for fruits, 97.1 and 242.1 for vegetables and 169.0 and 633.7 for fruits and vegetables combined. No significant associations between fruit and vegetable consumption and prostate cancer risk were observed. Relative risks (95% confidence intervals) in the top fifth of the distribution of consumption, compared to the bottom fifth, were 1.06 (0.84–1.34) for total fruits, 1.00 (0.81–1.22) for total vegetables and 1.00 (0.79–1.26) for total fruits and vegetables combined; intake of cruciferous vegetables was not associated with risk. These results suggest that total consumption of fruits and vegetables is not associated with the risk for prostate cancer.

Key words: *prostate cancer; etiology; fruits; vegetables; cruciferous vegetables*

Systematic reviews of the associations of diet with cancer risk have concluded that high consumption of fruits and vegetables reduces the risk for the development of some types of cancer.[1,2] The evidence for a protective effect of fruits and vegetables is most persuasive for cancers of the gastrointestinal tract. For prostate cancer, the evidence is inconsistent, and recent reviews have concluded that fruits are unlikely to influence prostate cancer risk substantially, while vegetables might have anti-prostate cancer properties.[1–3]

Although previous studies have suggested that total consumption of fruits and vegetables may not reduce the risk for prostate cancer, we think that further examination of this topic is important. The purpose of this article is to describe the associations of total fruit and vegetable consumption with prostate cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC), a large multicenter cohort study including subjects living in countries from the north to the south of Europe and thus spanning a wide range of fruit and vegetable consumption. In this article, we examine the associations of prostate cancer with total intake of fruits, total intake of vegetables and total intake of fruits and vegetables combined. To put the results in the context of various national 5-a-day programs (Department of Health, http://www.doh.gov.uk/fiveaday/; National Cancer Institute, http://www.5aday.gov/), we additionally examined risk in relation to the estimated number of portions of fruits and vegetables consumed each day, where 80 g of either fruits or vegetables is classed as one portion. We have also examined one subgroup of vegetables for which a specific protective effect has been hypothesized, cruciferous vegetables.[4]

MATERIAL AND METHODS

EPIC is a prospective study designed to investigate the relationships between diet, lifestyle and environmental factors and the incidence of different forms of cancer. The methods have been described in full elsewhere.[5] The total cohort comprises subcohorts of men and women recruited in 23 centers in 10 European countries: Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom. In this article, we describe data for men from 19 centers in 7 of these countries: Denmark, Germany, Italy, The Netherlands, Spain, Sweden and the United Kingdom; no data are presented for France or Norway because only women were recruited into EPIC in these 2 countries; no data are presented for Greece because the follow-up period was relatively short and only 8 cases of prostate cancer had been reported.

Study subjects

The men included in this analysis were recruited from the population residing in defined geographic areas in each of the 7 countries (general population in most centers, blood donors in Ragusa and Turin in Italy and in the Spanish centers), except for those in the Oxford health conscious subcohort, who were recruited throughout the United Kingdom in order to enroll a large number of vegetarians. Eligible subjects were invited to participate in the study, and those who accepted gave informed consent and completed questionnaires on their diet, lifestyle and medical history. Study participants were predominantly of European origin.

Men were not eligible for this analysis if they had previously been registered as having cancer at the time of completing the baseline questionnaires, if they had missing or inconsistent dietary or nondietary data for the variables of interest, or if they were in the top or bottom 1% of the distribution of the ratio of energy intake to energy requirement. Following these exclusions, complete data on diet and follow-up for cancer were available for 130,544 men out of a total of 131,318 men in the original data set.

Diet and lifestyle questionnaires

Diet was measured by country-specific validated food frequency questionnaires designed to capture local dietary habits and to provide high compliance, as previously described.[5,6] The questionnaires were self-administered in all centers except those in Spain and in Ragusa in Italy, where participants were interviewed using a computerized dietary program. Questions were structured by meals on the questionnaires used in Italy and Spain, and by broad food groupings in the other centers. The numbers of questions relating to specific fruit and vegetable intakes varied by center, broadly reflecting the usual variety of these foods available to participants. For example, the food frequency questionnaire used in the United Kingdom included 11 fruit items and 26 vegetable items. Participants were asked to report their average consumption of each food over the previous 12 months, according to precoded categories that varied from never or less than once per month to 6 or more times per day. Individual average portions were estimated in Germany, Italy, The Netherlands and Spain, whereas standard portions were assigned to all subjects in Denmark, the United Kingdom and Umeå, Sweden, and a combination of methods for estimating portion size was used in Malmö, Sweden. The nondietary questions covered education and socioeconomic status, occupation, history of previous illness and surgical operations, lifetime history of consumption of tobacco and alcoholic beverages and physical activity. Height and weight were measured at recruitment, except for men in the Oxford health conscious subcohort, among whom height and weight were self-reported. Information on family history of prostate cancer was not available for all subjects.

In order to improve the comparability of dietary data across the participating centers, dietary intakes from the questionnaires were calibrated using a 24-hr diet recall method common to all centers; these data were collected from an 8% random sample of the whole EPIC cohort and were available for 13,486 of the men in the current analysis. This second dietary measurement was administered via a face-to-face interview using a computerized 24-hr diet recall method developed *ad hoc*.[7] Using these data, food intakes estimated from the food frequency questionnaires can be transformed to a common scale, enabling comparisons of cancer risk in relation to food intake to be made across all EPIC centers as a whole.

Endpoints

Follow-up is provided by population-based cancer registries in 6 of the participating countries: Denmark, Italy, The Netherlands, Spain, Sweden and the United Kingdom. In Germany, follow-up is via self-completed questionnaires, and self-reported incident cancers are verified through medical records. By the end of June 2002, complete follow-up data had been reported to IARC up to a median date of 31 December 2000. The 10th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) was used, and cancer of the prostate as analyzed here was defined as code C61. Details of stage and grade of prostate cancers were not available.

Statistical methods

The dietary factors examined in this study are total intake of fruits, total intake of vegetables (excluding potatoes and other tubers), total intake of fruits and vegetables combined, as well as intake of cruciferous vegetables (broccoli, Brussels sprouts, cabbage, cauliflower, kale). Intakes estimated from the country-specific dietary questionnaires were calculated in g/day. These intakes were then calibrated to allow for systematic over- or underestimation of fruit and vegetable intake in individual centers in the 7 countries. A simple multiplicative calibration was used, that is, intakes of each food among men in center c were multiplied by a factor R_c/Q_c, where R_c is the 24-hr recall mean intake in center c and Q_c is the mean intake among men included in both the analysis and the calibration study in that center. After calibration, the dietary factors were divided into EPIC-wide fifths of intake. Energy intake was calibrated in the same way. Results for uncalibrated food intake data were also examined, but the results remained essentially the same, and data on calibrated dietary intakes are presented here. For total intake of fruits and vegetables combined, intakes were also categorized by estimated portions where an intake of 80 g/day was classified as one portion.

Follow-up was analyzed until censoring at the date of diagnosis of prostate cancer, death, emigration, other loss to follow-up, or the date at which follow-up ended, defined as the last date at which follow-up data from cancer registries were judged to be complete, or the last date of contact in the German centers that used active follow-up. Incidence rate ratios (IRRs) were calculated using Cox regression. In the model, subjects entered the study at time t_0, defined as their age in days at recruitment, and exited the study at time t_1, defined as their age in days at prostate cancer incidence or censoring. All results were stratified by center to control for any systematic differences that may occur due to follow-up procedures, questionnaire design and mode of detection between centers. Analyses were also adjusted for height (m), weight (kg) and calibrated energy intake (MJ/day) as continuous variables. These variables were included in the model to control primarily for differences in energy intake and body size, but also to help control for measurement error in the estimated intake of fruits and vegetables, because the errors involved in measuring different dietary components tend to be highly correlated. Tests for linear trend across fifths were calculated by scoring the categories 1 through 5. Various potential confounding variables, including education level, smoking and physical activity, were not clearly associated with prostate cancer risk; these variables were therefore omitted from the final analysis. The data were analyzed using the Stata statistical package, release 7.0 (Stata, College Station, TX).

RESULTS

Table I shows dietary and nondietary characteristics of the men in the 19 centers in 7 countries. Overall, median age at recruitment was 52, ranging from 43 in Bilthoven to 59 in Cambridge. Median height was 1.75 m, ranging from 1.68 in Granada and Murcia to 1.79 in Bilthoven. Median weight was 80 kg, ranging from 74.4 in the Oxford health conscious cohort to 82.3 in Heidelberg.

For both fruits and vegetables, the highest median calibrated intakes are in Murcia in the south of Spain, and the lowest are in Umeå in northern Sweden, with a 4.2-fold difference for fruits and a 3.5-fold difference for vegetables (Table I). Table II shows the mean fruit and vegetable intakes in EPIC-wide fifths of the distribution, estimated from 24-hr recalls in the calibration sample, as these provide a more accurate estimate of variation in dietary intake than values derived from the food frequency questionnaires. Mean intakes in the top fifth of intake were much higher than those in the bottom fifth: 7.7 times higher for fruits, 2.5 times higher for vegetables and 3.7 times higher for total fruits and vegetables combined.

After an average of 4.8 years of follow-up, there were 1,104 incident cases of prostate cancer among the 130,544 men. The median age at diagnosis of prostate cancer was 66 years (range, 47–91). Relative to Sweden, which had the largest number of cases, the IRRs for prostate cancer in the other countries were Denmark, 0.36 (95% CI = 0.29–0.46); Germany, 0.64 (0.53–

TABLE I – NONDIETARY AND DIETARY CHARACTERISTICS OF MEN IN 19 CENTERS

Center	Number of men	Median (range) age (years)	Median height (m)	Median weight (kg)	Median calibrated energy intake (MJ/day)	Median calibrated fruit intake (g/day)	Median calibrated vegetable intake (g/day)	Median calibrated fruit and vegetable intake (g/day)
Aarhus, Denmark	8,193	55 (50–65)	1.76	81.7	11.2	133.2	119.0	262.6
Copenhagen, Denmark	18,107	56 (50–65)	1.77	81.9	10.8	96.4	123.1	230.7
Heidelberg, Germany	11,189	52 (35–65)	1.76	82.3	9.8	129.6	150.0	279.7
Potsdam, Germany	10,279	53 (22–69)	1.75	81.5	10.2	173.0	134.6	323.2
Florence, Italy	3,306	49 (24–70)	1.73	78.0	11.1	318.7	186.4	519.5
Ragusa, Italy	2,750	47 (34–72)	1.69	77.6	10.1	316.4	149.7	487.5
Turin, Italy	5,492	49 (34–67)	1.72	77.0	10.6	341.5	214.6	574.7
Varese, Italy	2,335	53 (35–73)	1.71	76.6	11.2	301.6	166.5	485.9
Bilthoven, The Netherlands	9,660	43 (20–65)	1.79	80.9	11.6	109.4	128.1	246.8
Granada, Spain	1,693	50 (34–68)	1.68	81.0	10.7	268.8	206.2	513.1
Murcia, Spain	2,592	49 (33–68)	1.68	79.4	11.0	353.5	244.8	614.2
Oviedo, Spain	3,004	48 (33–67)	1.69	80.4	11.5	279.3	119.2	417.4
Pamplona, Spain	3,774	49 (30–67)	1.69	81.2	11.2	280.4	214.2	500.2
San Sebastian, Spain	4,036	50 (34–66)	1.70	80.2	12.5	319.8	222.5	569.2
Malmö, Sweden	10,260	58 (45–73)	1.76	81.0	9.6	111.3	108.4	230.2
Umeå, Sweden	11,965	49 (29–70)	1.78	81.0	10.8	84.2	69.1	166.8
Cambridge, UK	9,909	59 (39–78)	1.74	79.2	9.7	109.2	143.9	263.1
Oxford general, UK	1,830	54 (37–72)	1.76	81.0	9.8	119.9	146.8	280.5
Oxford health conscious, UK	10,170	44 (20–97)	1.78	74.4	9.9	152.5	175.7	343.2
All	130,544	52 (20–97)	1.75	80.0	10.6	141.0	139.0	294.0

TABLE II – MEAN 24-HR RECALL INTAKES OF FRUITS AND VEGETABLES (G/DAY) WITHIN EPIC-WIDE FIFTHS OF INTAKE, DERIVED FROM ESTIMATES BASED ON FOOD FREQUENCY QUESTIONNAIRE MEASUREMENT

Food	Fifth of intake				
	1	2	3	4	5
Total fruits	53.2	110.1	169.2	239.5	410.7
Total vegetables	97.1	124.6	152.7	176.2	242.1
Total fruits and vegetables	169.0	244.0	321.2	414.3	633.7

0.78); Italy, 0.51 (0.36–0.71); The Netherlands, 0.62 (0.37–1.02); Spain, 0.43 (0.33–0.55); and the United Kingdom, 0.43 (0.36–0.51).

Figure 1 shows the IRRs for prostate cancer in relation to total fruit consumption in individual countries with at least 50 cases of prostate cancer (stratified by center within country) and for all 7 countries together (stratified by center). There was no association between total fruit consumption and prostate cancer risk in any of the individual countries, and no evidence of heterogeneity between countries in the linear association between fruit intake and risk. For all countries together, the IRR for men in the top fifth of fruit intake, compared to men in the bottom fifth of intake, was 1.06 (95% CI = 0.84–1.34), with a *p*-value for linear trend of 0.741.

Figure 2 shows the IRRs for prostate cancer in relation to total vegetable consumption in individual countries with at least 50 cases of prostate cancer (stratified by center within country) and for all 7 countries together (stratified by center). There was no association between total vegetable consumption and prostate cancer risk in any of the individual countries, and no evidence of heterogeneity between countries in the linear association between vegetable intake and risk. For all countries together, the IRR for men in the top fifth of vegetable intake compared to men in the bottom fifth of intake was 1.00 (95% CI = 0.81–1.22), with a *p*-value for linear trend of 0.738.

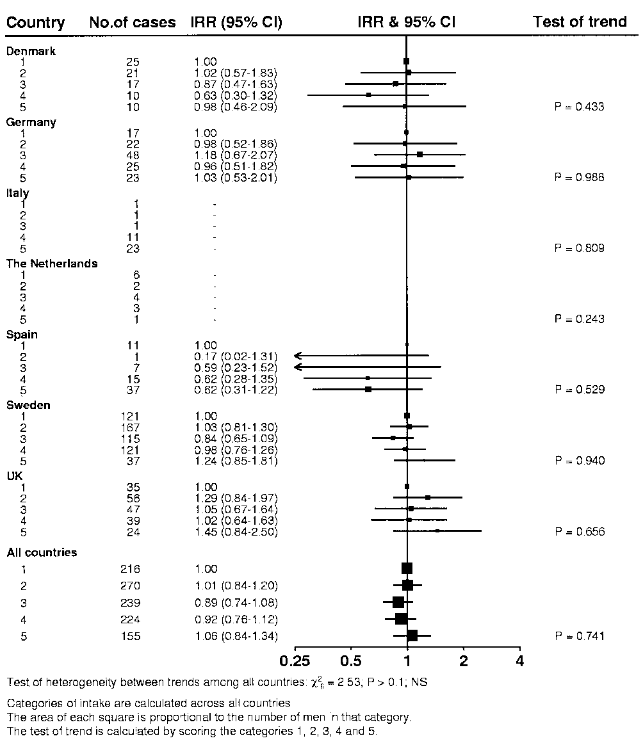

FIGURE 1 – Prostate cancer incidence rate ratios by fifth of calibrated fruit intake showing results for countries with 50 or more cases and for all countries combined, stratified by center and adjusted for height, weight and calibrated energy intake.

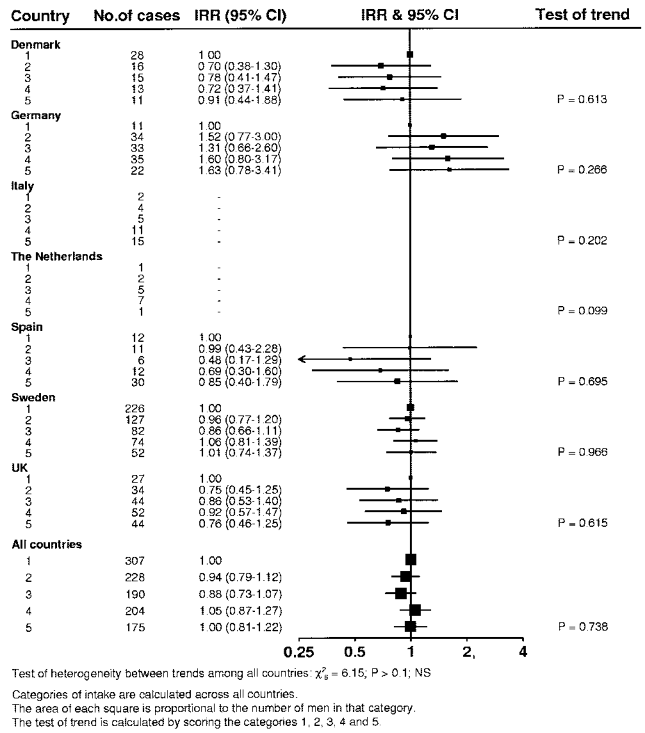

FIGURE 2 – Prostate cancer incidence rate ratios by fifth of calibrated vegetable intake showing results for countries with 50 or more cases and for all countries combined, stratified by center and adjusted for height, weight and calibrated energy intake.

The IRRs for prostate cancer were then estimated in relation to total consumption of fruits and vegetables combined in individual countries with at least 50 cases of prostate cancer (stratified by center within country) and for all 7 countries together (stratified by center). There was no association between total fruit and vegetable consumption and prostate cancer risk in any of the individual countries, and no evidence of heterogeneity between countries in the linear association between total fruit and vegetable intake and risk. For all countries together, the IRR for men in the top fifth of fruit and vegetable intake compared to men in the bottom fifth of intake was 1.00 (95% CI = 0.79–1.26), with a *p*-value for linear trend of 0.807.

The relative risk for prostate cancer was also examined in relation to total consumption of fruits and vegetables categorized as portions/day. For all countries together, the IRRs in comparison to men with an intake of less than 3 portions per day were 3–4 portions/day, 0.95 (95% CI = 0.82–1.09); 5–6 portions/day, 1.07 (0.89–1.29); 7 or more portions/day, 1.02 (0.80–1.30; $p = 0.724$ for linear trend).

In an analysis of a subgroup of vegetables, we examined the association between prostate cancer risk and the calibrated intake of cruciferous vegetables. Data from Umeå were excluded because these foods were not identified on the Umeå questionnaire, and this reduced the number of cases in the analysis from 1,104 to 972. Mean intakes of cruciferous vegetable in fifths of intake, as estimated from 24-hr recall data for men in the calibration study, were 9.7, 13.2, 18.8, 23.7 and 29.2 g/day, respectively. In relation to men in the lowest fifth of consumption of cruciferous vegetables, risks in increasing levels of consumption were 1.10 (0.87–1.39), 1.29 (1.04–1.60), 1.07 (0.87–1.32) and 1.01 (0.83–1.23), respectively; *p*-value for linear trend was 0.953.

The main analyses described above were repeated without adjustment for height, weight and energy intake; the results were essentially the same (data not shown). We also examined the associations of fruit intake and of vegetable intake with risk for prostate cancer after adjustment for each other; these mutual adjustments made no material difference to the findings (data not shown). Restricting the analysis to men diagnosed with prostate cancer under the age of 65 years also made no appreciable difference to the associations (data not shown).

Finally, to examine whether cancers diagnosed soon after recruitment may have influenced the results, additional analyses were conducted after excluding the first 2 years of follow-up, leaving 850 incident prostate cancer cases. Compared to men in the bottom fifth of intake, IRRs for men in the top fifth of intake were 1.04 (95% CI = 0.80–1.36) for fruits, 0.88 (0.70–1.11) for vegetables and 0.89 (0.68–1.17) for fruits and vegetables combined (p-values for linear trend = 0.418, 0.205, and 0.117, respectively).

DISCUSSION

In this prospective study of over 1,100 cases of prostate cancer, we observed no association of risk with total consumption of fruits or vegetables. This absence of an association was observed consistently among the 5 (out of 7) countries where there were enough cases (≥ 50) to examine the association, and there was no evidence of heterogeneity between the 7 countries.

The range of fruit and vegetable intake in EPIC is wide: in the data for men described in this article, using estimates from the 24-hr recall of diet in the calibration study, the mean intake of fruits in the top fifth was nearly 8 times higher than the mean intake of fruits in the bottom fifth; for vegetables, the mean in the top fifth was 2.5 times higher than the mean in the bottom fifth. It therefore seems unlikely that the range of intakes of these foods was too narrow to detect an association, if there was one. The analysis of total intake of fruits and vegetables in estimated portions/day suggests that consuming the recommended intake of 5 portions of fruits and vegetables/day, compared to a much lower intake, would not reduce the risk for prostate cancer.

As in other large epidemiologic studies, dietary intake in EPIC is estimated using relatively simple dietary questionnaires that are subject to substantial errors. Thus, it could be argued that the absence of any association of fruit and vegetable intake with prostate cancer risk could be because the methods for measuring diet are insufficiently accurate. Arguing against this interpretation is the fact that the questionnaires in all EPIC countries have been validated,[5,6] and we have calibrated the dietary intakes to account for possible systematic over- or underestimation of dietary intakes between the different centers. This calibration method has been carefully standardized,[7,8] but has some limitations in that it does not take into account within-person measurement error, although adjustment for calibrated energy intake should partially control for measurement error related to dietary intake. Further, EPIC has previously detected associations of fruit and vegetable intake with cancers of the upper gastrointestinal tract and colorectum,[9,10] suggesting that the methods employed by EPIC to estimate diet, together with the wide range in dietary intakes, are sufficient to detect associations of these foods with cancer risk.

Examination of the relative risks for prostate cancer in the 7 countries showed that the incidence rate was highest in Sweden, followed by Germany and The Netherlands, and with lower rates in Denmark, Italy, Spain and the United Kingdom. This pattern of incidence rates is broadly similar to recent rates published in the routine statistics from these countries (International Agency for Research on Cancer, Globocan, http://www-dep.iarc.fr/globocan/globocan.html), which have long shown much higher rates in Sweden than in the other European countries involved in this analysis. However, these differences in rates between centers should not unduly influence the associations of diet with prostate cancer risk, because all analyses are stratified by center. It is possible that this approach could lead to some underestimation of dietary associations, if for example the high rates of prostate cancer in Sweden were partly due to the low intake of fruits and vegetables. However, because there was no association between fruit and vegetable intake and prostate cancer risk in any country with at least 50 cases, and there was no evidence of heterogeneity between centers, we feel that analysis stratified by center is less likely to produce misleading results than an unstratified analysis.

Information on the stage and grade of prostate cancers or its mode of detection is not yet available for all centers in EPIC, although collection of these data is in progress. Although screening for prostate cancer using the prostate-specific antigen (PSA) test is not currently implemented as a national screening policy in any European country, it is likely that a moderate proportion of these cases were detected through PSA testing. This may lead to bias if any associations of diet with prostate cancer risk are related to the mode of detection. For example, it could be postulated that men who have a PSA test performed may also be more likely to eat fruits and vegetables. However, it seems unlikely that this type of bias, if it exists, would completely obscure a relationship of fruits and vegetables with prostate cancer.

The results for EPIC are broadly consistent with those from previous prospective studies. Nine cohort studies have published results on the association of total fruit intake with prostate cancer risk, relative risks for the highest intake compared with the lowest intake ranging from 0.66 to 1.57 with a median of 1.04.[11–19] Six cohort studies have published results on the association of total vegetable intake with prostate cancer risk, relative risks for the highest intake compared with the lowest intake ranging from 0.55 to 1.04 with a median of 0.85.[12–14,17,19,20] Furthermore, large randomized trials have shown that beta-carotene supplements do not alter the risk for prostate cancer.[21,22]

We examined risk in relation to one subgroup of vegetables, namely cruciferous vegetables. This subgroup was selected because a hypothesis for a specific protective effect for these foods against prostate cancer has been published,[4] and because variation due to cooking methods in the bioavailability of putative protective factors in cruciferous vegetables is not thought to be a major issue. We observed no association of prostate cancer with intake of cruciferous vegetables; in their recent review of this topic, Kristal and Lampe[4] concluded that previous studies provided modest support for the hypothesis that high intakes of cruciferous vegetables reduce prostate cancer risk, but only 3 prospective studies were evaluated and none observed a significant reduction in risk.

Thus, the worldwide data on fruits and vegetables and prostate cancer do not suggest that there is an association of risk with total consumption of these foods. It remains possible, however, that there may be an association with specific types of fruits and vegetables and their related nutrients. For example, several studies have suggested that tomatoes might be protective, perhaps due to their high lycopene content,[23] and future analyses of prostate cancer incidence in EPIC will include examination of the associations of risk with tomato consumption and with serum lycopene levels.

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