Vegetable and fruit consumption and prostate cancer risk

Vegetable and Fruit Consumption and Prostate Cancer Risk: A Cohort Study in the Netherlands[1]

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Abstract

The association between 21 vegetables and eight fruits and prostate cancer risk was assessed in the Netherlands Cohort Study among 58,279 men of ages 55–69 years at baseline in 1986. After 6.3 years of follow-up, 610 cases with complete vegetable data and 642 cases with complete fruit data were available for analysis. In multivariate case-cohort analyses, the following rate ratios (RRs) and 95% confidence intervals (CIs) for vegetable consumption were found (comparing highest *versus* lowest quintile): total vegetables (RR, 0.80; CI, 0.57–1.12); prepared vegetables (RR, 0.85; CI, 0.61–1.19); and raw vegetables (RR, 0.96; CI, 0.69–1.34). For vegetables categorized in botanical groups, no associations were found except for consumption of pulses (RR, 0.71; CI, 0.51–0.98; *P* for trend, 0.01). The RRs for total fruit and citrus fruit were 1.31 (CI, 0.96–1.79) and 1.27 (CI, 0.93–1.73), respectively; the corresponding *P*s for trend were 0.02 and 0.01, respectively. In a continuous model, no association for total fruit was observed. Individual vegetables and fruits were evaluated as continuous variables (g/day). Nonsignificant inverse associations (RRs per increment of 25 g/day) were found for consumption of kale (RR, 0.74), raw endive (RR, 0.72), mandarins (RR, 0.75), and raisins or other dried fruit (RR, 0.49). Observed positive associations were significant for consumption of leek (RR, 1.38) and oranges (RR, 1.07) and nonsignificant for sweet peppers (RR, 1.60) and mushrooms (RR, 1.49). Results in subgroups of cases were more or less consistent with the overall results. From our study, we cannot conclude that vegetable consumption is important in prostate cancer etiology, but for certain vegetables or fruits, an association cannot be excluded.

Introduction

Although prostate cancer is one of the types of cancer with a high incidence in Western countries, the etiology is largely unknown. In a recent review (1), it was concluded that environmental risk factors, including diet, may play an important role in the etiology of this disease. Among dietary factors, meat consumption and fat intake have been evaluated frequently, as have vegetable and fruit consumption. Vegetable and fruit consumption may be protective against cancer because of the anticarcinogenic agents in these foods. Some potentially anticarcinogenic substances are carotenoids, vitamins C and E, selenium, glucosinolates and indoles, flavonoids, protease inhibitors, and allium compounds and some possible mechanisms of action are induction of detoxification enzymes, inhibition of nitrosamine formation, alteration of hormone metabolism, and antioxidant effects (2, 3). Up to 1998, we identified 10 cohort studies (4–13) and 13 case-control studies (14–26) in which consumption of vegetables or fruit in relation to prostate cancer risk was evaluated. Many different vegetable groups or individual vegetables have been investigated, but thus far results are not conclusive. In the majority of these earlier studies, no extensive measurement of vegetable and fruit consumption was made, and no or only limited adjustment for potential confounding factors was used. Therefore, we further explored the possible association between vegetable and fruit consumption and prostate cancer risk in the NLCS,[3] which was specifically designed to investigate the relationship between diet and cancer. Besides the extensive assessment of the usual diet, information on other risk factors for cancer is also available, offering a possibility to control for dietary as well as nondietary factors in multivariate analyses. Moreover, subgroup analyses on tumor differentiation grade and tumor size could be performed to investigate the hypothesis (1) that clinically apparent tumors might have a different etiology than latent tumors.

Materials and Methods

The Cohort Study. The study design has been described elsewhere (27). In brief, the NLCS was initiated in September 1986. The male cohort consists of 58,279 men who completed a questionnaire on usual diet, life style, personal and family history of cancer, other risk factors for cancer, and demographic data. The study population originated from 204 municipal population registries throughout the country. For reasons of efficiency in data processing and analysis, the case-cohort approach (28, 29) was used. In a case-cohort approach, cases are derived from the entire cohort (providing numerator information for calculation of cancer incidence rates), whereas accumulated person years at risk in the total cohort are estimated

Received 10/20/97; revised 5/1/98; accepted 5/19/98.

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[1] The Netherlands Cohort Study was supported by the Dutch Cancer Society. This investigation was partly supported by Unilever Research Laboratorium, Vlaardingen, the Netherlands.

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[3] The abbreviations used are: NLCS, Netherlands Cohort Study; RR, rate ratio; CI, confidence interval; PALGA, Pathologisch Anatomisch Landelyk Geautomatiseerd Archief (Dutch National Database of Pathology Reports).

using a random subcohort sample (providing denominator information for the rates). In contrast to nested case-control sampling, this subcohort can be used for multiple disease end points. The subcohort (n = 1688) was sampled directly after identification of all cohort members and has been followed up biennially for vital status information. Follow-up for incidence of prostate cancer was established by computerized record linkage with all nine cancer registries in the Netherlands and with the Dutch national database of pathology reports (PALGA; Ref.30). No subcohort members were lost to follow-up, and completeness of follow-up of cancer was at least 96% (31). After a follow-up period of 6.3 years (September 1986-December 1992), 704 incident, microscopically or histologically confirmed, primary prostate cancer cases were detected.

The Questionnaire. The self-administered questionnaire has been described elsewhere (32). Usual consumption of food and beverages during the year preceding the start of the study was assessed with a 150-item semiquantitative food frequency questionnaire. Participants were asked to report their frequency of consumption of 12 prepared vegetables, 5 raw vegetables and 8 fruits (Table 1). Categories ranged from "never or less than once per month" to "3–7 times per week" (vegetables) or "6–7 times per week" (fruits). For onions, tomatoes, sweet peppers, and mushrooms, participants were asked to report the number they usually ate per week (onions and tomatoes) or month [sweet peppers and mushrooms (in boxes of 250 g)]. Frequency of vegetable consumption was asked separately for summer and winter, from which a combined consumption frequency was calculated. For string beans and endive, portion sizes were asked, which were used as indicators to calculate portion sizes of the other vegetables, according to a vegetable-specific algorithm. For fruits, subjects were asked to indicate how many pieces they ate each time. Frequency of consumption and portion size of tomato juice and processed orange/grapefruit juice was also asked. Mean daily vegetable and fruit consumption (in g/day) was calculated by multiplying consumption frequency, number of portions per occasion, and portion size. Standard sizes were assumed for each fruit. The questionnaire has been validated against a 9-day diet record; the Spearman correlation coefficient for total vegetable consumption was 0.4, and for total fruit consumption, this estimate was 0.6 (32).

Data Analysis. Questionnaire data were key-entered twice and processed for all incident cases in the cohort and for all subcohort members in a manner blinded with respect to case/subcohort status. This was done to minimize observer bias in coding and interpretation of the data. Subjects who reported a history of cancer other than skin cancer at baseline were excluded. Furthermore, according to criteria published before (32), subjects with incomplete or inconsistent dietary data were excluded; 642 men with prostate cancer and 1525 male subcohort members remained for analysis on fruit consumption. In addition, for vegetables we computed an error index based on the consistency of responses on vegetable questions. When this error index exceeded a certain value, *i.e.*, more than three errors, subjects were excluded for all analyses regarding consumption of vegetables. Therefore, data analysis regarding consumption of vegetables was based on 610 cases and 1456 subcohort members.

Mean intake levels (g/day) of vegetables and fruits and other characteristics were compared between prostate cancer cases and male subcohort members. Furthermore, the mean intakes of total vegetable and total fruit were compared in categories of potential confounding factors and tested with ANOVA. Variables that were considered as potential confounders were age, a family history of prostate cancer, socioeconomic status, fruit consumption (for analyses regarding vegetables), and vegetable consumption (for analyses regarding fruits). Total energy and total fat intake were not considered as potential confounding factors because no association with prostate cancer risk was observed (data not shown). RRs and 95% CIs were computed using the GLIM statistical package (33). Exponentially distributed survival times were assumed in the follow-up period. Because standard software was not available, specific macros were developed in GLIM to account for the additional variance introduced by using the subcohort instead of the entire cohort (34). Tests for trend were based on likelihood ratio tests; two-sided *P*s are used throughout this report. We first evaluated combined vegetable and fruit consumption, total vegetables, prepared and raw vegetables, vegetables categorized in botanical groups, total fruit, and citrus fruit, after

Table 1 Description of daily vegetable and fruit consumption in prostate cancer cases and subcohort members, Netherlands Cohort Study (1986–1992)

Vegetable/fruit consumption (g/day)	Cases mean ± SD	Subcohort mean ± SD
Vegetables	n = 610	n = 456
Total vegetables	183.3 ± 69.6	187.1 ± 76.3
Prepared vegetables	147.0 ± 59.8	150.8 ± 63.1
Raw vegetables	36.2 ± 28.7	36.2 ± 29.0
Pulses[a]	33.0 ± 22.7	34.7 ± 23.0
String/French beans	20.0 ± 15.3	20.5 ± 15.3
Broad beans	4.5 ± 7.0	4.7 ± 7.2
Brassicas	31.5 ± 19.7	32.7 ± 20.3
Cauliflower	14.3 ± 10.3	14.6 ± 11.1
Cabbage (white/green)	6.7 ± 9.1	7.2 ± 8.2
Kale	3.1 ± 3.3	3.3 ± 3.4
Brussels sprouts	7.4 ± 6.7	7.7 ± 6.7
Leafy vegetables, prepared	21.6 ± 15.2	21.6 ± 16.0
Endive, prepared	12.0 ± 10.2	12.0 ± 10.8
Spinach	9.5 ± 8.7	9.6 ± 8.9
Leafy vegetables, raw	9.7 ± 8.3	9.9 ± 9.2
Endive, raw	2.1 ± 4.1	2.4 ± 4.9
Lettuce	7.5 ± 6.5	7.6 ± 6.7
Alliums	27.6 ± 24.4	28.5 ± 24.2
Leek	9.2 ± 13.6	8.5 ± 10.9
Onions	18.4 ± 17.2	20.1 ± 19.0
Other vegetables		
Carrots, prepared	8.4 ± 7.0	9.0 ± 8.9
Carrots, raw	2.2 ± 9.4	2.1 ± 7.8
Sauerkraut	5.8 ± 5.8	5.9 ± 5.5
Red beets	7.5 ± 7.2	7.7 ± 8.7
Sweet peppers	2.5 ± 4.3	2.5 ± 4.0
Mushrooms	3.2 ± 3.9	3.2 ± 3.9
Tomatoes	19.7 ± 20.7	19.5 ± 20.1
Tomato juice	2.8 ± 16.0	1.9 ± 13.5
Gherkins	1.7 ± 4.7	1.9 ± 8.1
Rhubarb	2.1 ± 4.9	2.2 ± 5.7
Fruit	n = 642	n = 525
Total fruit	165.6 ± 112.6	154.4 ± 111.8
Citrus fruit	72.7 ± 74.1	64.8 ± 69.8
Oranges	49.8 ± 56.3	40.6 ± 51.5
Mandarins	3.3 ± 6.6	3.8 ± 7.2
Grapefruit	7.8 ± 26.4	6.6 ± 21.7
Processed orange/grapefruit juice	11.8 ± 30.9	13.8 ± 38.2
Grapes	4.2 ± 8.6	3.9 ± 8.5
Apples and pears	68.0 ± 70.7	67.4 ± 74.6
Bananas	13.1 ± 27.9	12.9 ± 25.0
Strawberries	6.8 ± 8.3	6.8 ± 7.8
Raisins/Other dried fruit	0.6 ± 2.3	0.7 ± 3.2

[a] Dried seeds were also included.

categorizing subjects into quintile levels of consumption. Age-adjusted as well as multivariate-adjusted analyses were done. In addition, cases detected during the first and the first 2 years of follow-up were excluded from analyses to evaluate whether preclinical symptoms might have influenced results. Second, vegetables and fruits were evaluated as continuous variables (g/day), and multivariate RRs were expressed per increment of 25 g/day, corresponding to a consumption frequency of a vegetable of approximately once per week. To assess the independent contribution of each specific vegetable or fruit on prostate cancer risk, total vegetable or total fruit consumption was added to the multivariate model. Analyses were also done for continuous variables in subgroups of cases, based on differentiation grade and size of the tumor, and for latent and nonlatent tumors. The differentiation grade and tumor size were unknown for 8.7 and 22.8% of all cases, respectively. Latent and nonlatent prostate tumors were defined based on information from pathology reports that have been obtained from PALGA. Prostate cancer cases detected incidentally during transurethral prostate resections were coded latent. Cases detected during surgical procedures used in the event of suspected prostate cancer (biopsy, radical prostatectomy) were coded nonlatent (35). If available, more than one pathology report per subject was used. Of all cases, 38.8% could not be grouped according to latency.

Results

In Table 1, mean daily consumption of total vegetables, vegetables combined into botanical groups, total fruit, citrus fruit, and all individual vegetables and fruits is presented for cases and subcohort members. Total and prepared vegetable consumption was slightly lower among cases compared with subcohort members. Onion consumption was slightly lower and leek consumption was higher among cases compared with subcohort members. For the other vegetable groups or individual vegetables, no large differences in mean daily consumption were observed. Total fruit, citrus fruit, and orange and grapefruit consumption was higher for cases than for subcohort members. No large differences in consumption of other fruit items between cases and subcohort members were found. Comparison of the distribution of potential confounding factors showed that cases were somewhat older and more highly educated than subcohort members and more often had a positive family history of prostate cancer (data not shown).

Mean vegetable and fruit consumption was also compared across categories of potential confounding factors. Total vegetable consumption was significantly lower for subjects with a positive family history of prostate cancer and significantly higher for subjects with the highest fruit consumption. Total fruit consumption varied slightly over categories of socioeconomic status but increased with age. A significantly increased total fruit consumption was found for subjects with a positive family history of prostate cancer and for subjects with the highest vegetable consumption (data not shown).

RRs for categories of groups of vegetables and fruit are presented in Table 2. Overall, age-adjusted and multivariate-adjusted RRs were similar. Vegetable and fruit consumption combined showed no association with prostate cancer risk. The RR for the highest *versus* the lowest quintile of consumption was 1.05 (95% CI, 0.76–1.45). Total vegetable consumption was neither associated with prostate cancer risk (RR, 0.80; 95% CI, 0.57–1.12 for the highest *versus* the lowest quintile of consumption). Also for prepared and raw vegetables, no associations were found (RRs of 0.85 and 0.96, respectively, for the same contrast). When the botanical groups were evaluated, RRs for pulses and brassicas were below unity, but there was a significantly decreasing trend in risk with increasing consumption only for pulses ($P = 0.01$). Only the RR in the highest quintile of consumption of pulses was significant (RR, 0.71; 95% CI, 0.51–0.98). In the other botanical groups, no clear associations were seen. For both total fruit consumption and citrus fruit consumption, a significant positive trend in risk was found (*P*s of 0.02 and 0.01, respectively). The RR for total fruit consumption (highest *versus* the lowest quintile) was 1.31 (95% CI, 0.96–1.79), and for citrus fruit, the estimate was 1.27 (95% CI, 0.93–1.73). Exclusion of cases detected in the first or the first 2 years of follow-up did not essentially change the results (data not shown).

Expressed as an increment of 25 g/day, the RR (95% CI) for vegetables and fruit combined was 1.00 (0.98–1.02; Table 3). For total vegetable consumption, the estimate was 0.98 (CI, 0.95–1.02). In contrast to the findings for total fruit evaluated as a categorized variable, fruit evaluated as a continuous variable showed no association with prostate cancer risk (RR, 1.01; 95% CI, 0.99–1.04). Also displayed in Table 3 are RRs (per 25-g increment) for individual vegetable and fruit items. For individual vegetable and fruit items, analyses were done without and with inclusion of total vegetable and total fruit consumption, respectively, in the model. For vegetables, RRs that were slightly increased in a multivariate model without total vegetable consumption in the model became somewhat stronger after inclusion of total vegetable consumption in the model. RRs that were decreased became somewhat less strong. For fruit, the estimates without and with total fruit consumption in the model were very similar. In the full multivariate model, no associations were found for the majority of individual vegetables. Decreased RRs were found only for kale and raw endive, although they were not significant [RRs of 0.74 (95% CI, 0.33–1.64) and 0.72 (95% CI, 0.41–1.25), respectively]. Leek showed a positive association with prostate cancer risk; the RR was 1.38 (95% CI, 1.08–1.76). Nonsignificant increased risks were seen for sweet peppers (RR, 1.60; 95% CI, 0.82–3.12) and mushrooms (RR, 1.49; 95% CI, 0.74–3.01). A slight decrease in risk was found for the consumption of mandarins (RR, 0.75; 95% CI, 0.50–1.11), and a strong inverse association was found for the consumption of raisins and other dried fruit, although it was not significant (RR, 0.49; 95% CI, 0.18–1.32). A decreased risk was observed for apples and pears (RR, 0.95; 95% CI, 0.90–0.99). Consumption of oranges showed an increased risk (RR, 1.07; 95% CI, 1.01–1.14). No associations for the consumption of other fruits were found.

The RRs for the main groups of vegetable and fruit consumption, evaluated in case subgroups by differentiation grade, are shown in Table 4. Again, the estimates are expressed per increment of 25 g. For all of the vegetable and fruit groups, the RRs did not differ to a large extent according to differentiation grade, and all estimates were around the null value. We also evaluated these vegetable and fruit groups according to tumor size (T_1 and T_2 tumors combined and T_3 and T_4 tumors combined) and for latent and nonlatent tumors separately. RRs between subgroups of tumor sizes did not differ to a large extent and were mostly around the null value; the same applied to latent and nonlatent tumors (data not shown).

Discussion

Before discussing the results in relation to the other literature, we discuss the strengths and limitations of the present study first. The strength of the NLCS is that recall bias is avoided because of the prospective nature of the study. Selection bias is

Table 2 RRs and 95% CIs for prostate cancer according to vegetable and fruit consumption, Netherlands Cohort Study (1986–1992)

Vegetable/fruit (g/day in quintiles)	Median intake in subcohort	Age-adjusted		Multivariate adjusted	
		No. of cases/Person years in subcohort	RR (95% CI)	No. of cases/Person years in subcohort	RR (95% CI)
Vegetables and fruit combined					
1 (low)	177.7	107/1756	1.00	107/1744	1.00[a,b]
2	257.1	123/1696	1.10 (0.80–1.53)	120/1674	1.08 (0.78–1.50)
3	319.0	121/1784	1.08 (0.78–1.50)	121/1772	1.07 (0.77–1.48)
4	392.9	136/1731	1.19 (0.86–1.64)	135/1725	1.16 (0.84–1.60)
5 (high)	519.0	123/1748	1.05 (0.76–1.45)	123/1741	1.05 (0.76–1.45)
			P-trend 0.56		*P*-trend 0.58
Total vegetables					
1 (low)	100.0	117/1725	1.00	116/1719	1.00[a,c]
2	144.0	126/1765	1.07 (0.78–1.46)	125/1749	1.06 (0.77–1.46)
3	175.0	127/1743	1.12 (0.82–1.54)	126/1730	1.08 (0.78–1.49)
4	214.0	145/1777	1.27 (0.93–1.74)	145/1764	1.28 (0.94–1.75)
5 (high)	285.0	95/1705	0.82 (0.59–1.14)	94/1693	0.80 (0.57–1.12)
			P-trend 0.61		*P*-trend 0.51
Prepared vegetables					
1 (low)	79.0	118/1757	1.00	117/1753	1.00[a,c]
2	115.0	127/1739	1.04 (0.76–1.42)	126/1720	1.03 (0.74–1.41)
3	143.0	139/1756	1.19 (0.87–1.62)	138/1743	1.19 (0.87–1.64)
4	174.0	123/1765	1.11 (0.81–1.53)	123/1740	1.13 (0.82–1.56)
5 (high)	234.0	103/1699	0.85 (0.61–1.18)	102/1699	0.85 (0.61–1.19)
			P-trend 0.40		*P*-trend 0.46
Raw vegetables					
1 (low)	7.0	125/1861	1.00	125/1848	1.00[a,c]
2	19.0	108/1673	0.94 (0.68–1.29)	107/1661	0.89 (0.64–1.23)
3	30.0	118/1752	1.03 (0.75–1.41)	117/1740	0.97 (0.71–1.34)
4	44.0	144/1722	1.19 (0.88–1.62)	142/1722	1.11 (0.81–1.51)
5 (high)	73.0	115/1707	1.04 (0.76–1.42)	115/1685	0.96 (0.69–1.34)
			P-trend 0.26		*P*-trend 0.61
Pulses					
1 (low)	11.0	149/1769	1.00	147/1750	1.00[a,c]
2	22.0	140/1918	0.90 (0.67–1.21)	139/1900	0.92 (0.68–1.24)
3	30.0	100/1655	0.75 (0.55–1.04)	100/1639	0.77 (0.55–1.06)
4	40.0	121/1646	0.92 (0.67–1.25)	121/1639	0.93 (0.68–1.27)
5 (high)	62.3	100/1727	0.69 (0.51–0.95)	99/1727	0.71 (0.51–0.98)
			P-trend 0.01		*P*-trend 0.01
Brassicas					
1 (low)	10.7	146/1936	1.00	145/1936	1.00[a,c]
2	21.0	130/1682	0.97 (0.72–1.31)	130/1669	0.98 (0.72–1.32)
3	29.0	102/1620	0.81 (0.59–1.11)	101/1598	0.81 (0.59–1.12)
4	40.0	129/1809	0.88 (0.65–1.19)	127/1796	0.87 (0.64–1.18)
5 (high)	58.3	103/1669	0.80 (0.58–1.10)	103/1656	0.82 (0.59–1.12)
			P-trend 0.06		*P*-trend 0.06
Leafy vegetables, prepared					
1 (low)	4.0	111/1739	1.00	111/1735	1.00[a,c]
2	12.0	126/1804	0.97 (0.70–1.33)	125/1792	0.93 (0.67–1.29)
3	19.0	129/1782	1.06 (0.77–1.46)	128/1769	1.04 (0.75–1.43)
4	27.0	131/1733	1.15 (0.84–1.58)	131/1714	1.13 (0.82–1.56)
5 (high)	41.0	113/1658	0.97 (0.70–1.35)	111/1645	0.95 (0.68–1.32)
			P-trend 0.67		*P*-trend 0.76
Leafy vegetables, raw					
1 (low)	1.0	104/1792	1.00	104/1779	1.00[a,c]
2	4.0	144/1872	1.47 (1.07–2.01)	144/1857	1.47 (1.07–2.01)
3	8.0	139/1632	1.56 (1.13–2.15)	136/1626	1.51 (1.09–2.08)
4	12.0	121/1684	1.29 (0.93–1.78)	120/1684	1.23 (0.88–1.71)
5 (high)	21.0	102/1734	1.10 (0.79–1.54)	102/1709	1.06 (0.75–1.50)
			P-trend 0.83		*P*-trend 0.85
Alliums					
1 (low)	0.0	123/1747	1.00	120/1741	1.00[a,c]
2	13.0	131/1798	1.05 (0.77–1.43)	130/1779	1.10 (0.81–1.51)
3	23.0	121/1708	1.08 (0.78–1.48)	121/1699	1.12 (0.81–1.55)
4	36.0	132/1723	1.12 (0.82–1.53)	132/1704	1.15 (0.84–1.59)
5	60.0	103/1739	0.90 (0.65–1.24)	103/1732	0.95 (0.69–1.33)
			P-trend 0.67		*P*-trend 0.90

Table 2 Continued

Vegetable/fruit (g/day in quintiles)	Median intake in subcohort	Age-adjusted		Multivariate adjusted	
		No. of cases/Person years in subcohort	RR (95% CI)	No. of cases/Person years in subcohort	RR (95% CI)
Total fruit					
1 (low)	34.0	116/1842	1.00	116/1823	1.00[a,d]
2	91.0	119/1805	1.08 (0.79–1.49)	118/1792	1.06 (0.77–1.46)
3	136.0	106/1815	0.94 (0.68–1.30)	104/1793	0.92 (0.66–1.27)
4	187.0	146/1828	1.17 (0.86–1.59)	144/1822	1.16 (0.85–1.58)
5 (high)	286.4	155/1832	1.30 (0.96–1.77)	155/1832	1.31 (0.96–1.79)
			P-trend 0.02		*P*-trend 0.02
Citrus fruit					
1 (low)	0.0	125/1925	1.00	124/1913	1.00[a,d]
2	17.0	100/1766	0.86 (0.62–1.18)	98/1741	0.86 (0.62–1.19)
3	41.0	115/1806	0.96 (0.70–1.32)	115/1803	0.96 (0.70–1.32)
4	83.0	142/1788	1.12 (0.83–1.52)	141/1776	1.11 (0.82–1.52)
5 (high)	167.0	160/1836	1.27 (0.94–1.70)	159/1830	1.27 (0.93–1.73)
			P-trend 0.01		*P*-trend 0.01

[a] Reference category.
[b] RRs adjusted for age, family history of prostate cancer, and socioeconomic status.
[c] RRs adjusted for age, family history of prostate cancer, socioeconomic status, and total fruit consumption.
[d] RRs adjusted for age, family history of prostate cancer, socioeconomic status, and total vegetable consumption.

also not very likely to have taken place because of the high completeness of follow-up of the cases and subcohort (31, 36). Another important strength of this investigation is that consumption of vegetables and fruits was extensively measured and covered the majority of regularly eaten vegetables and fruits during the preceding year.

One potential limitation is misclassification of exposure. Usual vegetable consumption is not easy to assess in food frequency questionnaires (nor in other methods of dietary assessment), particularly if portion sizes have to be estimated. Thus, the assessment of vegetable consumption may have biased the results. To reduce some of the measurement error, we excluded subjects with incomplete or inconsistent data. Furthermore, we excluded subjects who appeared not to have correctly understood how to fill in the questions on vegetable consumption; those subjects were defined by an extreme score on an error index. In the NLCS validation study, the correlation coefficient for total vegetable consumption was 0.4 (32), which is quite low, but comparable with the figure reported for other prospective studies (37–39). One possible reason for the low correlation may be the relative lack of true contrast in the frequency of total vegetable consumption in the NLCS. Most subjects are accustomed to a diet including one hot meal per day, which almost always includes vegetables. Due to individual preferences, however, contrast in consumption frequency of many specific vegetables is much higher. As can be seen in Table 3, the median intake in the highest quintile of, for example, pulses, is more than five times higher than the median intake in the lowest quintile. Also for brassicas, there is about a 5-fold difference between the median intake in the highest and lowest consumption quintile. For individual vegetables, the range in consumption is even higher because very often subjects in the lowest consumption quintile are nonconsumers of the specific vegetable. Therefore a smaller measurement error and a higher correlation is to be expected for specific vegetable items. It was not possible to assess the validity for specific vegetables in the NLCS validation study, because 9 days of dietary record are not sufficient to estimate consumption frequency of specific vegetables. In our validation study, the correlation coefficient for fruit consumption was 0.60, which may implicate that there is less measurement error regarding fruit consumption in the NLCS. For total fruit consumption, the range of difference between highest and lowest consumption quintile is about 252 g, which is not low, and, as for vegetables, the range in consumption of specific fruits is determined by individual preferences and should therefore also be large enough. Misclassification of both vegetable and fruit consumption is likely to be nondifferential, thus leading to an underestimation of the strength of association.

Another explanation that has to be considered in the interpretation of our results is that unmeasured or unknown factors may have caused residual confounding. We considered, however, most of the factors that have been implied in prostate cancer etiology, and factors showing an association with prostate cancer risk in our study were included into the multivariate model. Thus, total energy and fat intake were not included into the multivariate model. When we performed some analyses with these factors additionally in the multivariate model, risk estimates did not change. Therefore, factors other than energy or fat intake could be responsible for residual confounding. Preclinical symptoms are not likely to have influenced our results because after exclusion of cases detected in the first and in the first 2 years of follow-up, results were similar to results including all cases. Finally, chance will have played a role in our findings, in particular because of the multiple comparisons that were made.

There were only four other cohort studies on prostate cancer in which total vegetable consumption was investigated. In three studies, as in our study, no clear associations were observed (8, 9, 11); and in the other cohort study, a decreased risk was found (13). In one case-control study, total vegetables showed no association (20), and in three case-control studies in which "vegetables" were investigated, also no clear associations were noted (19, 22, 25). We found no association for prepared vegetables, but in one case-control study a decreased risk was noted (26). As in our study, raw vegetables showed no association in one cohort study (10). For consumption of pulses, we found a statistically significant inverse trend in risk. Beans, lentils, and peas combined were also inversely associated with prostate cancer risk in another cohort study (5) and two case-control studies (14, 26), but this was not supported by another case-control study reporting no association (24). All of the

Table 3 RRs and 95% CIs for prostate cancer for continuous variables of vegetable and fruit consumption, Netherlands Cohort Study (1986–1992)

Vegetable/fruit (g/day)	RR[a] (95% CI) per 25 g	RR[b] (95% CI) per 25 g
Vegetables and fruit combined	1.00 (0.98–1.02)[c]	
Total vegetables	0.98 (0.95–1.02)	
Total fruit	1.01 (0.99–1.04)	
Individual vegetable items		
String/French beans	0.94 (0.80–1.12)	0.98 (0.81–1.20)
Broad beans	0.90 (0.63–1.30)	0.95 (0.65–1.38)
Cauliflower	0.90 (0.71–1.14)	0.94 (0.73–1.23)
Cabbage (white/green)	0.88 (0.64–1.21)	0.94 (0.66–1.35)
Kale	0.67 (0.31–1.42)	0.74 (0.33–1.64)
Brussels sprouts	0.81 (0.55–1.21)	0.87 (0.56–1.36)
Endive, prepared	0.89 (0.71–1.12)	0.93 (0.72–1.13)
Spinach	1.03 (0.78–1.36)	1.12 (0.82–1.52)
Endive, raw	0.69 (0.40–1.18)	0.72 (0.41–1.25)
Lettuce	0.99 (0.67–1.46)	1.06 (0.71–1.59)
Leek	1.23 (0.99–1.54)	1.38 (1.08–1.76)
Onions	0.92 (0.80–1.05)	0.93 (0.79–1.10)
Carrots, prepared	0.83 (0.60–1.13)	0.87 (0.61–1.23)
Carrots, raw	1.04 (0.76–1.42)	1.08 (0.78–1.49)
Sauerkraut	1.01 (0.64–1.59)	1.15 (0.69–1.91)
Red beets	0.89 (0.65–1.23)	0.95 (0.67–1.35)
Sweet peppers	1.35 (0.72–2.56)	1.60 (0.82–3.12)
Mushrooms, prepared	1.33 (0.67–2.62)	1.49 (0.74–3.01)
Tomatoes	1.00 (0.88–1.14)	1.05 (0.90–1.22)
Tomato juice	1.11 (0.96–1.29)	1.12 (0.96–1.29)
Gherkins	0.89 (0.61–1.28)	0.92 (0.64–1.32)
Rhubarb	0.90 (0.55–1.47)	0.92 (0.56–1.51)
Individual fruit items		
Oranges	1.06 (1.02–1.11)	1.07 (1.01–1.14)
Mandarins	0.79 (0.54–1.17)	0.75 (0.50–1.11)
Grapefruit	1.03 (0.93–1.15)	1.01 (0.90–1.13)
Processed orange/grapefruit juice	0.96 (0.89–1.03)	0.96 (0.89–1.03)
Grapes	1.10 (0.83–1.44)	1.04 (0.78–1.39)
Apples and pears	0.99 (0.96–1.03)	0.95 (0.90–0.99)
Bananas	1.02 (0.92–1.12)	1.00 (0.91–1.11)
Strawberries	0.94 (0.69–1.29)	0.89 (0.65–1.24)
Raisins/other dried fruit	0.52 (0.20–1.39)	0.49 (0.18–1.32)

[a] Adjusted for age, family history of prostate cancer, socioeconomic status, and total fruit consumption (for vegetable items) or total vegetable consumption (for fruit items).
[b] Adjusted for age, family history of prostate cancer, socioeconomic status, total fruit and total vegetable consumption.
[c] Adjusted for age, family history of prostate cancer, and socioeconomic status.

Table 4 RRs and 95% CIs of prostate cancer for continuous variables of vegetable and fruit consumption in subgroups on differentiation grade, Netherlands Cohort Study (1986–1992)

Vegetable/fruit	Well differentiated (n = 181)	Moderately differentiated (n = 217)	Poorly or undifferentiated (n = 153)
	RR[a] (95% CI) per 25 g	RR[a] (95% CI) per 25 g	RR[a] (95% CI) per 25 g
Vegetables and fruit combined[b]	1.00 (0.97–1.03)	1.00 (0.98–1.02)	1.00 (0.98–1.03)
Total vegetables[c]	0.99 (0.93–1.04)	0.96 (0.91–1.01)	0.99 (0.94–1.05)
Prepared vegetables	0.89 (0.75–1.06)	0.97 (0.82–1.15)	1.08 (0.89–1.31)
Raw vegetables	1.12 (0.94–1.34)	1.03 (0.87–1.22)	0.93 (0.76–1.13)
Pulses	0.93 (0.76–1.15)	0.88 (0.72–1.08)	1.07 (0.87–1.32)
Brassicas	0.95 (0.73–1.24)	0.88 (0.68–1.13)	0.99 (0.75–1.30)
Leafy vegetables, prepared	0.88 (0.65–1.19)	1.11 (0.85–1.46)	1.13 (0.83–1.52)
Leafy vegetables, raw	1.23 (0.81–1.87)	0.78 (0.49–1.23)	0.89 (0.54–1.47)
Alliums	0.92 (0.75–1.15)	1.06 (0.87–1.29)	1.11 (0.89–1.37)
	n = 191	n = 229	n = 160
Total fruit[d]	1.00 (0.97–1.04)	1.03 (1.00–1.06)	1.02 (0.99–1.06)
Citrus fruit	1.01 (0.94–1.07)	1.02 (0.96–1.08)	1.02 (0.96–1.09)

[a] Adjusted for age, family history of prostate cancer, socioeconomic status, total fruit consumption, and total vegetable consumption.
[b] Not adjusted for total vegetable and total fruit consumption.
[c] Not adjusted for total vegetable consumption.
[d] Not adjusted for total fruit consumption.

estimates for vegetables of the brassica genus were below unity in our study, but not significant, and there was no clear trend in risk. In three other studies, cruciferous vegetables showed no clear associations with prostate cancer risk (8, 15, 20), but in two case-control studies, cabbage was inversely associated with prostate cancer risk (14, 21). For prepared and raw leafy vegetables and alliums, we found no increase or decrease in risk. For individual vegetables, evaluated as continuous variables, inverse associations were found for consumption of kale and raw endive, and positive associations were noted for consumption of leek, sweet peppers, and mushrooms. Only the RR for leek was statistically significant. In other studies, different (groups of) vegetables have been evaluated, and no associations were shown for consumption of green or yellow vegetables (7, 9), dark green (leafy) vegetables (9, 20, 26), "other" vegetables (4), "mixed" vegetables (11), tomatoes (20, 26), carrots (11, 20, 22–24), onions (26), spinach (11, 18), broccoli (11), cauliflower (14), bracken fern (19), and rutabaga (14). In some studies, positive associations were noted for consumption of fried vegetables (6) and mushrooms (19), and protective associations were noted for consumption of dark green vegetables for men aged less than 70 years (20), leafy green vegetables (24), tomatoes (5, 11, 14), carrots (14, 18, 21, 26), and spinach (19, 21).

Because so many different vegetables were evaluated and studies were carried out in various populations with different eating habits, the interpretation of results from these studies are hampered. In addition, studies differ in the level and range of exposure, thus leading to results that are not directly comparable. These drawbacks not only apply to studies on prostate cancer risk in relation to vegetable consumption but also in relation to fruit consumption (discussed below). Other drawbacks are that end points in previous studies were either incidence or mortality and, as a consequence, consistency in results is difficult to evaluate. Also, several epidemiological studies are hampered by the fact that no extensive measurement of consumption of vegetables and fruit was made. Therefore, no complete evaluation of vegetables and fruit was possible, and for those vegetables and fruit that were included, a random misclassification bias may have occurred, which would lead to an underestimation of effect. Another drawback is that because in several studies only limited adjustment was used, results in these studies might have been influenced by confounding. Finally, in none of the previous studies was the independent effect of individual vegetables or fruits assessed by including total vegetable or total fruit consumption into the multivariate model.

When quintiles of total fruit and citrus fruit consumption were evaluated in our cohort study, we observed significant positive trends in risk, but in a continuous model, no association with total fruit consumption was found. In most other cohort studies, no clear associations were found for total fruit (4, 5, 8, 9, 11) and fresh citrus fruit (5). Total fruit consumption was positively associated with prostate cancer in one cohort study (6) and one case-control study (25); also for citrus fruit, a positive association was noted in a case-control study (26). Null associations have been reported for consumption of canned or frozen fruit (5), fresh winter fruit (5), noncitrus fruit (26), or "other" fresh fruit (5, 10). In one case-control study, fresh fruit consumption was inversely associated with prostate cancer risk, but only for men aged 70 years and older (22). Except for mandarins and raisins, which were inversely associated with prostate cancer risk in the NLCS, no strong associations for individual fruits were found. There is only one other study in which consumption of raisins and other dried fruit was evaluated, and in this cohort study, an inverse association was also observed (5). Other individual fruits that have been evaluated are oranges (11), strawberries (11), pumpkin or mangoes, and papaya (20). A positive association with prostate cancer risk was observed only for papaya in men aged 70 years and older. In two cohort studies, consumption of vegetables and fruit combined showed no associations with prostate cancer risk (9, 12), and this was confirmed in our study.

It has been suggested before that latent and nonlatent or aggressive prostate tumors might have a different etiology (1). The RRs for groups of vegetables and fruits did not differ to a large extent between the different subgroups in our study. In one other study in which only carrots were evaluated, it was mentioned that a distinction in localized and advanced prostate tumors displayed results similar to overall results (23). Thus far, there have been no other studies regarding vegetable and fruit consumption and prostate cancer risk in which subgroup analyses based on tumor characterization were conducted.

In conclusion, for most vegetables, no consistent associations with prostate cancer risk have been observed thus far. Moreover, in most studies, including the present one, vegetable consumption seemed not to be associated with prostate cancer risk. However, different vegetables have been evaluated in different studies, which makes a comparison between studies difficult. We found some indication of a protective effect of consumption of pulses, kale, and raw endive and of a positive association between consumption of leek, sweet peppers, and mushrooms and prostate cancer risk. These results, however, need to be confirmed in other studies. For fruit, similar conclusions can be drawn. We found a positive trend in risk for total fruit consumption and citrus fruit consumption, but this has mostly not been reported from other studies. In a continuous model, fruit consumption showed no association with prostate cancer risk. Results from our study regarding individual fruits were not very convincing. Nevertheless, there was a tendency for a protective effect of consumption of raisins and other dried fruit. Because this effect was also reported in another study, more studies on a possible effect of raisins are warranted. Our results indicate no different association for latent and nonlatent or more advanced prostate tumors.

Acknowledgments

We are indebted to the participants of this study, and we thank the regional cancer registries (IKA, IKL, IKMN, IKN, IKO, IKR, IKST, IKW, and IKZ) and the Dutch national database of pathology (PALGA); A. Volovics for statistical advice; S. van de Crommert, J. Nelissen, H. Brants, M. Moll, W. van Dijk, C. Sloot, P. Florax, and A. Pisters for assistance; and H. van Montfort, R. Schmeitz, T. van Montfort, and M. de Leeuw for programming and statistical assistance.

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