Cancer Causes Control (2009) 20:1605–1615
DOI 10.1007/s10552-009-9406-z

ORIGINAL PAPER

Legume intake and the risk of cancer: a multisite case–control study in Uruguay

Dagfinn Aune · Eduardo De Stefani · Alvaro Ronco · Paolo Boffetta · Hugo Deneo-Pellegrini · Giselle Acosta · Maria Mendilaharsu

Received: 4 March 2009 / Accepted: 14 July 2009 / Published online: 4 August 2009
© Springer Science+Business Media B.V. 2009

Abstract
Background Previous studies have suggested that a high intake of legumes may decrease the risk of stomach and prostate cancer and some other cancers. However, the evidence is still limited. To further explore the association between legume intake and cancer risk we conducted a case–control study of 11 cancer sites in Uruguay between 1996 and 2004, including 3,539 cancer cases and 2,032 hospital controls.
Results The highest versus the lowest tertile of legume intake was associated with a significant decrease in the risk of cancers of the oral cavity and pharynx (OR = 0.48, 95% CI: 0.34–0.68), esophagus (OR = 0.54, 95% CI: 0.38–0.77), larynx (OR = 0.55, 95% CI: 0.40–0.77), upper aerodigestive tract (OR = 0.50, 95% CI: 0.40–0.63), stomach (OR = 0.69, 95% CI: 0.49–0.97), colorectum (OR = 0.43, 95% CI: 0.32–0.59), kidney (OR = 0.41, 95% CI: 0.24–0.71), and all sites combined (OR = 0.68, 95% CI: 0.59–0.78). No significant association was observed between legume intake and cancers of the lung (OR = 1.03, 95% CI: 0.83–1.27), breast (OR = 0.89, 95% CI: 0.65–1.20), prostate (OR = 0.87, 95% CI: 0.64–1.18) or bladder (OR = 0.82, 95% CI: 0.57–1.17). Similar results were found for both beans and lentils.
Conclusion Higher intake of legumes was associated with a decreased risk of several cancers including those of the upper aerodigestive tract, stomach, colorectum, and kidney, but not lung, breast, prostate or bladder. Further investigations of these associations in prospective cohort studies are warranted.

Keywords Legumes · Beans · Lentils · Diet · Food · Cancer

D. Aune (✉)
Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, P.O. Box 1122, 0317 Oslo, Norway
e-mail: dagfinn.aune@medisin.uio.no

D. Aune
Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway

E. De Stefani · H. Deneo-Pellegrini · G. Acosta · M. Mendilaharsu
Grupo de Epidemiología, Departamento de Anatomía Patológica, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

A. Ronco
Departamento de Epidemiologıa y Metodos Cientıficos, Facultad de Medicina, Centro Latinoamericano de Economıa Humana (CLAEH), Montevideo, Uruguay

P. Boffetta
International Agency for Research on Cancer, Lyon, France

Introduction

Legumes have been cultivated for thousands of years and have played an important role in the traditional diets in many areas of the world. Legumes are a diverse group of foods, including peas, beans, lentils, peanuts, and other podded plants. Legumes are good sources of dietary fiber and in particular soluble fiber which may decrease blood cholesterol and therefore could decrease cardiovascular risk [1]. In addition, legumes are good sources of dietary protein, vitamin E, B-vitamins such as pyridoxine and folic acid, selenium, isoflavones, and lignans with potential cancer-preventive effects [2].

Some studies have indicated reduced risk of cancers of the oral cavity and pharynx [3–5], larynx [6], stomach

[7–9], prostate [10–14], and breast [15–18] with higher intake of legumes. However, other studies did not confirm these findings [19–23] and most studies found no significant association between legume intake and cancers of the colorectum [24–26], lung [27, 28] or kidney cancer [29–32]. In the most recent report from the World Cancer Research Fund and American Institute for Cancer Research there was limited suggestive evidence for a protective effect of legumes on the risk of stomach and prostate cancer [33], however, the evidence for other cancer sites was considered too limited or inconsistent for any conclusion. To further clarify the effect of legume intake upon cancer risk we decided to explore these associations in a multisite case–control study of diet and cancer in Uruguay, between 1996 and 2004.

Materials and methods

Selection of cases

In the time period between 1996 and 2004 we conducted a case–control study including cancers of the mouth and pharynx ($n = 283$), esophagus ($n = 234$), stomach ($n = 275$), colon ($n = 176$), rectum ($n = 185$), larynx ($n = 281$), lung ($n = 931$), breast ($n = 461$), prostate ($n = 345$), bladder ($n = 254$), and kidney ($n = 114$). All the cases were <90 years old at diagnosis (age range 26–89 years, mean 63.6 years) and were drawn from the four major public hospitals of Montevideo. A total of 3,744 patients with newly diagnosed and microscopically confirmed primary cancers were considered eligible for the study. In total, 205 patients refused the interview or were too ill to be interviewed leaving a final total of 3,539 cases (response rate 94.5%). No proxy interviews were conducted neither for cases nor controls.

Selection of controls

In the same time period and in the same hospitals, 2,117 patients <90 years old (age range 23–89 years, mean 62.3 years) with nonneoplastic diseases not related to smoking, drinking, and without recent changes in their diets were considered eligible for this study. In total 85 patients refused the interview or were too ill to be interviewed, leaving a final total of 2,032 controls (response rate 96.0%). These patients were admitted with the following diseases: eye disorders ($n = 431$, 21.2%), abdominal hernia ($n = 422$, 20.8%), injuries and accidents ($n = 388$, 19.1%), varicose veins ($n = 112$, 5.5%), acute appendicitis ($n = 111$, 5.5%), diseases of the skin ($n = 137$, 6.7%), hydatid cyst ($n = 101$, 5.0%), urinary system diseases ($n = 96$, 4.7%), and various other conditions ($n = 234$, 11.5%).

Interviews and questionnaire

All the participants were administered a structured questionnaire by two trained social workers. All the interviews of cases and controls were conducted in the hospitals shortly after admittance. The questionnaire contained the following sections: (1) sociodemographics (age, sex, residence, education), (2) a complete occupational history (type of job and duration), (3) self-reported height and weight 5 years before the date of the interview, (4) a history of cancer in first degree relatives, (5) a complete history of tobacco smoking (age at start, age of quit, number of cigarettes smoked per day, type of tobacco, type of cigarette, inhalation practices), (6) a complete history of alcohol drinking (age at start, age of quit, number of glasses per day or week, type of alcoholic beverage), (7) a complete history of mate, coffee, and tea consumption (age at start, age of quit, number of cups or liters ingested per day), and (8) a detailed food frequency questionnaire (FFQ) with 64 food items which covered the dietary intake 1 year before diagnosis. This FFQ was considered as representative of the Uruguayan diet and allowed for the estimation of total energy intake. There were two questions on the frequency of intake of legumes (beans and lentils) in the FFQ, using a standard serving size of 82 grams and total legumes were calculated as the sum of beans and lentils. The correlation coefficient was 0.84 between beans and legumes and 0.87 between lentils and legumes, while it was 0.48 between beans and lentils. Although the FFQ was not validated, it was tested for reproducibility and the correlation coefficient between the two FFQs was 0.70 for legumes [34].

Statistical methods

We used unconditional logistic regression to estimate odds ratios and 95% confidence intervals (95% CIs) by tertiles of legume intake. The tertiles were based on the distribution of legume and bean intake among the controls. For comparison we used identical cut-points for beans and lentils. In addition we conducted analyses with more extreme categorizations of legume intake to assess whether higher intakes were more strongly associated with cancer risk. We also calculated ORs and 95% CIs on a continuous scale and the increment was 25 g/day for legumes, beans, and lentils. We used a multivariable model including the following covariates: age (continuous), sex (when applicable), residence (urban/rural), education (continuous), income (continuous), interviewer, smoking status (never smokers, former smokers, current smokers), age at starting

smoking (continuous), years since quitting smoking (continuous), cigarettes per day (continuous), duration of smoking (continuous), alcohol intake (0, 1–60, 61–120, 121–240, ≥241 ml/day), intake of grains (continuous), dairy products (continuous), fatty foods (continuous), fruits and vegetables (continuous), total meat (continuous), energy intake (continuous), mate drinking status (never drinkers, former drinkers, current drinkers), and BMI (continuous). Potential confounders were included in the multivariate model based on a review of the literature, from comparisons of cases versus controls and/or whether they modified the risk estimates 10% or more. In a sensitivity analysis we further adjusted for other potential dietary confounders, such as coffee, tea, total fat, and cholesterol, to assess whether residual confounding by these could explain the findings, and as an exploratory analysis we further adjusted for fiber, vitamin E, B-vitamins, and protein intake to test whether these nutrients accounted for part of the association between legume intake and cancer risk. Tests for linear trend were calculated by entering the categorical variables as continuous parameters in the models. Possible interactions between legume intake and age, sex, fruits and vegetables, total meat, smoking status, alcohol intake were assessed by including cross product terms in the multivariable models. A two-tailed p value of <0.05 was considered to be statistically significant. All statistical tests were carried out using STATA version 9.2.

Results

Sociodemographic characteristics and selected risk factors among the cases and controls are shown in Table 1. Compared with the controls, the cases were in general older ($p = 0.0001$ with a t-test, not shown in table) and were more likely to be current smokers ($p < 0.0001$, with chi-square test) and had a higher intake of alcohol ($p < 0.0001$) and meat ($p < 0.0001$), but a lower intake of legumes ($p = 0.007$), beans ($p = 0.05$), and lentils ($p = 0.008$), while intake of fruits and vegetables was similar ($p = 0.18$). Intake of beans contributed 45% and lentils contributed 55% of total legume intake.

The highest versus the lowest tertile of legume intake was associated with a significantly decreased risk of cancers of the oral cavity and pharynx (OR = 0.48, 95% CI: 0.34–0.68; $p_{trend} < 0.0001$), esophagus (OR = 0.54, 95% CI: 0.38–0.77; $p_{trend} = 0.001$), larynx (OR = 0.55, 95% CI: 0.40–0.77; $p_{trend} < 0.0001$), upper aerodigestive tract (oral cavity, pharynx, esophagus and larynx) (OR = 0.50, 95% CI: 0.40–0.63; $p_{trend} < 0.0001$), stomach (OR = 0.69, 95% CI: 0.49–0.97; $p_{trend} = 0.02$), colorectum (OR = 0.43, 95% CI: 0.32–0.59; $p_{trend} < 0.0001$), kidney (OR = 0.41, 95% CI: 0.24–0.71; $p_{trend} = 0.001$) and all cancers combined (OR = 0.68, 95% CI: 0.59–0.78; $p_{trend} < 0.0001$) (Table 2). There were no significant associations with cancers of the lung (OR = 1.03, 95%

Table 1 Sociodemographic characteristics and selected risk factors among cases and controls (numbers are means (standard deviations), except for sex and smoking (%))

Cancer site	n	Age (years)	Male sex (%)	Current smokers (%)	Former smokers (%)	Ethanol (g/day)	Fruit, vegetables (g/day)	Meat (g/day)	Legumes (g/day)	Beans (g/day)	Lentils (g/day)
Oral	283	59.9 (9.7)	96.8	82.0	15.2	168.3 (175.8)	326.6 (153.1)	253.2 (104.7)	6.5 (12.9)	3.3 (7.0)	3.2 (6.9)
Esophagus	234	66.3 (10.3)	78.6	51.7	27.8	97.1 (154.6)	306.3 (143.2)	230.5 (93.6)	7.0 (14.3)	3.1 (7.4)	3.9 (9.1)
Larynx	281	62.1 (10.0)	97.5	69.8	27.4	153.3 (183.0)	318.0 (139.2)	261.8 (99.7)	6.3 (12.7)	2.9 (6.5)	3.4 (7.0)
Upper aerodigestive tract	798	62.5 (10.3)	91.7	68.8	23.2	142.2 (174.8)	317.6 (145.5)	249.6 (100.5)	6.6 (13.2)	3.1 (6.9)	3.5 (7.6)
Stomach	275	65.6 (11.2)	69.3	40.5	25.2	67.5 (110.7)	332.8 (141.2)	225.9 (94.0)	5.8 (8.6)	2.3 (4.7)	3.5 (5.8)
Colon	176	64.3 (11.9)	49.4	27.8	26.1	36.1 (100.4)	322.5 (153.7)	220.2 (92.0)	5.6 (8.9)	2.2 (4.8)	3.4 (5.9)
Rectum	185	66.3 (10.2)	68.7	31.9	31.4	55.6 (94.3)	335.0 (171.4)	235.1 (98.6)	5.7 (10.5)	2.6 (7.0)	3.1 (7.3)
Colorectum	361	65.4 (11.1)	59.3	29.0	28.2	46.1 (97.7)	353.2 (189.5)	211.0 (91.0)	5.6 (9.7)	2.4 (6.0)	3.2 (6.6)
Lung	931	62.0 (10.1)	94.0	69.5	27.6	107.3 (146.6)	303.3 (166.0)	227.7 (98.7)	9.5 (14.9)	4.5 (8.5)	4.9 (8.6)
Breast	461	59.7 (13.1)	0	19.3	10.0	9.6 (40.7)	272.1 (155.6)	196.3 (81.2)	9.8 (12.5)	4.3 (7.0)	5.4 (7.5)
Prostate	345	70.6 (7.3)	100	27.5	45.8	76.1 (131.0)	336.6 (158.2)	195.4 (87.9)	7.4 (10.6)	3.3 (5.7)	4.1 (6.6)
Bladder	254	67.0 (10.0)	88.2	48.6	32.5	66.2 (102.5)	337.2 (185.7)	209.9 (102.2)	6.4 (9.7)	2.5 (5.0)	3.9 (7.5)
Kidney	114	60.6 (11.8)	67.5	48.2	21.9	61.6 (128.6)	310.6 (159.5)	195.6 (99.5)	5.3 (9.2)	2.8 (5.4)	2.5 (4.4)
All sites	3539	63.6 (11.0)	75.1	50.7	25.7	85.6 (139.5)	323.7 (162.6)	227.9 (110.7)	7.6 (12.5)	3.5 (7.0)	4.2 (7.5)
Controls	2032	62.3 (12.8)	66.2	37.9	26.3	59.5 (116.5)	329.8 (156.0)	195.8 (87.1)	8.5 (12.1)	3.8 (6.9)	4.7 (7.3)

Table 2 Intake of legumes, beans, and lentils in relation to cancer risk (multivariate-adjusted odds ratios and 95% confidence intervals) at different cancer sites

Cancer site	Cases/controls	Legumes	Cases/controls	Beans	Cases/controls	Lentils
Oral cavity and pharynx						
T1[a]	139/880	1.00	92/729	1.00	78/484	1.00
T2	81/488	0.83 (0.60–1.15)	126/771	0.75 (0.55–1.03)	143/892	0.78 (0.56–1.08)
T3	63/664	0.48 (0.34–0.68)	65/532	0.54 (0.37–0.79)	62/656	0.49 (0.33–0.72)
p_{trend}		<0.0001		0.001		<0.0001
Continuous[b]		0.58 (0.41–0.84)		0.49 (0.27–0.89)		0.39 (0.20–0.74)
Esophagus						
T1	120/880	1.00	88/729	1.00	75/484	1.00
T2	55/488	0.83 (0.58–1.17)	93/771	0.81 (0.59–1.12)	105/892	0.82 (0.59–1.14)
T3	59/664	0.54 (0.38–0.77)	53/532	0.59 (0.40–0.86)	54/656	0.52 (0.36–0.77)
p_{trend}		0.001		0.006		0.001
Continuous		0.63 (0.45–0.88)		0.43 (0.23–0.81)		0.59 (0.35–1.01)
Larynx						
T1	140/880	1.00	95/729	1.00	67/484	1.00
T2	70/488	0.75 (0.54–1.05)	129/771	0.83 (0.61–1.14)	149/892	1.04 (0.74–1.45)
T3	71/664	0.55 (0.40–0.77)	57/532	0.50 (0.34–0.73)	65/656	0.63 (0.42–0.93)
p_{trend}		<0.0001		<0.0001		0.014
Continuous		0.55 (0.39–0.80)		0.33 (0.17–0.65)		0.48 (0.27–0.87)
Upper aerodigestive tract						
T1	399/880	1.00	275/729	1.00	220/484	1.00
T2	206/488	0.81 (0.65–1.01)	348/771	0.80 (0.65–0.99)	397/892	0.87 (0.69–1.08)
T3	193/664	0.50 (0.40–0.63)	175/532	0.53 (0.41–0.68)	181/656	0.52 (0.40–0.66)
p_{trend}		<0.0001		<0.0001		<0.0001
Continuous		0.57 (0.45–0.71)		0.40 (0.27–0.59)		0.46 (0.32–0.67)
Stomach						
T1	142/880	1.00	114/729	1.00	59/484	1.00
T2	69/488	0.76 (0.55–1.05)	115/771	0.81 (0.61–1.09)	147/892	1.05 (0.75–1.48)
T3	64/664	0.69 (0.49–0.97)	46/532	0.54 (0.37–0.80)	69/656	0.84 (0.57–1.23)
p_{trend}		0.019		0.002		0.33
Continuous		0.67 (0.46–0.98)		0.36 (0.17–0.79)		0.73 (0.42–1.29)
Colon						
T1	98/880	1.00	83/729	1.00	44/484	1.00
T2	40/488	0.87 (0.58–1.30)	65/771	0.83 (0.58–1.18)	93/892	1.35 (0.91–2.00)
T3	38/664	0.47 (0.31–0.72)	28/532	0.47 (0.29–0.76)	39/656	0.70 (0.43–1.12)
p_{trend}		<0.0001		0.002		0.14
Continuous		0.41 (0.25–0.68)		0.21 (0.08–0.55)		0.38 (0.18–0.79)
Rectum						
T1	101/880	1.00	86/729	1.00	66/484	1.00
T2	47/488	0.99 (0.68–1.46)	66/771	0.69 (0.49–0.99)	80/892	0.76 (0.53–1.09)
T3	37/664	0.42 (0.28–0.64)	33/532	0.45 (0.29–0.71)	39/656	0.45 (0.29–0.70)
p_{trend}		<0.0001		<0.0001		<0.0001
Continuous		0.41 (0.25–0.66)		0.29 (0.13–0.66)		0.28 (0.13–0.61)
Colorectum						
T1	199/880	1.00	169/729	1.00	110/484	1.00
T2	87/488	0.89 (0.67–1.20)	131/771	0.73 (0.56–0.95)	173/892	0.99 (0.75–1.31)
T3	75/664	0.43 (0.32–0.59)	61/532	0.44 (0.31–0.61)	78/656	0.53 (0.38–0.75)
p_{trend}		<0.0001		<0.0001		<0.0001
Continuous		0.41 (0.29–0.59)		0.25 (0.13–0.47)		0.33 (0.19–0.57)

Table 2 continued

Cancer site	Cases/controls	Legumes	Cases/controls	Beans	Cases/controls	Lentils
Lung						
T1	391/880	1.00	256/729	1.00	236/484	1.00
T2	206/488	1.12 (0.89–1.42)	390/771	1.15 (0.93–1.43)	397/892	1.00 (0.80–1.25)
T3	334/664	1.03 (0.83–1.27)	285/532	1.16 (0.91–1.48)	298/656	1.03 (0.80–1.31)
p_{trend}		0.75		0.21		0.83
Continuous		1.02 (0.86–1.21)		1.03 (0.77–1.38)		1.02 (0.77–1.34)
Breast						
T1	165/266	1.00	166/280	1.00	110/141	1.00
T2	127/170	1.25 (0.90–1.72)	154/224	1.15 (0.85–1.56)	177/290	0.89 (0.64–1.24)
T3	169/250	0.89 (0.65–1.20)	141/182	1.06 (0.77–1.46)	174/255	0.86 (0.61–1.21)
p_{trend}		0.45		0.67		0.41
Continuous		0.82 (0.64–1.05)		0.82 (0.53–1.26)		0.71 (0.49–1.05)
Prostate						
T1	175/614	1.00	128/449	1.00	101/343	1.00
T2	73/318	0.89 (0.65–1.22)	138/547	0.98 (0.74–1.30)	149/602	1.02 (0.76–1.38)
T3	97/414	0.87 (0.64–1.18)	79/350	0.84 (0.60–1.19)	95/401	0.93 (0.66–1.31)
p_{trend}		0.33		0.34		0.66
Continuous		0.92 (0.70–1.21)		0.79 (0.48–1.28)		0.99 (0.63–1.54)
Bladder						
T1	122/880	1.00	101/729	1.00	67/484	1.00
T2	67/488	1.36 (0.96–1.93)	107/771	0.85 (0.62—1.16)	117/892	1.14 (0.80-1.60)
T3	65/664	0.82 (0.57–1.17)	46/532	0.59 (0.39–0.89)	70/656	1.06 (0.71–1.57)
p_{trend}		0.39		0.012		0.81
Continuous		0.69 (0.48–0.99)		0.36 (0.17–0.79)		0.79 (0.49–1.29)
Kidney						
T1	72/880	1.00	35/729	1.00	36/484	1.00
T2	21/488	0.68 (0.40–1.14)	60/771	1.69 (1.08–2.64)	58/892	0.95 (0.60–1.48)
T3	21/664	0.41 (0.24–0.71)	19/532	0.94 (0.51–1.72)	20/656	0.46 (0.25–0.82)
p_{trend}		0.001		0.75		0.011
Continuous		0.44 (0.23–0.84)		0.67 (0.27–1.65)		0.16 (0.05–0.54)
All sites						
T1	1665/880	1.00	1244/729	1.00	939/484	1.00
T2	856/488	0.95 (0.82–1.11)	1443/771	0.96 (0.83–1.10)	1615/892	0.98 (0.84–1.13)
T3	1018/664	0.68 (0.59–0.78)	852/532	0.72 (0.62–0.85)	985/656	0.74 (0.63–0.87)
p_{trend}		<0.0001		<0.0001		<0.0001
Continuous		0.72 (0.64–0.82)		0.59 (0.48–0.74)		0.65 (0.53–0.80)

Multivariable model: age, sex, residence, education, income, interviewer, smoking status, age at starting smoking, years since quitting smoking, cigarettes per day, duration of smoking, alcohol intake, intake of grains, dairy products, fatty foods (eggs, cake, custard, butter), fruits and vegetables, total meat, mate drinking status, energy intake, and BMI

[a] Cut-off values and medians for tertiles: Legumes: 0–2.7, 2.71–5.40, 5.41–164 g/day, median: 1.35, 5.39, 14.38 g/day. Beans: 0, 0.22–2.7, 2.71–82 g/day, median: 0, 2.70, 9.44 g/day. Lentils: 0, 0.22–2.7, 2.71–82 g/day, median: 0, 2.70, 11.68 g/day

[b] OR on a continuous scale for an increment of 25 g/day for legumes, beans and lentils

CI: 0.83–1.27; $p_{trend} = 0.75$), breast (OR = 0.89, 95% CI: 0.65–1.20; $p_{trend} = 0.45$), prostate (OR = 0.87, 95% CI: 0.64–1.18; $p_{trend} = 0.33$) or bladder (OR = 0.82, 95% CI: 0.57–1.17; $p_{trend} = 0.39$), but an inverse association was apparent for bladder cancer when analysed on a continuous scale (OR = 0.69, 95% CI: 0.48–0.99).

The results for beans and lentils were similar. The highest versus the lowest tertile of bean intake was associated with decreased risk of cancers of the oral cavity and pharynx (OR = 0.54, 95% CI: 0.37–0.79; $p_{trend} = 0.001$), esophagus (OR = 0.59, 95% CI: 0.40–0.86; $p_{trend} = 0.006$), larynx (OR = 0.50, 95% CI: 0.34–0.73; $p_{trend} < 0.0001$), upper

aerodigestive tract (OR = 0.53, 95% CI: 0.41–0.68; $p_{trend} < 0.0001$), stomach (OR = 0.54, 95% CI: 0.37–0.80; $p_{trend} = 0.002$), colorectum (OR = 0.44, 95% CI: 0.31–0.61; $p_{trend} < 0.0001$), bladder (OR = 0.59, 95% CI: 0.39–0.89; $p_{trend} = 0.01$) and all cancers combined (OR = 0.72, 95% CI: 0.62–0.85; $p_{trend} < 0.0001$) (Table 2). There were no significant associations with cancers of the lung (OR = 1.16, 95% CI: 0.91–1.48; $p_{trend} = 0.21$), breast (OR = 1.06, 95% CI: 0.77–1.46; $p_{trend} = 0.67$), prostate (OR = 0.84, 95% CI: 0.60–1.19; $p_{trend} = 0.34$), or kidney (OR = 0.94, 95% CI: 0.51–1.72; $p_{trend} = 0.75$). The highest versus the lowest tertile of lentil intake was associated with decreased risk of cancers of the oral cavity and pharynx (OR = 0.49, 95% CI: 0.33–0.72; $p_{trend} < 0.0001$), esophagus (OR = 0.52, 95% CI: 0.36–0.77; $p_{trend} = 0.001$), larynx (OR = 0.63, 95% CI: 0.42–0.93; $p_{trend} = 0.01$), upper aerodigestive tract (OR = 0.52, 95% CI: 0.40–0.66; $p_{trend} < 0.0001$), colorectum (OR = 0.53, 95% CI: 0.38–0.75; $p_{trend} < 0.0001$), kidney (OR = 0.46, 95% CI: 0.25–0.82; $p_{trend} = 0.01$) and all cancers combined (OR = 0.74, 95% CI: 0.63–0.87; $p_{trend} < 0.0001$) (Table 2). There were no significant associations with cancers of the stomach (OR = 0.84, 95% CI: 0.57–1.23; $p_{trend} = 0.33$), lung (OR = 1.03, 95% CI: 0.80–1.31; $p_{trend} = 0.83$), breast (OR = 0.86, 95% CI: 0.61–1.21; $p_{trend} = 0.41$), prostate (OR = 0.93, 95% CI: 0.66–1.31; $p_{trend} = 0.66$) or bladder (OR = 1.06, 95% CI: 0.71–1.57; $p_{trend} = 0.81$).

The result for legume intake and all cancer sites combined was stronger in the multivariable model (OR = 0.68, 95% CI: 0.59–0.78) compared with the simple age and sex-adjusted model (OR = 0.84, 95% CI: 0.74–0.95, data not shown). Stepwise addition of each of the confounders to the age and sex-adjusted model showed that adjustment for total meat and energy intake explained most of the strengthening of the effect estimate in the multivariable model (OR = 0.75, 95% CI: 0.65–0.85 and 0.74, 95% CI: 0.65–0.84, when adding total meat and energy intake, respectively, to the age and sex-adjusted model, data not shown). Further adjustment for intake of coffee, tea, total fat or cholesterol in addition to all the other covariates did not materially attenuate the estimate for legume intake and all cancer sites combined (OR = 0.70, 95% CI: 0.61–0.81), neither did further adjustment for fiber, folate, thiamine, riboflavin, pyridoxine, vitamin E, or protein as an exploratory analysis (OR = 0.71, 95% CI: 0.61–0.84, data not shown).

In a stratified analysis the inverse association with legume intake and all cancer sites combined persisted across most strata of age, sex, intake of fruits and vegetables, meat, smoking, and alcohol intake (Table 3) and none of the tests for interaction were significant, $p \geq 0.16$. Analyses using quintiles of intake yielded stronger results than in tertiles, the ORs and 95% CIs of all cancer sites combined were 0.53 (95% CI: 0.44–0.64) for >12.2 vs. ≤1.35 g/day of legumes, 0.57 (95% CI: 0.48–0.69) for >5.40 vs. 0 g/day of beans and 0.58 (95% CI: 0.48–0.70) for >6.74 vs. 0 g/day of lentils (data not shown).

Discussion

Our results suggest that higher intake of legumes, including beans and lentils decreases the risk of developing several types of cancer.

High intake of legumes, beans, and lentils was associated with decreased risk of cancers of the digestive tract including those of the oral cavity and pharynx, esophagus, larynx, stomach, and colorectum. Our results are consistent with some previous case–control studies, which have reported 40–60% decreased risk of oral and pharyngeal cancer with higher intake of legumes [3–6], although two other case–control studies reported nonsignificant elevations [19, 35]. The largest study did, however, find a protective effect [4]. Three previous case–control studies [36–38] and one cohort study [39] on legume intake and esophageal cancer all reported relative risks below one, but only in one small case–control study was the finding statistically significant [37]. The data for laryngeal cancer is considerably more limited, but a previous case–control study from Uruguay reported a nonsignificantly lower risk with higher legume intake [6]. The inverse association between legume intake and upper aerodigestive tract cancers is consistent with a large cohort study, which recently found a significant 20% reduced risk of head and neck cancers with legume intake [40], and a large case–control study, which reported a nonsignificant 28% reduction in the risk of head and neck cancer (although our results are stronger) [41], but not with a smaller cohort study [42]. Our study is consistent with most previous case–control studies [7–9, 43–45] and a cohort study [46], which reported significant or nonsignificant decreases in the risk of stomach cancer with higher intake of legumes, although another cohort study [47] reported no significant association and two case–control studies reported elevated risk [48, 49]. The WCRF/AICR 2007 report stated that there was limited suggestive evidence that legume intake protects against stomach cancer [33]. Former studies on legume intake and colorectal cancer have provided mixed results with some studies indicating an inverse association [50–52], no association [24–26, 53–55] or even an nonsignificantly increased risk [56] and only one [52] of the seven cohort studies [24–26, 52, 53, 57, 58] suggested a significant inverse association, while our study suggested a strong protective effect.

The results for lung cancer are consistent with most previous case–control studies [27, 59–62] and the results

Table 3 Intake of legumes in relation to risk of all cancer sites combined stratified by covariates (tertile 1 is the reference group)

All sites	Legumes			
	T2	T3	p_{trend}	$p_{interaction}$
Age (years)				
≤50	1.25 (0.85–1.85)	0.74 (0.52–1.06)	0.11	0.67
>50	0.91 (0.77–1.07)	0.67 (0.57–0.78)	<0.0001	
Sex[a]				
Men	0.95 (0.79–1.14)	0.71 (0.60–0.85)	<0.0001	0.19
Women	0.96 (0.73–1.26)	0.63 (0.48–0.81)	0.001	
Fruits, vegetables				
≤245.4 g/day	0.98 (0.76–1.27)	0.59 (0.45–0.76)	<0.0001	0.16
>245.4–381.5	0.99 (0.77–1.27)	0.68 (0.53–0.87)	0.003	
>381.5	0.92 (0.70–1.21)	0.76 (0.59–0.98)	0.033	
Meat				
≤120 g/day	1.02 (0.70–1.48)	0.66 (0.45–0.98)	0.002	0.56
>120–240	0.97 (0.79–1.19)	0.67 (0.55–0.82)	<0.0001	
>240	0.90 (0.68–1.19)	0.69 (0.54–0.90)	0.023	
Smoking[a]				
Never	0.88 (0.67–1.15)	0.65 (0.50–0.85)	0.001	0.86
Former	0.93 (0.69–1.25)	0.66 (0.49–0.87)	0.002	
Current	1.05 (0.83–1.31)	0.70 (0.56–0.87)	0.001	
Alcohol[a]				
Nondrinker	1.01 (0.80–1.27)	0.77 (0.62–0.96)	0.024	0.54
1–120 ml/day	0.87 (0.68–1.12)	0.60 (0.47–0.76)	<0.0001	
≥121	1.03 (0.74–1.44)	0.71 (0.51–0.97)	0.078	

Multivariable model: age, sex, residence, education, income, interviewer, smoking status, age at starting smoking, years since quitting smoking, cigarettes per day, duration of smoking, alcohol intake, intake of grains, dairy products, fatty foods, fruits and vegetables, mate drinking status, energy intake, BMI, total meat

[a] In the stratified analyses by sex, smoking and alcohol the respective covariates were not included in the multivariable model

from a pooled analysis of cohort studies [28] which indicated no significant association. Some previous case–control studies [63, 64] found no association between legume intake and breast cancer risk, consistent with our finding of no association. However, most case–control [16–18, 65, 66] studies and a cohort study [15] suggested significant or nonsignificant 20–30% reductions in breast cancer risk with high legume intake, and we cannot rule out a such a moderate protective effect, particularly in the analyses on a continuous scale. Most previous case–control studies [10, 13, 67, 68] and cohort studies [11, 12, 14] have suggested a significant or nonsignificant inverse association between legume intake and prostate cancer and none provided evidence for a significant increase in the risk [22, 23, 69–71]. Although our study found no significant association we cannot completely rule out a weak protective effect. The WCRF/AICR 2007 report stated that there was limited suggestive evidence that legume intake protects against prostate cancer [33].

Our study showed a significant reduction in the risk of bladder cancer with higher intake of beans and with intake of legumes when analysed on a continuous scale, but not with lentils and is consistent with one case–control study [72], but not with other case–control studies [73, 74] or a cohort study [75]. Our finding of a protective effect of legumes on kidney cancer risk is also consistent with one case–control study [76], but not with other case–control studies [29, 30] or cohort studies [31, 32].

As to the mechanism that could explain a possible protective effect of legume intake on cancer risk, there are several possible explanations. Higher intake of dietary fiber, which legumes are an important source of, has been associated with decreased risk of several cancers including those of the oral cavity, esophagus, and colorectum [33]. Higher intake of dietary fiber may increase stool bulk, decrease transit time and dilute potential carcinogens in the gastrointestinal tract [77]. Further, fiber stimulates bacterial anaerobic fermentation which results in production of short-chain fatty acids, such as butyrate, which inhibits growth, induces apoptosis and cell cycle arrest, and promotes differentiation in colon cancer cells [77]. Short-chain fatty acids may also reduce pH and the conversion of

primary bile acids to secondary bile acids, which are carcinogenic in the colorectum [78]. Fiber may also increase fecal excretion of sex hormones and reduce enterohepatic circulation of estrogens, leading to lower serum estrogen levels [79, 80], and in addition, fiber may increase the levels of sex-hormone binding globulin [81], which binds estradiol and reduces its bioavailability. Higher fiber intake may improve glycemic control and may lead to better satiety and weight control [82]. Legumes are also good sources of folate, which may protect against cancers of the pancreas, esophagus, and colorectum [33]. Folate has an important role in the synthesis and methylation of DNA [83]. Folate deficiency may lead to misincorporation of uracil instead of thymine into DNA and abnormal DNA methylation leads to aberrant gene expression and is known to occur in several types of cancer [83]. However, neither adjustment for fiber, folate or other B-vitamins, vitamin E or protein attenuated the estimates materially, suggesting that other factors in legumes may explain the inverse associations. Some legumes are good sources of calcium which may reduce the risk of colorectal cancer by binding secondary bile acids [84] and by influencing intracellular signal pathways leading to reduced colonic cell proliferation and increased apoptosis [85]. Legumes are good sources of isoflavones, such as daidzein and genistein, which may have cancer-preventive properties. These may compete with estrogens by binding to the estrogen receptor and thereby reduce cancer risk [86]. In addition, genistein has been found to be a tyrosine kinase inhibitor [86] and phyto-estrogens may influence the activity of enzymes that are involved in the cell cycle, differentiation, proliferation, and apoptosis [87]. Phyto-estrogens may also have antioxidant effects and may increase the activity of antioxidant enzymes [87]. Soyfoods have a particularly high phyto-estrogen content, but other legumes may also contribute significantly to phytoestrogen intake [87]. The legume intake in the Uruguayan population, however, consists mostly of legumes other than soy.

Legume intake was more strongly associated with protection against digestive system cancers than breast, lung, and prostate cancers. It is possible that this is because the organs of the digestive system are in direct contact with the potential cancer preventive constituents of legumes and thus may to a larger extent be influenced by diet. Of note, is also that by and large the cancers for which legumes seem to exert a protective effect are those that also are linked to fruit and vegetable intake [33]. Although we cannot completely exclude potential residual confounding by fruit and vegetable intake, the correlations with fruit and vegetables (and most other food groups) were low (rho = 0.13) and in addition, one would expect a stronger effect of legume intake among those with a high fruit and vegetable intake, which is the opposite of what we observed in the stratified analysis (although the test for interaction was not significant). On the other hand if common mechanisms exist for the two food groups, one might expect some type of compensatory effect, which is supported by the results in the stratified analysis. The results were in general similar for beans and lentils for most, but not all cancer sites. For example, intake of beans was associated with a significantly decreased risk of stomach and bladder cancer, but lentils were not associated, while for kidney cancer lentils, but not beans, were associated with decreased risk. We are not aware of any biologic mechanism that could explain these differences and speculate that they may be due to chance and/or the multiple comparisons that was undertaken. The results in our study are stronger than those reported from several [23–26, 39, 46, 47, 72, 73, 75], but not all studies [4, 5, 7, 10, 11, 13, 15–17, 52, 66]. The absolute intake of legumes in our study is not particularly high compared with other studies [10–13, 15, 25, 65], thus the amount of legume intake in this population does not seem to be an explanation for the possibly stronger results in our study. It is also possible that differences in the types of legumes consumed may explain the stronger results we found or that they may reflect a specific local dietary pattern.

In addition to the direct cancer preventive effects of legume intake, indirect effects may be at work as well. Higher intake of legumes may replace other sources of protein in the diet such as meat, which has been shown to be a rather strong risk factor for several cancers in the Uruguayan population [88]. Although, we did adjust for the intake of meat and other foods we cannot exclude the possibility of residual confounding. However, the correlations between legume intake and other food groups were low (range: 0.03–0.13), thus this seems less likely. Further, the stratified analysis showed a protective effect of high legume intake in most strata of age, sex, fruit and vegetable intake, meat intake, smoking status, and alcohol intake (Table 3), suggesting an independent protective effect of high legume intake upon cancer risk.

Our study has several potential limitations; as with any case–control study we cannot rule out the possibility of recall bias or selection bias. The participation rates were very high, thus minimizing the potential for selective participation according to lifestyle practices. Recall bias is a potential problem in case–control studies because of the retrospective assessment of diet. The participants in this study were generally of low socioeconomic status, with minimal knowledge about the role of diet in affecting cancer risk and there has been little focus on legume intake as a risk factor for cancer in the media, which should make recall bias less likely. Nevertheless, we cannot exclude the possibility that recall bias could explain some of our findings. We cannot exclude the possibility of residual confounding by unknown or unmeasured factors. Further, we were not able to adjust for physical activity which is an

important risk factor for several cancer sites. However, we found that adjustment for most other food groups did not substantially influence the association between legume intake and cancer risk, and further adjustment for coffee, tea, and potentially mediating nutrients did not materially alter the results. Nevertheless, other unmeasured variables could still confound some of our findings. Since we investigated legume intake and multiple cancers, some of our findings may have been due to chance.

Our study also has some strengths. To our knowledge this is the first publication on legume intake in relation to a range of cancers. A suggestion of an inverse dose-response relationship between legume intake and the risk of several cancers were noted in this study and in addition, stronger risk reductions were observed when we utilized more extreme cut-points for categorizing legume intake, suggesting an underlying biological effect of legume intake on cancer risk. We adjusted for a number of important confounders, although we did not have information on all confounding factors for every cancer site. All the cases in this study were microscopically confirmed and in addition the response rate was very high among both cases and controls. Our finding of a protective effect of legumes on cancer risk is important both because legumes may provide direct protection against cancer and because they could provide a nutritious alternative to the typically high meat diet in the Uruguayan population. Further, the level of legume intake that was found to be protective in this study is not particularly high and is easily achievable in most populations by including two small portions or approximately 100 g of legumes per week. If confirmed by further prospective investigations, such dietary advice could have important public health implications.

In conclusion, our results suggest an inverse association between high intake of legumes and risk of cancers of the upper aerodigestive tract, stomach, colorectum, and kidney, but not lung, breast, prostate, or bladder cancers. Further investigations of these associations in prospective cohort studies are warranted.

Acknowledgments This work is supported by a grant from International Agency for Research on Cancer, Lyon, France.

References

1. Anderson JW, Johnstone BM, Cook-Newell ME (1995) Meta-analysis of the effects of soy protein intake on serum lipids. N Engl J Med 333:276–282
2. Messina MJ (1999) Legumes and soybeans: overview of their nutritional profiles and health effects. Am J Clin Nutr 70:439S–450S
3. De Stefani E, Boffetta P, Ronco AL et al (2005) Dietary patterns and risk of cancer of the oral cavity and pharynx in Uruguay. Nutr Cancer 51:132–139
4. Kreimer AR, Randi G, Herrero R, Castellsague X, La Vecchia C, Franceschi S (2006) Diet and body mass, and oral and oropharyngeal squamous cell carcinomas: analysis from the IARC multinational case-control study. Int J Cancer 118:2293–2297
5. Marchioni DL, Fisberg RM, do Rosario M, Latorre DO, Wunsch V (2002) Diet and cancer of oral cavity and pharynx: a case-control study in Sao Paulo, Brazil. IARC Sci Publ 156:559–561
6. De Stefani E, Deneo-Pellegrini H, Mendilaharsu M, Ronco A (1999) Diet and risk of cancer of the upper aerodigestive tract–I. Foods. Oral Oncol 35:17–21
7. Palli D, Russo A, Ottini L et al (2001) Red meat, family history, and increased risk of gastric cancer with microsatellite instability. Cancer Res 61:5415–5419
8. Takezaki T, Gao CM, Wu JZ et al (2001) Dietary protective and risk factors for esophageal and stomach cancers in a low-epidemic area for stomach cancer in Jiangsu Province, China: comparison with those in a high-epidemic area. Jpn J Cancer Res 92:1157–1165
9. Ward MH, Lopez-Carrillo L (1999) Dietary factors and the risk of gastric cancer in Mexico City. Am J Epidemiol 149:925–932
10. Jain MG, Hislop GT, Howe GR, Ghadirian P (1999) Plant foods, antioxidants, and prostate cancer risk: findings from case-control studies in Canada. Nutr Cancer 34:173–184
11. Mills PK, Beeson WL, Phillips RL, Fraser GE (1989) Cohort study of diet, lifestyle, and prostate cancer in Adventist men. Cancer 64:598–604
12. Park SY, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN (2008) Legume and isoflavone intake and prostate cancer risk: the multiethnic cohort study. Int J Cancer 123:927–932
13. Kolonel LN, Hankin JH, Whittemore AS et al (2000) Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. Cancer Epidemiol Biomarkers Prev 9:795–804
14. Schuurman AG, Goldbohm RA, Dorant E, van den Brandt PA (1998) Vegetable and fruit consumption and prostate cancer risk: a cohort study in The Netherlands. Cancer Epidemiol Biomarkers Prev 7:673–680
15. Adebamowo CA, Cho E, Sampson L et al (2005) Dietary flavonols and flavonol-rich foods intake and the risk of breast cancer. Int J Cancer 114:628–633
16. Bessaoud F, Daures JP, Gerber M (2008) Dietary factors and breast cancer risk: a case control study among a population in southern France. Nutr Cancer 60:177–187
17. Shu XO, Jin F, Dai Q et al (2001) Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. Cancer Epidemiol Biomarkers Prev 10:483–488
18. Ronco A, De Stefani E, Boffetta P, Deneo-Pellegrini H, Mendilaharsu M, Leborgne F (1999) Vegetables, fruits, and related nutrients and risk of breast cancer: a case-control study in Uruguay. Nutr Cancer 35:111–119
19. Garrote LF, Herrero R, Reyes RM et al (2001) Risk factors for cancer of the oral cavity and oro-pharynx in Cuba. Br J Cancer 85:46–54
20. Risch HA, Jain M, Choi NW et al (1985) Dietary factors and the incidence of cancer of the stomach. Am J Epidemiol 122:947–959
21. Tokui N, Yoshimura T, Fujino Y et al (2005) Dietary habits and stomach cancer risk in the JACC Study. J Epidemiol 15(Suppl 2):S98–S108
22. Deneo-Pellegrini H, De Stefani E, Ronco A, Mendilaharsu M (1999) Foods, nutrients and prostate cancer: a case-control study in Uruguay. Br J Cancer 80:591–597
23. Kirsh VA, Peters U, Mayne ST et al (2007) Prospective study of fruit and vegetable intake and risk of prostate cancer. J Natl Cancer Inst 99:1200–1209
24. Park Y, Subar AF, Kipnis V et al (2007) Fruit and vegetable intakes and risk of colorectal cancer in the NIH-AARP diet and health study. Am J Epidemiol 166:170–180

25. Michels KB, Giovannucci E, Joshipura KJ et al (2000) Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. J Natl Cancer Inst 92:1740–1752
26. Voorrips LE, Goldbohm RA, van Poppel G, Sturmans F, Hermus RJ, van den Brandt PA (2000) Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: The Netherlands cohort study on diet and cancer. Am J Epidemiol 152:1081–1092
27. De Stefani E, Brennan P, Ronco A et al (2002) Food groups and risk of lung cancer in Uruguay. Lung Cancer 38:1–7
28. Smith-Warner SA, Spiegelman D, Yaun SS et al (2003) Fruits, vegetables and lung cancer: a pooled analysis of cohort studies. Int J Cancer 107:1001–1011
29. Bravi F, Bosetti C, Scotti L et al (2007) Food groups and renal cell carcinoma: a case-control study from Italy. Int J Cancer 120:681–685
30. Boeing H, Schlehofer B, Wahrendorf J (1997) Diet, obesity and risk for renal cell carcinoma: results from a case control-study in Germany. Z Ernahrungswiss 36:3–11
31. Lee JE, Giovannucci E, Smith-Warner SA, Spiegelman D, Willett WC, Curhan GC (2006) Intakes of fruits, vegetables, vitamins A, C, and E, and carotenoids and risk of renal cell cancer. Cancer Epidemiol Biomarkers Prev 15:2445–2452
32. van Dijk BA, Schouten LJ, Kiemeney LA, Goldbohm RA, van den Brandt PA (2005) Vegetable and fruit consumption and risk of renal cell carcinoma: results from the Netherlands cohort study. Int J Cancer 117:648–654
33. World Cancer Research Fund/American Insitute for Cancer Research (2007) Food, nutrition, physical activity and the prevention of cancer: a global perspective. AICR, Washington, DC
34. Ronco AL, De Stefani E, Boffetta P, Deneo-Pellegrini H, Acosta G, Mendilaharsu M (2006) Food patterns and risk of breast cancer: a factor analysis study in Uruguay. Int J Cancer 119:1672–1678
35. Zheng T, Boyle P, Willett WC et al (1993) A case-control study of oral cancer in Beijing, People's Republic of China. Associations with nutrient intakes, foods and food groups. Eur J Cancer B Oral Oncol 29B:45–55
36. Cook-Mozaffari PJ, Azordegan F, Day NE, Ressicaud A, Sabai C, Aramesh B (1979) Oesophageal cancer studies in the Caspian Littoral of Iran: results of a case-control study. Br J Cancer 39:293–309
37. Gao CM, Takezaki T, Ding JH, Li MS, Tajima K (1999) Protective effect of allium vegetables against both esophageal and stomach cancer: a simultaneous case-referent study of a high-epidemic area in Jiangsu Province, China. Jpn J Cancer Res 90:614–621
38. Zhang ZF, Kurtz RC, Yu GP et al (1997) Adenocarcinomas of the esophagus and gastric cardia: the role of diet. Nutr Cancer 27:298–309
39. Freedman ND, Park Y, Subar AF et al (2007) Fruit and vegetable intake and esophageal cancer in a large prospective cohort study. Int J Cancer 121:2753–2760
40. Freedman ND, Park Y, Subar AF et al (2008) Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. Int J Cancer 122:2330–2336
41. Peters ES, Luckett BG, Applebaum KM, Marsit CJ, McClean MD, Kelsey KT (2008) Dairy products, leanness, and head and neck squamous cell carcinoma. Head Neck 30:1193–1205
42. Kjaerheim K, Gaard M, Andersen A (1998) The role of alcohol, tobacco, and dietary factors in upper aerogastric tract cancers: a prospective study of 10, 900 Norwegian men. Cancer Causes Control 9:99–108
43. Buiatti E, Palli D, Bianchi S et al (1991) A case-control study of gastric cancer and diet in Italy. III. Risk patterns by histologic type. Int J Cancer 48:369–374
44. Gonzalez CA, Sanz JM, Marcos G et al (1991) Dietary factors and stomach cancer in Spain: a multi-centre case-control study. Int J Cancer 49:513–519
45. Harrison LE, Zhang ZF, Karpeh MS, Sun M, Kurtz RC (1997) The role of dietary factors in the intestinal and diffuse histologic subtypes of gastric adenocarcinoma: a case-control study in the U.S. Cancer 80:1021–1028
46. Botterweck AA, van den Brandt PA, Goldbohm RA (1998) A prospective cohort study on vegetable and fruit consumption and stomach cancer risk in The Netherlands. Am J Epidemiol 148:842–853
47. Freedman ND, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC (2008) Fruit and vegetable intake and gastric cancer risk in a large United States prospective cohort study. Cancer Causes Control 19:459–467
48. Li JY, Ershow AG, Chen ZJ et al (1989) A case-control study of cancer of the esophagus and gastric cardia in Linxian. Int J Cancer 43:755–761
49. Falcao JM, Dias JA, Miranda AC, Leitao CN, Lacerda MM, da Motta LC (1994) Red wine consumption and gastric cancer in Portugal: a case-control study. Eur J Cancer Prev 3:269–276
50. Franceschi S, Favero A, La Vecchia C et al (1997) Food groups and risk of colorectal cancer in Italy. Int J Cancer 72:56–61
51. Iscovich JM, L'Abbe KA, Castelleto R et al (1992) Colon cancer in Argentina. I: risk from intake of dietary items. Int J Cancer 51:851–857
52. Singh PN, Fraser GE (1998) Dietary risk factors for colon cancer in a low-risk population. Am J Epidemiol 148:761–774
53. Lin J, Zhang SM, Cook NR et al (2005) Dietary intakes of fruit, vegetables, and fiber, and risk of colorectal cancer in a prospective cohort of women (United States). Cancer Causes Control 16:225–233
54. Peters RK, Pike MC, Garabrant D, Mack TM (1992) Diet and colon cancer in Los Angeles County, California. Cancer Causes Control 3:457–473
55. Steinmetz KA, Potter JD (1993) Food-group consumption and colon cancer in the Adelaide Case-Control Study. I. Vegetables and fruit. Int J Cancer 53:711–719
56. Evans RC, Fear S, Ashby D et al (2002) Diet and colorectal cancer: an investigation of the lectin/galactose hypothesis. Gastroenterology 122:1784–1792
57. Steinmetz KA, Kushi LH, Bostick RM, Folsom AR, Potter JD (1994) Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. Am J Epidemiol 139:1–15
58. Yeh CC, You SL, Chen CJ, Sung FC (2006) Peanut consumption and reduced risk of colorectal cancer in women: a prospective study in Taiwan. World J Gastroenterol 12:222–227
59. Brennan P, Fortes C, Butler J et al (2000) A multicenter case-control study of diet and lung cancer among non-smokers. Cancer Causes Control 11:49–58
60. Fortes C, Forastiere F, Farchi S et al (2003) The protective effect of the Mediterranean diet on lung cancer. Nutr Cancer 46:30–37
61. Koo LC (1988) Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. Nutr Cancer 11:155–172
62. Wu-Williams AH, Dai XD, Blot W et al (1990) Lung cancer among women in north-east China. Br J Cancer 62:982–987
63. Franceschi S, Parpinel M, La Vecchia C, Favero A, Talamini R, Negri E (1998) Role of different types of vegetables and fruit in the prevention of cancer of the colon, rectum, and breast. Epidemiology 9:338–341
64. Morales Suarez-Varela M, Jimenez Lopez MC, Almenar CD, Llopis GA (1998) Effect of the ingestion of food and gynecologic risk factors on breast cancer risk in Valencia. Nutr Hosp 13: 325–329

65. Dos Santos Silva I, Mangtani P, McCormack V, Bhakta D, Sevak L, McMichael AJ (2002) Lifelong vegetarianism and risk of breast cancer: a population-based case-control study among South Asian migrant women living in England. Int J Cancer 99:238–244
66. Shannon J, Ray R, Wu C et al (2005) Food and botanical groupings and risk of breast cancer: a case-control study in Shanghai, China. Cancer Epidemiol Biomarkers Prev 14:81–90
67. Cohen JH, Kristal AR, Stanford JL (2000) Fruit and vegetable intakes and prostate cancer risk. J Natl Cancer Inst 92:61–68
68. Key TJ, Silcocks PB, Davey GK, Appleby PN, Bishop DT (1997) A case-control study of diet and prostate cancer. Br J Cancer 76:678–687
69. Darlington GA, Kreiger N, Lightfoot N, Purdham J, Sass-Kortsak A (2007) Prostate cancer risk and diet, recreational physical activity and cigarette smoking. Chronic Dis Can 27:145–153
70. Ewings P, Bowie C (1996) A case-control study of cancer of the prostate in Somerset and east Devon. Br J Cancer 74:661–666
71. Smit E, Garcia-Palmieri MR, Figueroa NR et al (2007) Protein and legume intake and prostate cancer mortality in puerto rican men. Nutr Cancer 58:146–152
72. Schabath MB, Spitz MR, Lerner SP et al (2005) Case-control analysis of dietary folate and risk of bladder cancer. Nutr Cancer 53:144–151
73. Kellen E, Zeegers M, Paulussen A, Van Martien D, Buntinx F (2006) Fruit consumption reduces the effect of smoking on bladder cancer risk. The Belgian case control study on bladder cancer. Int J Cancer 118:2572–2578
74. Balbi JC, Larrinaga MT, De Stefani E et al (2001) Foods and risk of bladder cancer: a case-control study in Uruguay. Eur J Cancer Prev 10:453–458
75. Zeegers MP, Goldbohm RA, van den Brandt PA (2001) Consumption of vegetables and fruits and urothelial cancer incidence: a prospective study. Cancer Epidemiol Biomarkers Prev 10:1121–1128
76. Maclure M, Willett W (1990) A case-control study of diet and risk of renal adenocarcinoma. Epidemiology 1:430–440
77. Lipkin M, Reddy B, Newmark H, Lamprecht SA (1999) Dietary factors in human colorectal cancer. Annu Rev Nutr 19:545–586
78. Bingham SA (1990) Mechanisms and experimental and epidemiological evidence relating dietary fibre (non-starch polysaccharides) and starch to protection against large bowel cancer. Proc Nutr Soc 49:153–171
79. Goldin BR, Woods MN, Spiegelman DL et al (1994) The effect of dietary fat and fiber on serum estrogen concentrations in premenopausal women under controlled dietary conditions. Cancer 74:1125–1131
80. Gorbach SL, Goldin BR (1987) Diet and the excretion and enterohepatic cycling of estrogens. Prev Med 16:525–531
81. London S, Willett W, Longcope C, McKinlay S (1991) Alcohol and other dietary factors in relation to serum hormone concentrations in women at climacteric. Am J Clin Nutr 53:166–171
82. Ludwig DS, Pereira MA, Kroenke CH et al (1999) Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. JAMA 282:1539–1546
83. Kim YI (2004) Folate and DNA methylation: a mechanistic link between folate deficiency and colorectal cancer? Cancer Epidemiol Biomarkers Prev 13:511–519
84. Lapre JA, De Vries HT, Koeman JH, Van der Meer R (1993) The antiproliferative effect of dietary calcium on colonic epithelium is mediated by luminal surfactants and dependent on the type of dietary fat. Cancer Res 53:784–789
85. Lamprecht SA, Lipkin M (2003) Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. Nat Rev Cancer 3:601–614
86. Messina M, Wu AH (2009) Perspectives on the soy-breast cancer relation. Am J Clin Nutr 89:1673S–1679S
87. Liggins J, Bluck LJ, Runswick S, Atkinson C, Coward WA, Bingham SA (2000) Daidzein and genistein contents of vegetables. Br J Nutr 84:717–725
88. Aune D, Ronco A, Boffetta P et al (2009) Meat consumption and cancer risk: a multisite case-control study in Uruguay. Cancer Ther 7:174–187