RESEARCH COMMUNICATION

# Fruits, Vegetables and the Risk of Cancer: a Multisite Case-Control Study in Uruguay

**Dagfinn Aune[1]*, Eduardo De Stefani[2], Alvaro Ronco[3], Paolo Boffetta[4], Hugo Deneo-Pellegrini[2], Giselle Acosta[2], Maria Mendilaharsu[2]**

## Abstract

**Introduction: Previous studies have suggested that high intake of fruit and vegetables may decrease the risk of a wide range of cancers, but this evidence has been challenged by the results of recent studies. Methods: To further explore the association between fruit and vegetable 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. We used unconditional logistic regression to estimate odds ratios and 95% confidence intervals (CIs) of cancer associations. Results: In the multivariable model higher intake of fruits and vegetables combined was associated with a decreased risk of cancers of the esophagus (odds ratio, OR=0.63, 95% CI: 0.42-0.97), lung (OR=0.75, 95% CI: 0.57-0.98), breast (OR=0.47, 95% CI: 0.31-0.71), prostate (OR=0.63, 95% CI: 0.44-0.92) and all sites combined (OR=0.73, 95% CI: 0.61-0.87). When evaluated separately, fruit intake was more strongly associated with decreased cancer risk than vegetables. These inverse associations were mainly observed in men, among persons with high intake of meat, alcohol drinkers and among smokers. Conclusion: Our results provide some evidence that high intake of fruits and vegetables and particularly fruit may decrease the risk of cancer. However, because of the possibility that these findings could be due to residual confounding from intake of meat, alcohol drinking and tobacco smoking, further studies in populations with a large number of participants with low or no exposure to these potential confounding factors are warranted.**

**Key Words:** Diet - fruits - vegetables - cancer - epidemiology

*Asian Pacific J Cancer Prev,* **10**, 419-428

## Introduction

Despite the fact that the relationship between fruit and vegetable consumption and cancer risk has been assessed in several hundreds of studies, for no cancer was the evidence of a protective effect from high fruit and vegetable intake considered to be convincing in the recent report of the World Cancer Research Fund and the American Institute of Cancer Research (WCRF/AICR, 2007) . However, there was probable or limited suggestive evidence for a protective effect of non-starchy vegetables in relation to cancers of the mouth, pharynx, larynx, esophagus and stomach and of fruit intake in relation to cancers of the mouth, pharynx, larynx, esophagus, lung and stomach.

Few studies have previously explored the association between fruit and vegetable intake in relation to a range of cancers and to our knowledge no such study from Southern-America has been published. Because of the unique dietary pattern in Uruguay, with low intake of fruit and vegetables and high meat intake, we decided to investigate the association between fruit and vegetable intake and cancer risk in a multisite case-control study of diet and cancer conducted between 1996 and 2004.

## Materials and Methods

*Selection of cases*

In the time period between 1996 and 2004 we conducted a multisite case-control study including cancers of the mouth and pharynx (n=283), esophagus (n=234), stomach (n=274), colon (n=176), rectum (n=185), larynx (n=281), lung (n=931), breast (n=461), prostate (n=345), bladder (n=255) and kidney (n=114). All the cases were <90 years old at diagnosis (age range 23-89 years, mean 63.1 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, which were all included in the present study (response rate 94.5%). There were no proxy interviews which were conducted, either for the cases or the controls.

*Selection of controls*

In the same time period and in the same hospitals, 2,117 patients <90 years old (age range 22-89 years, mean 62.9 years) with non-neoplastic diseases not related with

*[1]Department of Nutrition, University of Oslo, Norway, [2]Grupo de Epidemiología, Departamento de Anatomía Patológica, Hospital de Clínicas, Facultad de Medicina, [3]Departamento de Epidemiologia y Metodos Cientificos, Facultad de Medicina, Centro Latinoamericano de Economıa Humana (CLAEH), Montevideo, Uruguay, [4]International Agency for Research on Cancer, Lyon, France *For correspondence: dagfinn.aune@medisin.uio.no*

smoking, drinking and without recent changes in their diet were considered eligible for this study. Sixty seven patients refused the interview, leaving a final total of 2,032 controls (response rate 96.0%). These patients presented with the following diseases: eye disorders (21.2%), abdominal hernia (20.8%), injuries and accidents (19.1%), venous diseases (5.5%), acute appendicitis (5.5%), diseases of the skin (6.7%), hydatid cyst (5.0 %), urinary system diseases (4.7%) and various other conditions (11.5%). The controls were not matched to the cases on any factors.

*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. No proxy interviews were conducted for either cases or controls. The questionnaire included the following sections: 1) socio-demographic characteristics (age, sex, residence, education), 2) a complete occupational history based in their jobs and its duration, 3) self-reported height and weight five 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 drunk 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) on the intake of 64 food items which covered the dietary intake one year before diagnosis.

This FFQ was considered as representative of the Uruguayan diet and allowed for the estimation of total energy intake. Although the FFQ was not validated, it has been tested for reproducibility with reasonable results (Ronco et al., 2006). The obtained correlation coefficients between the two diet assessments were 0.59 for fruit and vegetables, 0.54 for fruits and 0.46 for vegetables (Ronco et al., 2006).

*Statistical methods*

Relative risks and 95% confidence intervals of cancer, approximated by the odds ratios, were estimated with unconditional logistic regression, comparing the highest two categories of fruit and vegetable intake with the lowest referent category and also on a continuous scale for a 200 grams per day increment in the intake. Cut-points for the categories were based on the absolute intake and reflected an increase in the intake of approximately one serving for each category for total fruit and total vegetables. We used a multivariable model including the following covariates: age (continuous), sex (when applicable), residence (urban/rural), education (continuous), income (continuous), interviewer (categorical), smoking status (never, former, current), 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/d), total meat (continuous), grains (continuous), fatty foods (continuous, includes eggs, butter, cheese, custard, desserts), mate drinking status (never, former, current), total energy intake (continuous) and BMI (continuous). Fruit intake and vegetable intake were mutually adjusted. Tests for linear trend were calculated by entering the categorical variables as continuous parameters in the models. Possible interactions between fruit and vegetable intake and age, sex, total meat, legumes, smoking status and 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 cases and the controls are shown in Table 1. Compared with the controls, the cases were in general older ($p=0.0001$ with t-test, not shown in the Table), they also smoked more ($p<0.0001$) and had a higher intake of alcohol ($p<0.0001$) and meat ($p<0.0001$), but intake of fruits and vegetables was not significantly different

**Table 1. Socio-demographic Characteristics and Selected Risk Factors among Cases and Controls** (Values are means (standard deviations), except for sex (%))

| Cancer | Number | Age (years) | Men (%) | Smoking (Cig./d) | Ethanol (ml/d) | Fruits, vegetables (g/d) | Meat (g/d) |
|---|---|---|---|---|---|---|---|
| Oral cavity | 283 | 59.9 (9.7) | 96.8 | 27.6 (15.9) | 213.1 (222.5) | 335.7 (155.3) | 258.7 (108.7) |
| Esophagus | 234 | 66.3 (10.3) | 78.6 | 22.2 (18.8) | 122.9 (195.7) | 317.7 (146.6) | 238.0 (99.8) |
| Larynx | 281 | 62.1 (10.0) | 97.5 | 32.6 (21.3) | 194.0 (231.6) | 327.8 (141.8) | 265.0 (101.4) |
| Upper aerodigestive tract | 798 | 62.5 (10.3) | 91.7 | 27.8 (19.2) | 179.9 (221.3) | 327.6 (148.1) | 254.9 (104.1) |
| Stomach | 275 | 65.5 (11.2) | 69.3 | 16.0 (17.7) | 85.4 (140.2) | 342.9 (143.9) | 230.1 (99.2) |
| Colon | 176 | 64.3 (11.9) | 49.4 | 13.7 (19.0) | 45.7 (127.1) | 322.5 (153.7) | 220.2 (92.0) |
| Rectum | 185 | 66.3 (10.2) | 68.6 | 14.8 (17.2) | 70.3 (119.3) | 335.0 (171.4) | 235.1 (98.6) |
| Colorectum | 361 | 65.3 (11.1) | 59.3 | 14.2 (18.0) | 58.3 (123.6) | 328.9 (162.9) | 227.8 (95.6) |
| Lung | 931 | 62.0 (10.0) | 94.0 | 31.6 (19.8) | 135.9 (185.6) | 317.8 (169.7) | 232.6 (100.6) |
| Breast | 461 | 59.7 (13.1) | 0.0 | 4.1 (8.7) | 12.1 (51.5) | 282.5 (157.5) | 198.1 (82.1) |
| Prostate | 345 | 70.6 (7.3) | 100.0 | 18.0 (18.5) | 96.4 (165.9) | 347.1 (163.8) | 205.1 (94.3) |
| Bladder | 254 | 66.9 (10.0) | 88.2 | 19.3 (18.0) | 83.7 (129.7) | 348.5 (190.0) | 220.2 (112.7) |
| Kidney | 114 | 60.6 (11.8) | 67.5 | 15.6 (16.3) | 78.0 (162.8) | 323.5 (163.6) | 201.5 (103.8) |
| All cases | 3,539 | 63.6 (11.0) | 75.1 | 21.4 (20.1) | 108.4 (176.6) | 323.7 (162.6) | 227.9 (100.7) |
| Controls | 2,032 | 62.3 (12.8) | 64.8 | 13.5 (15.8) | 75.3 (147.4) | 329.8 (156.0) | 195.8 (87.1) |

**Table 2. Intake of Fruits and Vegetables in Relation to Cancer Risk**

| Cancer site | Fruits and vegetables | | OR (95% CI)[1] | Fruits | OR (95% CI) | Vegetables | OR (95% CI) |
|---|---|---|---|---|---|---|---|
| Oral | 1[2] | 63 | 1.00 | 127 | 1.00 | 47 | 1.00 |
| | 2 | 122 | 0.87 (0.61-1.25) | 76 | 0.69 (0.50-0.96) | 99 | 0.62 (0.41-0.93) |
| | 3 | 98 | 1.02 (0.68-1.53) | 80 | 0.78 (0.55-1.10) | 137 | 0.84 (0.55-1.27) |
| | $P_{trend}$ | | 0.73 | | 0.12 | | 0.97 |
| | Continuous3 | | 1.04 (0.85-1.27) | | 0.82 (0.61-1.09) | | 1.00 (0.82-1.23) |
| Esophagus | 1 | 62 | 1.00 | 107 | 1.00 | 33 | 1.00 |
| | 2 | 103 | 0.77 (0.54-1.09) | 69 | 0.69 (0.49-0.96) | 94 | 0.80 (0.52-1.23) |
| | 3 | 69 | 0.63 (0.42-0.97) | 58 | 0.59 (0.41-0.85) | 107 | 0.87 (0.55-1.37) |
| | $P_{trend}$ | | 0.038 | | 0.004 | | 0.78 |
| | Continuous | | 0.76 (0.61-0.94) | | 0.52 (0.37-0.71) | | 0.97 (0.78-1.21) |
| Larynx | 1 | 62 | 1.00 | 123 | 1.00 | 38 | 1.00 |
| | 2 | 125 | 0.78 (0.55-1.11) | 85 | 0.74 (0.54-1.03) | 96 | 0.70 (0.46-1.08) |
| | 3 | 94 | 0.74 (0.50-1.11) | 73 | 0.63 (0.45-0.89) | 147 | 0.95 (0.61-1.46) |
| | $P_{trend}$ | | 0.17 | | 0.009 | | 0.57 |
| | Continuous | | 0.81 (0.66-0.99) | | 0.68 (0.51-0.91) | | 1.06 (0.86-1.31) |
| Upper aerodigestive tract | 1 | 187 | 1.00 | 357 | 1.00 | 118 | 1.00 |
| | 2 | 350 | 0.83 (0.65-1.04) | 230 | 0.74 (0.60-0.92) | 289 | 0.72 (0.55-0.95) |
| | 3 | 261 | 0.76 (0.58-0.99) | 211 | 0.63 (0.50-0.79) | 391 | 0.87 (0.66-1.16) |
| | $P_{trend}$ | | 0.046 | | <0.0001 | | 0.93 |
| | Continuous | | 0.83 (0.73-0.95) | | 0.64 (0.53-0.77) | | 1.11 (0.91-1.34) |
| Stomach | 1 | 51 | 1.00 | 119 | 1.00 | 25 | 1.00 |
| | 2 | 129 | 0.88 (0.61-1.27) | 65 | 0.50 (0.36-0.70) | 112 | 1.30 (0.82-2.08) |
| | 3 | 95 | 0.84 (0.56-1.25) | 91 | 0.67 (0.49-0.93) | 138 | 1.50 (0.93-2.41) |
| | $P_{trend}$ | | 0.40 | | 0.011 | | 0.10 |
| | Continuous | | 0.93 (0.76-1.14) | | 0.75 (0.56-0.99) | | 1.19 (0.97-1.46) |
| Colon | 1 | 47 | 1.00 | 66 | 1.00 | 23 | 1.00 |
| | 2 | 70 | 0.98 (0.65-1.48) | 57 | 0.92 (0.63-1.36) | 84 | 1.13 (0.68-1.86) |
| | 3 | 59 | 1.13 (0.69-1.84) | 53 | 0.88 (0.58-1.36) | 69 | 1.18 (0.68-2.05) |
| | $P_{trend}$ | | 0.57 | | 0.59 | | 0.55 |
| | Continuous | | 0.92 (0.72-1.17) | | 0.84 (0.61-1.16) | | 1.08 (0.83-1.40) |
| Rectum | 1 | 47 | 1.00 | 69 | 1.00 | 33 | 1.00 |
| | 2 | 81 | 0.86 (0.58-1.28) | 51 | 0.73 (0.49-1.08) | 79 | 0.62 (0.40-0.98) |
| | 3 | 57 | 0.63 (0.39-1.01) | 65 | 0.80 (0.53-1.19) | 73 | 0.59 (0.36-0.96) |
| | $P_{trend}$ | | 0.056 | | 0.26 | | 0.068 |
| | Continuous | | 0.81 (0.65-1.01) | | 0.81 (0.60-1.09) | | 0.79 (0.62-1.02) |
| Lung | 1 | 298 | 1.00 | 418 | 1.00 | 167 | 1.00 |
| | 2 | 349 | 0.65 (0.52-0.82) | 236 | 0.70 (0.56-0.87) | 387 | 0.74 (0.57-0.97) |
| | 3 | 284 | 0.75 (0.57-0.98) | 277 | 0.94 (0.74-1.19) | 377 | 0.74 (0.56-0.99) |
| | $P_{trend}$ | | 0.041 | | 0.41 | | 0.099 |
| | Continuous | | 0.93 (0.81-1.07) | | 1.00 (0.84-1.20) | | 0.89 (0.77-1.02) |
| Breast | 1 | 169 | 1.00 | 186 | 1.00 | 79 | 1.00 |
| | 2 | 216 | 0.94 (0.70-1.25) | 191 | 1.06 (0.80-1.42) | 283 | 0.93 (0.66-1.32) |
| | 3 | 76 | 0.47 (0.31-0.71) | 84 | 0.60 (0.42-0.87) | 99 | 0.53 (0.35-0.81) |
| | $P_{trend}$ | | 0.001 | | <0.0001 | | 0.002 |
| | Continuous | | 0.58 (0.48-0.71) | | 0.83 (0.62-1.11) | | 0.72 (0.59-0.89) |
| Prostate | 1 | 80 | 1.00 | 113 | 1.00 | 45 | 1.00 |
| | 2 | 136 | 0.63 (0.45-0.87) | 127 | 0.94 (0.69-1.27) | 139 | 1.02 (0.68-1.52) |
| | 3 | 129 | 0.63 (0.44-0.92) | 105 | 0.62 (0.45-0.87) | 161 | 1.04 (0.69-1.58) |
| | $P_{trend}$ | | 0.041 | | 0.005 | | 0.84 |
| | Continuous | | 0.93 (0.78-1.11) | | 0.67 (0.53-0.86) | | 1.02 (0.84-1.24) |
| Bladder | 1 | 57 | 1.00 | 97 | 1.00 | 32 | 1.00 |
| | 2 | 114 | 1.01 (0.70-1.7) | 68 | 0.70 (0.49-1.00) | 122 | 1.09 (0.70-1.69) |
| | 3 | 83 | 0.88 (0.56-1.36) | 89 | 0.91 (0.63-1.31) | 100 | 0.92 (0.56-1.49) |
| | $P_{trend}$ | | 0.54 | | 0.55 | | 0.51 |
| | Continuous | | 1.02 (0.74-1.25) | | 0.98 (0.76-1.26) | | 0.93 (0.74-1.16) |
| Kidney | 1 | 37 | 1.00 | 45 | 1.00 | 19 | 1.00 |
| | 2 | 3136 | 0.75 (0.46-1.23) | 37 | 0.90 (0.56-1.43) | 51 | 0.90 (0.51-1.58) |
| | 3 | | 0.83 (0.47-1.49) | 32 | 0.78 (0.46-1.32) | 44 | 1.02 (0.54-1.93) |
| | $P_{trend}$ | 0.48 | | 0.36 | | 0.81 | |
| | Continuous | | 0.95 (0.72-1.26) | | 0.85 (0.58-1.24) | | 1.04 (0.76-1.42) |
| All sites | 1 | 973 | 1.00 | 1,470 | 1.00 | 541 | 1.00 |
| | 2 | 1,486 | 0.79 (0.68-0.92) | 1,062 | 0.78 (0.68-0.90) | 1,546 | 0.86 (0.72-1.02) |
| | 3 | 1,080 | 0.73 (0.61-0.87) | 1,007 | 0.71 (0.61-0.83) | 1,452 | 0.86 (0.71-1.04) |
| | $P_{trend}$ | | 0.001 | | <0.0001 | | 0.20 |
| | Continuous | | 0.85 (0.78-0.93) | | 0.78 (0.69-0.88) | | 0.96 (0.84-1.10) |
| Controls | | 489 | (266/223) | 701 | (437/264) | 308 | (186/122) |
| | | 915 | (620/295) | 683 | (450/233) | 938 | (584/354) |
| | | 628 | (460/168) | 648 | (459/189) | 786 | (576/210) |

[1]Multivariate adjustment for: age, sex, residence, income, interviewer, education, smoking status, age at starting smoking, age at quitting smoking, cigarettes per day, alcohol, total meat, grains, fatty foods (eggs, butter, cheese, custard, desserts), mate drinking status, total energy intake and BMI. Fruit and vegetable intakes mutually adjusted. [2]Total fruit and vegetables: 0-220, >220-380, >380 g/d, medians: 173.9, 284.9 and 477.4 g/d. Total fruit: 0-80, >80-160, >160 g/d; 52.5, 112.6 and 241.1 g/d. Total vegetables: 0-100, >100-200, >200; 76.2, 148.7 and 261.9. Continuous: per 200g/d

**Table 3. Intake of Fruits and Vegetables in Relation to Risk of All Cancer Sites Combined in Strata of Covariates**

| | | Total fruits and vegetables | | Interaction | Fruits | | Interaction | Vegetables | | Interaction |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 3 | P | 2 | 3 | P | 2 | 3 | P |
| Age | ≤69 yrs | 0.73 (0.61-0.87) | 0.65 (0.53-0.81) | 0.18 | 0.73 (0.61-0.86) | 0.65 (0.54-0.78) | 0.07 | 0.85 (0.69-1.05) | 0.88 (0.70-1.10) | 0.50 |
| | ≥70 yr | 0.95 (0.72-1.25) | 0.91 (0.67-1.25) | | 0.94 (0.73-1.21) | 0.87 (0.67-1.13) | | 0.89 (0.64-1.23) | 0.81 (0.57-1.14) | |
| Sex | Men | 0.65 (0.54-0.78) | 0.58 (0.46-0.72) | 0.008 | 0.70 (0.59-0.83) | 0.59 (0.49-0.71) | 0.002 | 0.80 (0.65-1.00) | 0.78 (0.62-0.99) | 0.33 |
| | Women | 1.07 (0.83-1.38) | 1.07 (0.77-1.47) | | 0.96 (0.74-1.23) | 1.06 (0.80-1.42) | | 0.97 (0.71-1.31) | 0.95 (0.67-1.34) | |
| Total meat (g/d) | | | | | | | | | | |
| | ≤197.8 | 0.86 (0.71-1.05) | 0.94 (0.74-1.21) | 0.006 | 0.81 (0.67-0.99 | 0.87 (0.70-1.08) | 0.016 | 0.76 (0.61-0.96) | 0.86 (0.66-1.11) | 0.91 |
| | >197.8 | 0.70 (0.55-0.89) | 0.56 (0.43-0.74) | | 0.77 (0.62-0.95) | 0.59 (0.57-0.73) | | 1.03 (0.78-1.37) | 0.93 (0.70-1.25) | |
| Legumes | | | | | | | | | | |
| | ≤median | 0.76 (0.62-0.94) | 0.70 (0.54-0.90) | 0.80 | 0.72 (0.59-0.89) | 0.75 (0.61-0.94) | 0.52 | 0.84 (0.67-1.07) | 0.77 (0.60-1.00) | 0.12 |
| | >median | 0.82 (0.66-1.03) | 0.78 (0.61-1.01) | | 0.86 (0.70-1.06) | 0.68 (0.55-0.84) | | 0.91 (0.70-1.19) | 1.02 (0.77-1.35) | |
| Smoking | | | | | | | | | | |
| | Never | 1.01 (0.77-1.32) | 1.24 (0.90-1.70) | 0.02 | 0.85 (0.66-1.10) | 1.11 (0.84-1.46) | 0.02 | 0.99 (0.72-1.35) | 1.11 (0.78-1.57) | 0.12 |
| | Former | 0.65 (0.47-0.90) | 0.46 (0.32-0.66) | | 0.64 (0.48-0.86) | 0.46 (0.34-0.63) | | 0.82 (0.57-1.18) | 0.79 (0.54-1.17) | |
| | Current | 0.75 (0.60-0.94) | 0.69 (0.53-0.90) | | 0.84 (0.68-1.05) | 0.69 (0.55-0.87) | | 0.85 (0.65-1.11) | 0.78 (0.59-1.04) | |
| Alcohol | Non | 0.96 (0.76-1.20) | 1.04 (0.79-1.36) | 0.04 | 0.99 (0.80-1.22) | 1.08 (0.85-1.37) | 0.004 | 0.87 (0.67-1.14) | 0.93 (0.69-1.24) | 0.80 |
| | 1-120/yr | 0.62 (0.48-0.79) | 0.49 (0.36-0.66) | | 0.64 (0.50-0.81) | 0.49 (0.38-0.63) | | 0.79 (0.59-1.06) | 0.69 (0.50-0.95) | |
| | 121+ /yr | 0.73 (0.51-1.03) | 0.62 (0.42-0.93) | | 0.68 (0.49-0.93) | 0.62 (0.44-0.88) | | 0.96 (0.64-1.44) | 1.03 (0.67-1.57) | |

(p=0.18).

In the multivariable model high vs. low intake of fruit and vegetables was associated with a significantly decreased risk of cancers of the esophagus (OR=0.63, 95% CI: 0.42-0.97; $p_{trend}$=0.04), upper aerodigestive tract (includes oral cavity, pharynx, esophagus and larynx, OR=0.76, 95% CI: 0.58-0.99; $p_{trend}$=0.046), lung (OR=0.75, 95% CI: 0.57-0.98; $p_{trend}$=0.04), breast (OR=0.47, 95% CI: 0.31-0.71; $p_{trend}$=0.001), prostate (OR=0.63, 95% CI: 0.44-0.92; $p_{trend}$=0.04) and all sites combined (OR=0.73, 95% CI: 0.61-0.87; $p_{trend}$=0.001) (Table 2). In addition, there was an inverse association between fruit and vegetable intake and laryngeal cancer when assessed on a continuous scale (OR=0.81, 95% CI: 0.66-0.99) and a borderline significant association with rectal cancer (OR=0.63, 95% CI: 0.39-1.01; $p_{trend}$=0.06). There was no significant association with cancers of the oral cavity and pharynx, stomach, colon, bladder or kidney.

Total fruit intake was associated with a significant decrease in the risk of cancers of the esophagus (OR=0.59, 95% CI: 0.41-0.85; $p_{trend}$=0.004), larynx (OR=0.63, 95% CI: 0.45-0.89; $p_{trend}$=0.009), upper aerodigestive tract (OR=0.63, 95% CI: 0.50-0.79; $p_{trend}$<0.0001), stomach (OR=0.67, 95% CI: 0.49-0.93; $p_{trend}$=0.01), breast (OR=0.60, 95% CI: 0.42-0.87; $p_{trend}$<0.0001), prostate (OR=0.62, 95% CI: 0.45-0.87; $p_{trend}$=0.005) and all sites combined (OR=0.71, 95% CI: 0.61-0.83; $p_{trend}$<0.0001) (Table 2). There was no association with cancers of the oral cavity and pharynx, lung, bladder or kidney.

Total vegetables was associated with a significant decrease in the risk of cancers of the rectum (OR=0.59, 95% CI: 0.36-0.96; $p_{trend}$=0.07), lung (OR=0.74, 95% CI: 0.56-0.99; $p_{trend}$=0.10) and breast (OR=0.53, 95% CI: 0.35-0.81; $p_{trend}$=0.002) (Table 2). There was no association between vegetable intake and cancers of the oral cavity and pharynx, esophagus, larynx, upper aerodigestive tract, stomach, colon, prostate, bladder or kidney. There was a non-significant positive association between vegetable intake and stomach cancer (OR=1.50, 95% CI: 0.93-2.41; $p_{trend}$=0.10) and a non-significant inverse association between vegetable intake and all cancer sites combined (OR=0.86, 95% CI: 0.71-1.04; p trend=0.20).

In a secondary analysis we used more extreme cutpoints (deciles) to evaluate whether even higher intake could reduce the risk of all cancers combined further. The ORs for the highest vs. the lowest decile were 0.53 (95% CI: 0.40-0.71) for fruits and vegetables combined (624.2 vs. 127.0 g/d), 0.59 (95% CI: 0.45-0.77) for fruits (370.7 vs 16.3 g/d) and 0.90 (0.68-1.19) for vegetables (369.2 vs. 66.0 g/d) (results not shown). In stratified analyses the protective effect of fruits and vegetables for all cancer sites combined was stronger in younger persons (although the test for interaction was not significant, $p_{interaction}$=0.18), among men ($p_{interaction}$=0.008), among those with a high intake of meat ($p_{interaction}$=0.006), among alcohol drinkers ($p_{interaction}$=0.04) and among current and former smokers ($p_{interaction}$=0.02) (Table 3). The protective effect of fruits was also stronger among the younger persons ($p_{interaction}$=0.07), men ($p_{interaction}$=0.002), among those with a high intake of meat ($p_{interaction}$=0.016), among current and former smokers ($p_{interaction}$=0.02) and among alcohol drinkers ($p_{interaction}$=0.004). There were no significant interactions in the stratified analysis of vegetable intake and all cancer sites combined (p≥0.12 for all comparisons).

## Discussion

Our results suggest that higher intake of fruits and vegetables and perhaps especially fruit, decreases the risk of developing several types of cancer.

We found no overall association between intake of fruits and vegetables combined and oral and pharyngeal cancer risk, although we cannot exclude a slight inverse association with the intake of fruit and vegetables, separately. This is somewhat in contrast to previous meta-analyses which found up to a 50% reduction in the risk of oral and pharyngeal cancer with intake of fruit and vegetables (Riboli and Norat, 2003; Pavia et al., 2006) and also in contrast to the recent AICR/WCRF report which stated that non-starchy vegetables and fruit probably protect against oral and pharyngeal cancer (although studies of laryngeal cancer were grouped together with oral and pharyngeal cancer in this judgement) (World Cancer Research Fund/American Institute for Cancer Research, 2007) . More recent studies have also provided evidence of a protective effect (Kreimer et al., 2006;

Suzuki et al., 2006; Heck et al., 2008; Sapkota et al., 2008), although not always statistically significant.

Higher intake of total fruits and vegetables was associated with decreased risk of esophageal cancer, however the protective effect was restricted to fruit and not observed with vegetables in this study. Two previous meta-analyses (Riboli and Norat, 2003; Pavia et al., 2006) have also suggested a stronger protective effect of fruits than vegetables for this cancer site and the WCRF/AICR report stated that fruit and vegetables probably protect against esophageal cancer, but also here did the pooled effect estimate seem stronger for fruits than vegetables. However, there are currently few cohort studies available (Pan et al., 1999; Sauvaget et al., 2003; Tran et al., 2005; Gonzalez et al., 2006; Freedman et al., 2007;Yamaji et al., 2008), but most of these also suggested significant or non-significant inverse associations which were stronger for fruit in some (Pan et al., 1999;Sauvaget et al., 2003; Tran et al., 2005; Freedman et al., 2007), but not all studies (Gonzalez et al., 2006;Yamaji et al., 2008).

Fruit and vegetables combined were inversely associated with the risk of laryngeal cancer, but the result was statistically significant only on the continuous scale. Also for this site was there evidence for an inverse association with fruit intake, but no association with vegetables. Previous studies have consistently found reduced risk with higher intake of both fruits and vegetables (World Cancer Research Fund/American Institute for Cancer Research, 2007), and our results are in line with a meta-analysis which found a stronger protective effect of fruit intake, than with vegetables (Riboli and Norat, 2003). The recent WCRF/AICR report stated that there was probable evidence that fruits and vegetables protect against laryngeal cancer, but this statement was for oral, pharyngeal and laryngeal cancer combined. To our knowledge only one cohort study has reported on fruit and vegetable intake in relation to laryngeal cancer, specifically, and found a non-significant inverse association (Freedman et al., 2008a).

We found no association between fruit and vegetable intake overall and stomach cancer risk, but an inverse association appeared for fruit intake, while a slight non-significant positive association appeared for vegetable intake. Previous meta-analyses reported a stronger protective effect of fruits and vegetables in case-control studies than in cohort studies (Riboli and Norat, 2003; Vainio and Weiderpass, 2006) and in the more recent one was there a significant effect only for fruit intake in cohort studies (Vainio and Weiderpass, 2006). In the AICR/WCRF report both fruit and vegetable intake was judged to be probably protective against stomach cancer, although none of these associations were statistically significant in cohort studies (World Cancer Research Fund/American Institute for Cancer Research, 2007). More recent case-control (Campos et al., 2006; Fei and Xiao, 2006; Lunet et al., 2006; 2007; Navarro Silvera et al., 2008) and cohort studies (Nouraie et al., 2005; Gonzalez et al., 2006; Larsson et al., 2006a; Freedman et al., 2008b) have reported inverse associations (Nouraie et al., 2005;Campos et al., 2006; Fei and Xiao, 2006; Larsson et al., 2006a; Lunet et al., 2006; 2007) or no associations (Gonzalez et al., 2006; Freedman et al., 2008b; Navarro Silvera et al., 2008).

There was little evidence for a protective effect of fruit and vegetable intake on risk of colon cancer in this study, but a marginally significant inverse association was observed for total fruit and vegetable intake on risk of rectal cancer and a significant inverse association was found for vegetables. Most previous case-control studies have reported non-significant or significant inverse associations between vegetable intake and colorectal cancer, and less consistently so with fruit intake (Vainio and Weiderpass, 2006). However the evidence from cohort studies have been much weaker and generally not statistically significant (Riboli and Norat, 2003;Vainio and Weiderpass, 2006) and a pooled analysis of 14 cohort studies found only weak non-significant associations with fruits and/or vegetables and colon cancer risk, but the association was significant for distal colon cancers (Koushik et al., 2007). More recently, an inverse association between vegetable intake and colorectal cancer was reported among men, but not women, in a large American cohort study (George et al., 2009) and similarly the Multiethnic cohort study also reported an inverse association between fruit and vegetable intake among men, but not among women (Nomura et al., 2008). In the European EPIC-study a marginally significant inverse association was found between fruit and vegetable intake and colorectal cancer which was restricted to former and never smokers (van Duijnhoven et al., 2009). Thus, although we cannot exclude a weak inverse association the available evidence does not allow for any strong conclusions (World Cancer Research Fund/American Institute for Cancer Research, 2007).

We found a significantly reduced lung cancer risk with higher intake of fruits and vegetables combined and with vegetables alone, but not with intake of fruits. Most previous studies have indicated an inverse association with fruit intake and lung cancer risk, while the evidence for vegetables has been weaker. In a pooled analysis of cohort studies there was a significant effect for intake of fruits, but not vegetables (Smith-Warner et al., 2003) and similar results were reported from the EPIC-study (Miller et al., 2004). In the AICR/WCRF report it was concluded that fruits probably protect against lung cancer, but there was only limited-suggestive evidence for a protective effect of vegetables (World Cancer Research Fund/American Institute for Cancer Research, 2007).

Both fruit and vegetables combined and separately were associated with a strong decrease in the risk of breast cancer in the present study. Previous studies have reported conflicting evidence on the role of fruit and vegetables in breast cancer prevention. A meta-analysis found evidence that fruit intake was inversely associated with breast cancer risk in cohort studies, but not in case-control studies, while for vegetables there was an inverse association among case-control studies, but not cohort studies (Vainio and Weiderpass, 2006). In a pooled analysis of eight cohort studies there was evidence only of a possible weak effect of fruit and vegetable intake (Smith-Warner et al., 2001) while in the EPIC-study there was little evidence of an association (van Gils et al., 2005). In a large American

cohort there was a slight positive association with vegetables, but a slight inverse association with fruit intake (George et al., 2009). The AICR/WCRF report (2007) it was stated that the data on fruits and vegetables and breast cancer was too limited or inconsistent for any conclusion (World Cancer Research Fund/American Institute for Cancer Research, 2007).

Fruit and vegetable intake was inversely associated with prostate cancer in this study, but the protective effect was restricted to fruits and there was no association with vegetables. Most case-control and cohort studies have reported no association between fruit or vegetable intake and prostate cancer risk (Vainio and Weiderpass, 2006) and in the AICR/WCRF report it was considered that the evidence was too limited or inconsistent to draw any conclusion (World Cancer Research Fund/American Institute for Cancer Research, 2007).

We found no association between fruit or vegetable intake and bladder cancer. Previous studies have indicated significant or non-significant inverse associations (Shibata et al., 1992; Chyou et al., 1993; Nagano et al., 2000; Kellen et al., 2006; Garcia-Closas et al., 2007; Sacerdote et al., 2007; Larsson et al., 2008) or no association (Michaud et al., 1999; 2002; George et al., 2009). We also found no association between fruit and vegetable intake and kidney cancer, although we cannot exclude a weak protective effect. Previous cohort studies found significant or non-significant inverse associations between fruit and/or vegetable intake and kidney cancer risk (Fraser et al., 1990; Rashidkhani et al., 2005; van Dijk et al., 2005; Lee et al., 2006; George et al., 2009), while another study reported no association (Weikert et al., 2006).

There was an inverse association between fruit and vegetable intake and risk of all cancer sites combined, although again was the association stronger for fruit than for vegetables. It should be noted that our estimate for all sites combined is not equal to total cancer incidence, because we did not have information on all types of cancers. Upon stratification the result from our study suggested that the inverse association between fruit and vegetable intake and all cancer sites combined was restricted to men. In contrast an American cohort study suggested an inverse association with fruits and vegetables, which was limited to women (Shibata et al., 1992). Three cohort studies found protective effects for fruit intake upon risk of total cancer incidence (Jansen et al., 2004) or mortality (Appleby et al., 2002; Sauvaget et al., 2003), while the results were null for raw vegetable salads (Appleby et al., 2002) and weaker for green-yellow vegetables (Sauvaget et al., 2003) or total vegetables (Jansen et al., 2004). However, several larger cohort studies found little or no association between fruit and vegetable intake and total cancer incidence (Hung et al., 2004; Olsen et al., 2005; Takachi et al., 2008; George et al., 2009). In contrast, a Greek cohort with a very high intake and very large range of intake of fruits and vegetables reported a 23% reduction in total cancer incidence with high intake of fruit and vegetables combined (Benetou et al., 2008). The only study that has investigated fruit and vegetable intake in childhood and adult total cancer incidence found a strong reduction in the risk of cancer with intake of fruit (RR=0.62, 95% CI: 0.43-0.90), but there was no significant association with vegetables (Maynard et al., 2003). Thus, altogether the results from this study are in line with previous results for some cancer sites, but not for others. The finding of a slightly stronger effect of fruit seems to be consistent with several, but not all previous studies.

Fruits and vegetables contain a wide range of constituents which have potential anti-cancer properties and which could explain some of the protective effect. They are a source of vitamin C, vitamin E and folate which have been shown to prevent cancer cell growth in in vitro studies and in experimental animal studies (Steinmetz and Potter, 1991). Although randomized controlled trials have not provided much evidence that supplementation with individual or combinations of antioxidants, vitamins or minerals protects against cancer (World Cancer Research Fund/American Institute for Cancer Research, 2007), and in some cases even may increase risk (Albanes et al., 1996), these results do not negate potential cancer preventive effects of whole foods with a myriad of constituents that may interact through various biological pathways. Further, fruits and vegetables contain numerous other constituents which may have cancer-preventive effects, including dietary fiber, flavonoids, dithiolthiones, glucosinolates, indoles, isothiocyanates, phenols and protease inhibitors. These agents may prevent cancer by inducing the activity of detoxifying enzymes, reducing oxidative stress and inflammation, altering hormone metabolism, increasing stool bulk and diluting carcinogens in the intestinal tract (Steinmetz and Potter, 1991). Because fruits and vegetables generally have a high fiber and water content and a low energy content, they may also decrease the risk of developing overweight or obesity (He et al., 2004; Bes-Rastrollo et al., 2006; Vioque et al., 2008), which are established risk factors for a wide range of cancers. Nevertheless, the associations we found were not materially altered by adjustment for BMI (results not shown), suggesting that the observations we found may not be mediated by BMI. In our study fruit intake was more strongly associated with decreased cancer risk than vegetables. Fruits are usually eaten raw, while vegetables may be consumed both cooked and raw and it is possible that some of the beneficial constituents of vegetables get destroyed during cooking and this may be part of the reason for the different results between fruits and vegetables in our study and in other studies (Link and Potter, 2004). We also cannot exclude the possibility that misclassification of vegetable intake is larger than for fruit, thus leading to weaker results, however we have no evidence to support such an explanation.

In addition to the direct cancer preventive effects of fruit and vegetable intake, indirect effects may be at work as well. Higher intake of fruit and vegetables may track with other dietary and lifestyle factors that are beneficial with regard to cancer prevention, such as higher intake of whole grains and legumes, lower intake of meat and alcohol and lower prevalence of tobacco use. Although we did adjust for total meat intake, alcohol and tobacco smoking, residual confounding remains a concern. Upon stratification we found that the inverse association between

fruit and vegetables combined and fruit intake was modified by intake of total meat and alcohol and by smoking status. We observed no association between fruit and vegetables cobined and fruit intake alone and all cancer sites combined among participants with lower meat intake, who were non-drinkers and were non-smokers and there was a statistically significant interaction with all these three variables. The overall null-findings in these subgroups and the significant interaction suggest that the inverse association we found between fruit and vegetable intake and cancer risk may be due to residual confounding from intake of meat, alcohol and/or tobacco smoking, consistent with an American cohort with regard to tobacco smoking (George et al., 2009). It is also possible that residual confounding from meat, alcohol and tobacco could explain the interaction we found with regards to sex because most of the women were non-smokers and non-drinkers of alcohol in contrast to the men, and in addition the women also had a lower meat intake.

Our study has several potential limitations; as with any case-control study we cannot rule out the possibility of recall bias or selection bias. 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, which should make recall bias less likely, but nevertheless we cannot exclude the possibility that it may 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. Because of the moderate number of cases for some sites we may not have had adequate statistical power to detect a weak protective effect for some cancers. Since we investigated fruit and vegetable intake and multiple cancers some of our findings may have been due to chance.

Our study has some strengths as well; the relatively large dietary variation in the Uruguayan population increased the power to detect significant associations. In addition the high response rate and detailed assessment and adjustment for important confounders, such as smoking, alcohol, BMI, meat and total energy are additional strengths of this study. To our knowledge this is the first study of fruit and vegetable intake and risk of multiple cancers from Southern America. We acknowledge the fact that the evidence relating fruits and vegetable intake to lower cancer risk has become weaker in recent years, due to the emergence of large cohort studies (which are free from recall bias and less prone to selection bias) which have provided weaker evidence than the previous evidence mostly based on case-control studies (World Cancer Research Fund/American Institute for Cancer Research, 2007). However, the possibility that measurement errors in the dietary assessment in cohort studies may obscure associations between diet and disease risk (Bingham et al., 2008) and that lack of data on changes in dietary intake before or during follow-up to take into account dietary changes (Sonestedt et al., 2007) could also partly contribute to inconsistent findings, cannot be excluded. Further assessments of these relationships in other populations around the world, where different dietary traditions prevail, could lead to important findings. Assessment of whether specific types of fruits and vegetables or botanical groups are more beneficial than others (Larsson et al., 2006b; World Cancer Research Fund/American Institute for Cancer Research, 2007) and whether more extreme levels of intake of fruits and vegetables leads to stronger reductions in cancer risk (Larsson et al., 2008) is warranted. Also, the possibility that fruit or vegetable intake in early life or early adulthood may decrease cancer risk needs further assessment (Maynard et al., 2003).

In conclusion our study suggest that higher intake of fruits and vegetables, and particularly fruits, may protect against several types of cancer, and that this protective effect is primarily seen in men, persons with a high intake of meat, alcohol and among tobacco smokers. However, we cannot exclude the possibility that these findings could be due to residual confounding or other forms of bias.

## Acknowledgements

This project was supported by a grant from International Agency for Research on Cancer, Lyon, France.

## References

Albanes D, Heinonen OP, Taylor PR, et al (1996). Alpha-tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. *J Natl Cancer Inst*, **88**, 1560-70.

Appleby PN, Key TJ, Burr ML, Thorogood M (2002). Mortality and fresh fruit consumption. IARC Sci Publ, 156: 131-3.

Benetou V, Orfanos P, Lagiou P, et al (2008) Vegetables and fruits in relation to cancer risk: evidence from the Greek EPIC cohort study. *Cancer Epidemiol Biomarkers Prev*, **17**, 387-92.

Bes-Rastrollo M, Martinez-Gonzalez MA, Sanchez-Villegas A, de la Fuente AC, Martinez JA (2006). Association of fiber intake and fruit/vegetable consumption with weight gain in a Mediterranean population. *Nutrition,* **22**, 504-11.

Bingham S, Luben R, Welch A, et al (2008). Associations between dietary methods and biomarkers, and between fruits and vegetables and risk of ischaemic heart disease, in the EPIC Norfolk Cohort Study. *Int J Epidemiol*, (in press).

Campos F, Carrasquilla G, Koriyama C, Serra M, Carrascal E et al (2006). Risk factors of gastric cancer specific for tumor location and histology in Cali, Colombia. *World J Gastroenterol*, **12**, 5772-9.

Chyou PH, Nomura AM, Stemmermann GN (1993). A prospective study of diet, smoking, and lower urinary tract cancer. *Ann Epidemiol*, **3**, 211-6.

Fei SJ, Xiao SD (2006). Diet and gastric cancer: a case-control study in Shanghai urban districts. *Chin J Dig Dis*, **7**, 83-8.

Fraser GE, Phillips RL, Beeson WL (1990). Hypertension, antihypertensive medication and risk of renal carcinoma in California Seventh-Day Adventists. *Int J Epidemiol*, **19**, 832-8.

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**, 2753-60.

Freedman ND, Park Y, Subar AF, et al (2008a). Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. *Int J Cancer*, **122**, 2330-6.

Freedman ND, Subar AF, Hollenbeck AR, et al (2008b). Fruit and vegetable intake and gastric cancer risk in a large United States prospective cohort study. *Cancer Causes Control*, **19**, 459-67.

Garcia-Closas R, Garcia-Closas M, Kogevinas M, et al (2007). Food, nutrient and heterocyclic amine intake and the risk of bladder cancer. *Eur J Cancer*, **43**, 1731-40.

George SM, Park Y, Leitzmann MF, et al (2009). Fruit and vegetable intake and risk of cancer: a prospective cohort study. *Am J Clin Nutr*, **89**, 347-53.

Gonzalez CA, Pera G, Agudo A, et al (2006) .Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Int J Cancer*, **118**, 2559-66.

He K, Hu FB, Colditz GA, et al (2004). Changes in intake of fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women. *Int J Obes Relat Metab Disord*, **28**, 1569-74.

Heck JE, Sapkota A, Vendhan G, et al (2008). Dietary risk factors for hypopharyngeal cancer in India. *Cancer Causes Control*, **19**, 1329-37.

Hung HC, Joshipura KJ, Jiang R, et al (2004). Fruit and vegetable intake and risk of major chronic disease. *J Natl Cancer Inst*, **96**, 1577-84.

Jansen MC, Bueno-de-Mesquita HB, Feskens EJ, et al (2004). Quantity and variety of fruit and vegetable consumption and cancer risk. *Nutr Cancer*, **48**, 142-8.

Kellen E, Zeegers M, Paulussen A, Van Dongen M, 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**, 2572-8.

Koushik A, Hunter DJ, Spiegelman D, et al (2007). Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. *J Natl Cancer Inst*, **99**, 1471-83.

Kreimer AR, Randi G, Herrero R, et al (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.

Larsson SC, Andersson SO, Johansson JE, Wolk A (2008). Fruit and vegetable consumption and risk of bladder cancer: a prospective cohort study. *Cancer Epidemiol Biomarkers Prev*, **17**, 2519-22.

Larsson SC, Bergkvist L, Wolk A (2006a). Fruit and vegetable consumption and incidence of gastric cancer: a prospective study. Cancer Epidemiol Biomarkers Prev, 15, 1998-2001.

Larsson SC, Hakansson N, Naslund I, Bergkvist L, Wolk A (2006b). Fruit and vegetable consumption in relation to pancreatic cancer risk: a prospective study. *Cancer Epidemiol Biomarkers Prev*, **15**, 301-5.

Lee JE, Giovannucci E, Smith-Warner SA, et al (2006). Intakes of fruits, vegetables, vitamins A, C, and E, and carotenoids and risk of renal cell cancer. *Cancer Epidemiol Biomarkers Prev*, **15**, 2445-52.

Link LB, Potter JD (2004). Raw versus cooked vegetables and cancer risk. *Cancer Epidemiol Biomarkers Prev*, **13**, 1422-35.

Lunet N, Valbuena C, Carneiro F, Lopes C, Barros H (2006). Antioxidant vitamins and risk of gastric cancer: a case-control study in Portugal. *Nutr Cancer*, **55**, 71-7.

Lunet N, Valbuena C, Vieira AL, et al (2007). Fruit and vegetable consumption and gastric cancer by location and histological type: case-control and meta-analysis. *Eur J Cancer Prev*, **16**, 312-27.

Maynard M, Gunnell D, Emmett P, Frankel S, Davey SG (2003). Fruit, vegetables, and antioxidants in childhood and risk of adult cancer: the Boyd Orr cohort. *J Epidemiol Community Health*, **57**, 218-25.

Michaud DS, Pietinen P, Taylor PR, et al (2002). Intakes of fruits and vegetables, carotenoids and vitamins A, E, C in relation to the risk of bladder cancer in the ATBC cohort study. *Br J Cancer*, **87**, 960-5.

Michaud DS, Spiegelman D, Clinton SK, et al (1999). Fruit and vegetable intake and incidence of bladder cancer in a male prospective cohort. *J Natl Cancer Inst*, **91**, 605-13.

Miller AB, Altenburg HP, Bueno-de-Mesquita B, et al (2004). Fruits and vegetables and lung cancer: Findings from the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*, **108**, 269-76.

Nagano J, Kono S, Preston DL, et al (2000). Bladder-cancer incidence in relation to vegetable and fruit consumption: a prospective study of atomic-bomb survivors. *Int J Cancer*, **86**, 132-8.

Navarro Silvera SA, Mayne ST, Risch H, et al (2008). Food group intake and risk of subtypes of esophageal and gastric cancer. *Int J Cancer*, **123**, 852-60.

Nomura AM, Wilkens LR, Murphy SP, et al (2008). Association of vegetable, fruit, and grain intakes with colorectal cancer: the Multiethnic Cohort Study. *Am J Clin Nutr*, **88**, 730-7.

Nouraie M, Pietinen P, Kamangar F, et al (2005). Fruits, vegetables, and antioxidants and risk of gastric cancer among male smokers. *Cancer Epidemiol Biomarkers Prev*, **14**, 2087-92.

Olsen A, Stripp C, Christense J, et al (2005). Re: Fruit and vegetable intake and risk of major chronic disease. *J Natl Cancer Inst*, **97**, 1307-8.

Pan G, Takahashi K, Feng Y, et al (1999). Nested case-control study of esophageal cancer in relation to occupational exposure to silica and other dusts. *Am J Ind Med*, **35**, 272-80.

Pavia M, Pileggi C, Nobile CG, Angelillo IF (2006). Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. *Am J Clin Nutr*, 83, 1126-34.

Rashidkhani B, Lindblad P, Wolk A (2005). Fruits, vegetables and risk of renal cell carcinoma: a prospective study of Swedish women. *Int J Cancer*, **113**, 451-5.

Riboli E, Norat T (2003) Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *Am J Clin Nutr*, **78**, 559S-69S.

Ronco AL, De Stefani E, Boffetta P, et al (2006). Food patterns and risk of breast cancer: A factor analysis study in Uruguay. *Int J Cancer*, **119**, 1672-8.

Sacerdote C, Matullo G, Polidoro S, et al (2007). Intake of fruits and vegetables and polymorphisms in DNA repair genes in bladder cancer. *Mutagenesis*, **22**, 281-5.

Sapkota A, Hsu CC, Zaridze D, et al (2008). Dietary risk factors for squamous cell carcinoma of the upper aerodigestive tract in central and eastern Europe. *Cancer Causes Control*, **19**, 1161-70.

Sauvaget C, Nagano J, Hayashi M, et al (2003). Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. *Br J Cancer*, **88**, 689-94.

Shibata A, Paganini-Hill A, Ross RK, Henderson BE (1992). Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. *Br J Cancer*, **66**, 673-9.

Smith-Warner SA, Spiegelman D, Yaun SS, et al (2001). Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. *JAMA*, **285**, 769-76.

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**, 1001-11.

Sonestedt E, Gullberg B, Wirfalt E (2007). Both food habit change in the past and obesity status may influence the association between dietary factors and postmenopausal breast cancer. *Public Health Nutr*, **10**, 769-79.

Steinmetz KA, Potter JD (1991). Vegetables, fruit, and cancer. II. Mechanisms. *Cancer Causes Control*, **2**, 427-42.

Suzuki T, Wakai K, Matsuo K, et al (2006). Effect of dietary antioxidants and risk of oral, pharyngeal and laryngeal squamous cell carcinoma according to smoking and drinking habits. *Cancer Sci*, **97**, 760-7.

Takachi R, Inoue M, Ishihara J, et al (2008). Fruit and vegetable intake and risk of total cancer and cardiovascular disease: Japan Public Health Center-Based Prospective Study. *Am J Epidemiol*, **167**, 59-70.

Tran GD, Sun XD, Abnet CC, et al (2005). Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer*, **113**, 456-63.

Vainio H, Weiderpass E (2006). Fruit and vegetables in cancer prevention. *Nutr Cancer*, **54**, 111-42.

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**, 648-54.

van Duijnhoven FJ, Bueno-de-Mesquita HB, Ferrari P, et al (2009) Fruit, vegetables, and colorectal cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr*, (in press).

van Gils CH, Peeters PH, Bueno-de-Mesquita HB, et al (2005). Consumption of vegetables and fruits and risk of breast cancer. *JAMA*, **293**, 183-93.

Vioque J, Weinbrenner T, Castello A, Asensio L, Garcia de la HM (2008). Intake of fruits and vegetables in relation to 10-year weight gain among Spanish adults. *Obesity*, **16**, 664-70.

Weikert S, Boeing H, Pischon T, et al (2006). Fruits and vegetables and renal cell carcinoma: findings from the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer*, **118**, 3133-9.

World Cancer Research Fund/American Insitute for Cancer Research (2007). Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. Washington DC: AICR.

Yamaji T, Inoue M, Sasazuki S, et al (2008). Fruit and vegetable consumption and squamous cell carcinoma of the esophagus in Japan: the JPHC study. *Int J Cancer*, **123**, 1935-40.