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# **Fruits, vegetables and breast cancer risk: a systematic review and meta-analysis of prospective studies**

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**Abstract:**

**Background:** Evidence for an association between fruit and vegetable intake and breast cancer risk is inconclusive. To clarify the association we conducted a systematic review and meta-analysis of the evidence from prospective studies.

**Methods:** We searched PubMed for prospective studies of fruit and vegetable intake and breast cancer risk until April 30<sup>th</sup> 2011. We included fifteen prospective studies that reported relative risk estimates and 95% confidence intervals (CIs) of breast cancer associated with fruit and vegetable intake. Random effects models were used to estimate summary relative risks.

**Results:** The summary relative risk (RR) for the highest versus the lowest intake was 0.89 (95% CI, 0.80-0.99,  $I^2=0\%$ ) for fruit and vegetables combined, 0.92 (95% CI, 0.86–0.98,  $I^2=9\%$ ) for fruit and 0.99 (95% CI, 0.92-1.06,  $I^2=20\%$ ) for vegetables. In dose-response analyses, the summary RR per 200 g/d was 0.96 (95% CI: 0.93-1.00,  $I^2=2\%$ ) for fruit and vegetables combined, 0.95 (95% CI: 0.91-1.00,  $I^2=32\%$ ) for fruits and 1.00 (95% CI: 0.96-1.03,  $I^2=21\%$ ) for vegetables.

**Conclusion:** In this meta-analysis of prospective studies high intake of fruits and fruit and vegetables combined, but not vegetables, is associated with a weak reduction in risk of breast cancer.

**Key words:** Fruits, vegetables, breast cancer, systematic review, meta-analysis

**Word count abstract:** 193

## **Introduction**

Breast cancer is the most common cause of cancer in women, with 1.38 million new cases diagnosed in 2008 worldwide, accounting for about 23% of all cancer cases and 14% of all cancer deaths among women [1]. The large international variation in breast cancer rates, coupled with the rapidly increasing rates observed in secular trend studies [2; 3] and migration studies [4; 5], suggest the importance of modifiable risk factors in breast cancer etiology.

Although dietary factors have long been suspected to be implicated in breast cancer etiology, few convincing dietary risk factors have been identified [6]. Fruit and vegetables contain numerous constituents that may reduce breast cancer risk, including fiber which can bind estrogens during the enterohepatic circulation [7] and antioxidants and several vitamins which can prevent oxidative DNA damage [8]. However, epidemiological studies of fruit and vegetable intake and breast cancer risk have provided inconsistent results. Case-control studies have generally found reduced breast cancer risk with high intake of fruit and vegetables [9], however, the interpretation of these studies, which may have been affected by recall bias and selection bias, have made conclusions difficult. This, in particular because most [10-23], but not all [24] prospective studies (which are less prone to such biases) in contrast have found no statistically significant association between fruit or vegetable intake

and breast cancer risk. In the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report from 2007, it was stated that the evidence for an association between fruit and vegetable intake and breast cancer risk was too limited or inconsistent for a conclusion to be made. At least 7 prospective studies have reported results for fruit and vegetable intake and breast cancer risk since that report [18-24], and this should provide even more statistical power to detect an association. Thus we aimed to clarify the evidence by conducting a systematic review and meta-analysis of the evidence from prospective studies.

## **Methods**

### Search strategy

As part of the Continuous Update Project of the WCRF/AICR we updated the systematic literature review published in 2007 [6] and searched the PubMed database up to April 30<sup>th</sup> 2011 for studies of fruit and vegetable intake and breast cancer risk. We followed a prespecified protocol, which includes details of the search terms used, for the review ([http://www.dietandcancerreport.org/downloads/SLR\\_Manual.pdf](http://www.dietandcancerreport.org/downloads/SLR_Manual.pdf)). The reference lists of all the included studies and the reference lists of the published systematic reviews and meta-analyses were also searched for any additional studies [6; 9; 25-27]. We followed standard criteria for conducting and reporting meta-analyses [28].

### Study Selection

To be included, the study had to have a prospective cohort, case-cohort or nested case-control design and to investigate the association between the intake of fruit and vegetables and breast cancer incidence. Estimates of the relative risk (RR) (such as hazard ratio or risk ratio) and

95% confidence intervals had to be available in the publication. For the dose-response analysis, a quantitative measure of intake and the total number of cases and person-years had to be available in the publication. When multiple publications from the same study were available we used the publication with the largest number of cases. We identified 26 potentially eligible full text publications [10-24; 29-39]. We excluded three publications on breast cancer mortality [29-31], six duplicate publications [33-38] and two studies of childhood [32] or adolescent dietary intake [39]. One study was excluded from the dose-response analysis because the comparison was provided only for the highest vs. the lowest intake [19]. In total, 15 publications were included in the analyses (Figure 1, Table 1).

#### Data extraction

We extracted the following data from each study: first author's last name, publication year, country where the study was conducted, study name, follow-up period, sample size, gender, age, number of cases, dietary assessment method (type, number of items and whether it was validated), exposure, frequency or quantity of intake, RRs and 95% CIs and variables adjusted for in the analysis. The search and data extraction of articles published up to December 30<sup>th</sup>, 2005 was conducted by several reviewers at the Istituto Nazionale Tumori Milan during the systematic literature review for the WCRF/AICR report ([http://www.dietandcancerreport.org/downloads/SLR/Breast\\_SLR.pdf](http://www.dietandcancerreport.org/downloads/SLR/Breast_SLR.pdf)). The search from January 2006 and up to April 30<sup>th</sup>, 2011 was conducted by two of the authors (D. S. M. C. and A.R.V). Data was extracted into a database by two authors (D. S. M. C., and A.R.V.) and was checked for accuracy by two authors (D.A. and T. N). We did not assess study quality using a quality score, but investigated whether specific study characteristics such as duration of follow-up, number of cases, menopausal status and adjustment for confounders, which are indicators of study quality, influenced the results in subgroup analyses.

## Statistical methods

To take into account heterogeneity between studies, we used a random effects models to calculate summary RRs and 95% CIs for the highest versus the lowest level of fruit and vegetable intake and for the dose-response analysis [40]. The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted by the inverse of its variance. A two-tailed  $p < 0.05$  was considered statistically significant.

For the dose-response analysis we used the method described by Greenland and Longnecker [41] to compute linear trends and 95% CIs from the natural logs of the RRs and CIs across categories of fruit and vegetable intake. The method requires that the distribution of cases and person-years or non-cases and the RRs with the variance estimates for at least three quantitative exposure categories are known. We estimated the distribution of cases or person-years in studies that did not report these, but reported the total number of cases/person-years. For example if the total number of person-years was provided and the exposure variable was categorized by quintiles, we divided the number of person-years by five. The median or mean level of fruit and vegetable intake in each category of intake was assigned to the corresponding relative risk for each study when provided in the paper. For studies that reported fruit and vegetable intake by ranges of intake we estimated the mean intake in each category by calculating the average of the lower and upper bound. When the highest category was open-ended we assumed the open-ended interval length to be the same as the adjacent interval. When the lowest category was open-ended we set the lower boundary to zero. If the intakes were reported in densities (i.e. gram per 1000 kcal or gram per 1000 kJ) we recalculated the reported intakes to absolute intakes using the mean or median energy intake [24]. Consistent with previous meta-analyses of fruit and vegetable intake and cancer risk [26; 42] we used 80 grams as a serving size for recalculation of the

intakes to a common scale (grams per day) in studies that reported intakes as frequency. For one study that reported results in cup equivalents [24] we used 160 grams as a cup equivalent size for vegetables because the definition of the cup equivalent for vegetables was twice as large as the definition of a serving per day from another paper from the same study (1 cup equivalent = 2 cups of leafy vegetables or 1 cup of other vegetables, 1 serving = 1 cup of leafy vegetables, or ½ cup of other vegetables) [43]. For fruits, the definition of cup equivalents was similar to the definition for servings, thus 80 grams was used as a cup equivalent size for fruit. The study reported that results were similar using serving size and cup equivalents. The linear dose-response results are presented for a 200 gram per day increment. We examined a potential nonlinear dose-response relationship between fruit and vegetable intakes and breast cancer using fractional polynomial models [44]. We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity [44]. In the analysis of total fruit and vegetables combined we used 100 g/d as a reference category because there were no studies with zero intake in the reference.

Heterogeneity between studies was assessed using Q and I<sup>2</sup> statistics [45]. Potential sources of heterogeneity were investigated in subgroup and meta-regression analyses by menopausal status, duration of follow-up, number of cases, geographic location and adjustment for confounding factors. Small-study bias, such as publication bias, was assessed using a funnel plot and Egger's test with results considered to indicate potential small-study bias when p<0.10. In a sensitivity analysis we examined the impact of including studies of breast cancer mortality on the results as well.

Stata version 10.1 software (StataCorp, College Station, TX, USA) was used for the statistical analyses.



## Results

We identified 14 cohort studies [10-18; 20-24] and one nested case-control study [19] that was included in the analysis of fruit and/or vegetable intake and breast cancer risk (Table 1, Figure 1). Five of the studies were from Europe, seven from America and three from Asia (Table 1).

### Total fruit and vegetables

#### *High vs. low analysis*

Seven cohort studies [10; 12; 14; 16; 18; 21; 23] investigated the association between total fruit and vegetable intakes and breast cancer risk and included 6273 cases among 233036 participants. Six of these studies [10; 12; 14; 16; 18; 21] were included in the high vs. low analysis (one study reported only continuous results [23]). The summary RR for high vs. low intake was 0.89 (95% CI: 0.80-0.99), with no heterogeneity,  $I^2=0\%$  and  $p_{\text{heterogeneity}}=0.67$  (n=6) (Figure 2a). There was no evidence of publication bias with Egger's test,  $p=0.44$  or with Begg's test,  $p=0.45$ .

#### *Dose-response analysis*

Six cohort studies [10; 14; 16; 18; 21; 23] were included in the dose-response analysis. The summary RR per 200 grams per day (g/d) was 0.96 (95% CI: 0.93-1.00,  $p$  for association=0.045), with no evidence of heterogeneity,  $I^2=2\%$  and  $p_{\text{heterogeneity}}=0.41$  (n=6) (Figure 2b). There was no evidence of a nonlinear association between total fruit and vegetables and breast cancer risk,  $p_{\text{nonlinearity}}=0.20$  (Figure 3).

## Fruits

### *High vs. low analysis*

Ten cohort studies [10; 11; 13-15; 17; 20-22; 24] were included in the analysis fruit intake and breast cancer risk, including 16763 cases among 785668 participants. The summary RR for high vs. low intake was 0.92 (95% CI: 0.86-0.98), with little heterogeneity,  $I^2=9%$ ,  $p_{\text{heterogeneity}}=0.36$  (n=10) (Figure 4a). There was no evidence of publication bias with Egger's test,  $p=0.41$  or Begg's test,  $p=0.42$ .

### *Dose-response analysis*

The summary RR per 200 g/d was 0.95 (95% CI: 0.91-1.00,  $p$  for association=0.029), with little heterogeneity,  $I^2=32%$ ,  $p_{\text{heterogeneity}}=0.15$  (n=10) (Figure 4b). There was no evidence of a nonlinear association between fruit intake and breast cancer risk,  $p_{\text{nonlinearity}}=0.68$  (Figure 5a).

## Vegetables

### *High vs. low analysis*

Nine cohort studies [10; 11; 13; 14; 17; 20-22; 24] and one nested case-control study [19] was included in the analysis of high vs. low vegetable intake and breast cancer, including 16600 cases among 751965 participants. The summary RR was 0.99 (95% CI: 0.92-1.06). There was little evidence of heterogeneity,  $I^2=20%$ ,  $p_{\text{heterogeneity}}=0.26$  (Figure 6a). There was no evidence of small-study bias with Egger's test,  $p=0.23$  or with Begg's test,  $p=0.72$ .

### *Dose-response analysis*

Nine cohort studies [10; 11; 13; 14; 17; 19-22; 24] were included in the dose-response analysis. The summary RR per 200 grams per day was 1.00 (95% CI: 0.96-1.03) with little evidence of heterogeneity,  $I^2=21\%$ ,  $p_{\text{heterogeneity}}=0.25$  (Figure 6b). There was some evidence of a nonlinear slight positive association between vegetable intake and breast cancer risk,  $p_{\text{nonlinearity}}=0.02$  (Figure 5b).

### *Subgroup and sensitivity analyses*

In stratified analyses (Table 2), the association between high versus low fruit intake and breast cancer risk was inverse in most strata, although usually not statistically significant. There was marginally significant heterogeneity ( $p=0.06$ ) in the results for vegetables among pre- and postmenopausal women, with a significant inverse association among premenopausal, but not postmenopausal women, however, there was only two studies among premenopausal women (Table 2). Too few studies reported results stratified by hormone receptor status to conduct subgroup analyses of these. For fruits or fruits and vegetables combined, there was no evidence of a difference in the results by menopausal status, although the inverse association with fruit intake only was significant among postmenopausal women. There was a suggestion of a difference in the results between studies of fruit intake that adjusted or not for oral contraceptive use,  $p$  for heterogeneity=0.07, with no association among the two studies that adjusted for oral contraceptive use, but an inverse association among studies which did not. For vegetables there was suggestion of heterogeneity between studies that adjusted or not for age at menarche or age at 1<sup>st</sup> birth,  $p$  for heterogeneity=0.07

for both, with a suggestive inverse association among the studies that made these adjustments, but not for those which did not.

For one study that reported the intake in cup equivalents per day [24] we also conducted a sensitivity analysis using data reported in servings per day from another publication from the same study [43]. The estimated RR per 200 g/d of fruit for the study changed from 0.93 (95% CI: 0.88-0.99) to 0.95 (95% CI: 0.92-0.99), however, the summary estimate was not materially affected, RR=0.96 (95% CI: 0.92-1.00,  $p$  for association=0.033). For vegetables, the estimated RR per 200 g/d was almost identical 1.04 (95% CI: 1.00-1.08) and thus the summary estimate was the same as before, summary RR=1.00 (95% CI: 0.96-1.03).

When we further stratified the studies by the median range of intake, the summary RR was 0.88 (95% CI: 0.73-1.07) and 0.89 (95% CI: 0.78-1.02) for studies with a range of fruit and vegetable intake of  $\geq 441$  and  $< 441$  g/d, respectively. The summary RR was 0.87 (95% CI: 0.77-0.99) and 0.93 (95% CI: 0.85-1.02) for studies with a range of fruit intake of  $\geq 275$  and  $< 275$  g/d, respectively, and 1.03 (95% CI: 0.96-1.10) and 0.92 (95% CI: 0.82-1.02) for studies with a range of vegetable intake of  $\geq 273$  and  $< 273$  g/d, respectively (results not shown).

We also assessed the influence of including studies on breast cancer mortality on our results. Two additional studies were included in the high vs. low analysis of fruit [30; 31] and one of these in the dose-response [31]. The summary RR for high vs. low intake was 0.92 (95% CI: 0.86-0.97) with no heterogeneity,  $I^2=3\%$ ,  $p_{\text{heterogeneity}}=0.42$  and per 200 g/d was 0.95 (95% CI: 0.92-0.99) with no significant heterogeneity,  $I^2=25\%$ ,  $p_{\text{heterogeneity}}=0.21$  similar to the original analysis.

## Discussion

In this meta-analysis high versus low intake of fruit and fruit and vegetables combined, but not vegetables, were associated with small, but statistically significant reductions in breast cancer risk. In the dose-response analyses, fruit and fruit and vegetables combined, but not vegetables, were associated with reduced risk, although only marginally significantly so.

Our results are similar to those of a pooled analysis of eight prospective studies which found a non-significant reduction of ~7% for high vs. low intake of fruits and fruit and vegetables combined, but no association with intake of vegetables [46]. In the 2<sup>nd</sup> report from the WCRF/AICR it was stated that the evidence for an association between intake of fruit and non-starchy vegetables and breast cancer risk was too limited or inconsistent for a conclusion, thus a downgrading of the judgement of the evidence for fruit since the 1<sup>st</sup> report [6]. However, with additional large prospective studies published after the report we found significant inverse associations between high vs. low intake of fruit and fruit and vegetables combined and breast cancer risk. To our knowledge this is the first meta-analysis to have assessed a possible nonlinear association between fruit and vegetable intake and breast cancer risk, but the inverse association with fruit and fruit and vegetable intake combined appeared to be linear. This meta-analysis included a larger number of studies than previous meta-analyses and had more than twice as many cases and participants as the pooled analysis, thus we had statistical power to detect moderate associations, although the associations for fruits and vegetables and fruits were still only marginally significant in the dose-response analysis. This may partly be due to the range being larger in the high vs. low analysis than in the linear dose-response analysis. For example, the summary estimate for a 400 g/d increment in fruit intake reached statistical significance, RR=0.91 (95% CI: 0.83-0.99). In addition, gains in

statistical power by increasing sample size are less when effect estimates are small and the sample size already is large.

Our meta-analysis may have several limitations that need to be discussed. We cannot exclude the possibility that the observed inverse association between fruit and vegetable intake and breast cancer risk could be due to unmeasured or residual confounding. Higher intake of fruit and vegetables is often associated with other lifestyle factors including higher levels of physical activity, lower prevalence of overweight/obesity and lower intakes of alcohol and dietary fat. Many, but not all of the studies adjusted for these and other potential confounders. In subgroup and meta-regression analyses, there was a suggestion of a difference in the results between studies of fruit intake that adjusted or not for oral contraceptive use,  $p$  for heterogeneity=0.07, and for vegetables among between studies that adjusted or not for age at menarche or age at 1<sup>st</sup> birth,  $p$  for heterogeneity=0.07 for both. However, the few studies in some of these subgroups make the interpretation of these findings difficult. Because of the few studies published we were not able to examine the association between specific types of fruits and vegetables and breast cancer risk.

Measurement errors in the assessment of the exposure variable are known to bias effect estimates, however, bias toward the null is most likely because we included only prospective studies. Almost all the studies included in our meta-analysis used validated food-frequency questionnaires, but only one of the studies corrected the risk estimates for measurement error. However, the results did not differ substantially before and after calibration [17]. Dietary changes during follow-up can obscure associations between dietary intake and disease risk if dietary intake only is assessed at baseline. One study reported a RR of 0.59 (95% CI: 0.40-0.87) for high vs. low intake of fruit, berries and vegetables among women without a dietary change in the past, while there was no association among persons who reported that they had changed their dietary intake, RR=1.26 (95% CI: 0.63-2.55) [37].

If the relevant exposure window is in the distant past or in adolescence it is possible that most studies may have missed an effect, because most of the studies published to date have been conducted primarily among middle-aged and older persons. In addition, measurement errors due to different dietary questionnaires or nutrient databases may have affected the results. Because some studies reported intakes in frequency we had to convert the intakes to grams per day based on a standard serving size (80 grams). It is possible that this may have introduced some measurement error because different types of fruit and vegetables may have different serving sizes. Any further studies should report results in grams per day to provide more accurate data on fruit and vegetable intake. Considering the weak associations we observed, future studies might want to clarify whether improved exposure assessment by using biomarkers of fruit and vegetable intake or by correcting for measurement error might lead to more conclusive results.

Although small study bias, such as publication bias can be a problem in meta-analyses of published studies, we found no statistical evidence of publication bias in this meta-analysis and there was also no asymmetry in the funnel plots when inspected visually.

Several potential mechanisms may explain an inverse association between fruit and vegetables and breast cancer risk. Fruit and vegetables are good sources of fiber which may prevent breast cancer by binding estrogens during the enterohepatic reabsorption of estrogens in the colon [47]. In addition, fruit and vegetables are good sources of various antioxidants, such as carotenoids [48-50], glucosinolates, indoles, isothiocyanates [51] which may prevent breast cancer by inducing the activity of detoxifying enzymes, reducing oxidative stress and inflammation. High intake of fruit and vegetables may also decrease the risk of overweight/obesity [52] which is an established risk factor for postmenopausal breast cancer.

Strengths of our meta-analysis include the prospective design of the included studies which minimize the possibility for recall and selection bias, and the large number of cases

and participants (up to 780 000 participants and >16000 cases), which provides statistical power to detect moderate associations. Our results for fruit and vegetable intake and breast cancer risk are relatively weak, but of similar size as our previously reported associations with colorectal cancer risk [53]. However, if consistent across cancer sites such a reduction in cancer risk could still have a moderate, but nevertheless important impact on overall cancer risk.

In conclusion, we found weak and linear inverse associations between intake of fruit and fruit and vegetables combined, but not vegetables, and breast cancer risk. Further studies of specific types of fruits and vegetables, with improved exposure assessment methods, adjustment for more confounding factors and stratified by menopausal status and hormone receptor status are warranted.

#### Contributors

The systematic literature review team at the Istituto Nazionale Tumori Milan conducted the search, data selection and data extraction up to December 2005. RV was responsible for developing and managing the database for the Continuous Update Project. T. Norat wrote the protocol for the review, and is the PI of and coordinates the Continuous Update Project at Imperial College. D. S.M. Chan and A.R. Vieira did the updated literature search and data extraction. D. Aune did the study selection, statistical analyses and wrote the first draft of the original manuscript. DC Greenwood was expert statistical advisor and contributed towards the statistical analyses. All authors contributed to the revision of the manuscript.

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The sponsor of this study had no role in the decisions about the design and conduct of the study, collection, management, analysis or interpretation of the data or the preparation, review or approval of the manuscript.

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Table 1: Prospective studies of fruits, vegetable intake and breast cancer risk

Author, publication year, country/region	Study name	Follow-up period	Study size, gender, age, number of cases	Dietary assessment	Exposure	Quantity	RR (95% CI)	Adjustment for confounders
Lof M et al, 2011, Sweden	Swedish Women's Lifestyle and Health Cohort Study	1991-1992 – 2006, 14 yrs	44848 pre- & postm. w., age 30-49 yrs: 1067 cases	Validated FFQ, ~80 items	Fruits and vegetables	Per 200 g/d	0.94 (0.86-1.03)	Age, education, BMI, smoking, energy intake, alcohol
Brasky TM et al, 2010, USA	VITamins And Lifestyle (VITAL) Cohort	2000-2002 – 2007, 6 yrs	35016 postm. w., age 50-76 yrs: 880 cases	Validated FFQ, 120 items	Fruits Vegetables	>2.14 vs. ≤1.04 serv/d >2.85 vs. ≤1.73 serv/d	0.86 (0.73-1.02) 0.97 (0.82-1.15)	Age
Boggs DA et al, 2010, USA	Black Women's Health Study	1995 – 2007, 12 yrs	51928 pre- & postm. w., age 21-69 yrs: 1268 cases	Validated FFQ, 68/85 items	Fruits and vegetables Total vegetables Total fruits	≥4 vs. <1 serv/d ≥2 serv/d vs. <4/wk ≥2 serv./d vs. <2 /wk	0.87 (0.71-1.07) 0.87 (0.73-1.05) 0.91 (0.74-1.11)	Age, energy intake, age at menarche, BMI at age 18 years, FH – BC, education, geographic location, parity, age at 1 <sup>st</sup> birth, OC use, menopausal status, age at menopause, menopausal hormone use, vigorous activity, smoking status, alcohol intake, multivitamin use
Butler LM et al, 2010, Singapore	Singapore Chinese Health Study	1993-98 – 2005, 10.7 yrs	34028 postm. w., age 45-74 yrs: 629 cases	Validated FFQ, 165 items	Total vegetables Total fruits	173.7 vs. 51.0 g/d 357.0 vs. 39.0 g/d	0.86 (0.63-1.16) 1.03 (0.77-1.38)	Age, dialect group, interview year, education, parity, BMI, 1 <sup>st</sup> degree relative with BC, total energy
Jayalekshmi P et al, 2009, India	Karunagappally Cohort	1990-2004, 14 yrs	792 pre-& postm. controls, age ≥20 yrs: 264 cases	FFQ	Vegetables	Occasional vs. regular	0.71 (0.49-1.06)	Age, religion, place of residence
George SM et al, 2009, USA	NIH-AARP Diet and Health Study	1995-96 – 2003, 8 yrs	195229 postm. w., age 50-71 yrs: 5815 cases	Validated FFQ, 124 food items	Total fruit Total vegetables	≥1.90 vs. ≤0.60 cup equiv/d ≥1.43 vs. ≤0.56 cup equiv/d	0.91 (0.84-1.00) 1.08 (1.00-1.18)	Age, smoking, energy intake, BMI, alcohol, physical activity, education, race, marital status, FH – cancer, menopausal HT, mutual adjustment between fruit and vegetables

Sonestedt E et al, 2008, Sweden	Malmo Diet and Cancer Study	1991-1996 – 2004, 10.3 yrs	15773 pre- & postm. w, age 46-75 yrs: 544 cases	Validated assessment; 7 day menu book, 168 item FFQ and 1 hour interview	Fruits, berries, vegetables	629 vs. 118 g/d	0.78 (0.59-1.03)	Age, season of data collection, diet interviewer, method version, total energy, weight, height, educational status, smoking habits, leisure-time physical activity, hours of household activities, alcohol, age at menopause, parity, current use of HRT
Van Gils CH et al, 2005, Europe	European Prospective Investigation into Cancer and Nutrition	1992-2001, 5.4 yrs	285526 pre- & postm. w., age 25-70 yrs: 3659 cases	Validated FFQs, ≤350 items, dietary interview, diet history, 7 day menu book, 7 day record	Total vegetables Total fruits	245.95 vs. 122.22 g/d 372.17 vs. 115.39 g/d	0.98 (0.84-1.14) 1.09 (0.94-1.25)	Age, center, energy intake (divided into fat and nonfat sources), alcohol intake, SFA intake, height, weight, age at menarche, parity, current OC use, current HRT use, menopausal status, smoking status, physical activity, education

<b>Olsen A et al, 2003, Denmark</b>	<b>Diet, Cancer and Health</b>	<b>1993-1997 – 2000, 4.7 yrs</b>	<b>23798 postm. w., age 50-64 yrs: 425 cases</b>	Validated FFQ, 192 food items	<b>Total fruits, vegetables and juice</b>	<b>Per 100g/day</b>	<b>1.02 (0.98-1.06)</b>	<b>Age, time under study, parity, previous benign breast tumor surgery, education, HRT use and duration, alcohol, BMI</b>
<b>Zhang S et al, 1999, USA</b>	<b>Nurses' Health Study</b>	1980-1994, 14 yrs	<b>83234 pre- &amp; postm. w., age 33-60 yrs: 2697 cases</b>	Validated FFQ, 61/126 items	<b>Prem: Fruits Vegetables Fruits and vegetables Postm: Fruits Vegetables Fruits and vegetables</b>	<b>≥5.0 vs. &lt;2 serv/d ≥5.0 vs. &lt;2 serv/d ≥5.0 vs. &lt;2 serv/d ≥5.0 vs. &lt;2 serv/d</b>	<b>0.74 (0.45-1.24) 0.64 (0.43-0.95) 0.77 (0.58-1.02) 0.84 (0.64-1.09) 1.02 (0.85-1.24) 1.03 (0.81-1.31)</b>	<b>Age, length of follow-up, energy intake, age at 1st birth, age at menarche, FH - BC, benign breast disease, alcohol, BMI at age 18 years, weight change from age 18 years, height. Postm.women: age at menopause and HRT</b>
<b>Key TJ et al, 1999, Japan</b>	<b>Life Span Study</b>	<b>1969-1970, 1979-1980 – 1993, 14 yrs</b>	<b>34759 pre- &amp; postm. w: 427 cases</b>	FFQ, 19 items	<b>Fruits</b>	<b>≥5/wk vs. ≤1/wk</b>	<b>0.95 (0.71-12.7)</b>	<b>Age, calendar period, city, age at time of bombing and radiation dose</b>
<b>Verhoeven DTH et al, 1997, Netherlands</b>	<b>Netherlands Cohort Study</b>	1986-1990, 4.3 yrs	<b>1812 postm. w., age 55-69 yrs: 650 cases</b>	Validated FFQ, 150 food items	<b>Vegetables Fruits</b>	<b>303 vs. 108 g/d 343.1 vs. 64.9 g/d</b>	<b>0.94 (0.67-1.31) 0.76 (0.54-1.08)</b>	<b>Age, energy intake, alcohol intake, benign breast disease, maternal breast cancer, breast cancer in sister(s), age at menarche, age at menopause, age at first birth, parity</b>
<b>Byrne C et al, 1996, USA</b>	<b>National Health Epidemiologic Follow-up Study</b>	1982-1984 – NA, 3.9 yrs	<b>6156 pre- &amp; postm. w., age 32-86 yrs: 53</b>	FFQ, 93 food items	<b>Fruits and vegetables</b>	<b>&gt;3 vs. ≤3 serv/d</b>	<b>0.7 (0.4-1.5)</b>	<b>Age</b>



			<b>cases</b>					
<b>Rohan T et al, 1993, Canada</b>	<b>National Breast Screening Study</b>	<b>1982-1987, ~5 yrs</b>	<b>56837 pre- &amp; postm. w., age 40-59 yrs: 519 cases</b>	Validated FFQ, 86 food items	<b>Fruit Vegetables</b>	<b>≥491 vs. &lt;189 g/d</b> <b>≥433 vs. &lt;203 g/d</b>	<b>0.81 (0.57-1.14)</b> <b>0.86 (0.61-1.23)</b>	<b>Age, age at menarche, FH – BC, surgical menopause, age at 1<sup>st</sup> livebirth, years of education, benign breast disease, other contributors to total food intake</b>
<b>Shibata et al, 1992, USA</b>	<b>Leisure World Cohort study</b>	<b>1981-1985 – 1989, 6 yrs</b>	~7299 postm. w., age 65-84 yrs: 219 cases	<b>FFQ, 59 food items</b>	<b>Vegetables and fruit</b> <b>Vegetables</b> <b>Fruit</b>	10.06 vs. 4.54 serv/d 5.98 vs. 2.34 serv/d 4.58 vs. 1.66 serv/d	<b>0.87 (0.63-1.21)</b> <b>0.96 (0.69-1.34)</b> <b>0.82 (0.60-1.12)</b>	<b>Age, smoking</b>

BMI=Body Mass Index, FFQ=food frequency questionnaire, FH - BC=Family history of breast cancer, HRT/HT=hormone therapy, MET=metabolic equivalent task, OC use= oral contraceptive use, prem=premenopausal, postm.= postmenopausal, w=women, SFA= saturated fatty acids, yrs = years

Table 2: Subgroup analyses of fruit and vegetable intakes and breast cancer, high versus low intake

	<b>Total fruit and vegetables</b>					<b>Fruits</b>					<b>Vegetables</b>				
	<i>n</i>	RR (95% CI)	<i>I</i> <sup>2</sup> (%)	<i>P</i> <sub>h</sub> <sup>1</sup>	<i>P</i> <sub>h</sub> <sup>2</sup>	<i>n</i>	RR (95% CI)	<i>I</i> <sup>2</sup> (%)	<i>P</i> <sub>h</sub> <sup>1</sup>	<i>P</i> <sub>h</sub> <sup>2</sup>	<i>n</i>	RR (95% CI)	<i>I</i> <sup>2</sup> (%)	<i>P</i> <sub>h</sub> <sup>1</sup>	<i>P</i> <sub>h</sub> <sup>2</sup>
All studies	6	0.89 (0.80-0.99)	0	0.71		10	0.92 (0.86-0.98)	9.4	0.36		10	0.99 (0.92-1.06)	19.6	0.26	
Duration of follow-up															
<10 yrs follow-up	3	0.94 (0.77-1.16)	0	0.43	0.54	6	0.91 (0.83-1.01)	39.9	0.14	0.98	6	1.03 (0.97-1.10)	0	0.60	0.27

≥10 yrs follow-up	3	0.87 (0.77-0.98)	0	0.66		4	0.91 (0.80-1.03)	0	0.67		4	0.95 (0.81-1.11)	42.4	0.16		
Menopausal status																
Premenopausal	2	0.82 (0.67-1.02)	0	0.47	0.82/ 0.43 <sup>3</sup>	2	0.92 (0.71-1.20)	0.3	0.32	0.12/ 0.79 <sup>3</sup>	2	0.76 (0.60-0.95)	0.8	0.32	0.14/ 0.06 <sup>3</sup>	
Pre- & postmenopausal	2	0.77 (0.59-0.99)	0	0.77		3	1.00 (0.85-1.17)	27.2	0.25		3	1.03 (0.82-1.29)	47.3	0.15		
Postmenopausal	4	0.93 (0.79-1.08)	20.5	0.29		7	0.89 (0.83-0.95)	0	0.85		7	1.03 (0.96-1.09)	0	0.53		
Geographic location																
Europe	2	0.91 (0.67-1.23)	56.3	0.13	0.83	2	0.94 (0.67-1.33)	71.9	0.06	0.31	2	0.97 (0.85-1.12)	0	0.83	0.71	
America	4	0.88 (0.78-1.00)	0	0.89		6	0.89 (0.83-0.95)	0	0.91		6	0.98 (0.90-1.07)	28.5	0.22		
Asia	0					2	0.99 (0.80-1.22)	0	0.70		2	1.08 (0.67-1.76)	74.1	0.05		
Number of cases																
Cases <500	3	0.94 (0.77-1.16)	0	0.43	0.86	2	0.89 (0.72-1.10)	0	0.50	0.41	2	1.15 (0.79-1.67)	54.2	0.14	0.71	
Cases 500-<1500	2	0.84 (0.71-0.99)	0	0.54		5	0.88 (0.79-0.98)	0	0.70		5	0.91 (0.82-1.01)	0	0.90		
Cases ≥1500	1	0.91 (0.76-1.09)				3	0.95 (0.82-1.09)	66.8	0.05		3	1.02 (0.94-1.12)	29.8	0.24		
Adjustment for confounders																
Hormone therapy	Yes	4	0.90 (0.80-1.00)	0	0.49	0.67	4	0.94 (0.84-1.05)	51.0	0.11	0.35	4	0.98 (0.89-1.09)	50.0	0.11	0.80

	No	2	0.83 (0.62-1.12)	0	0.56		6	0.87 (0.78-0.97)	0	0.77		6	0.97 (0.86-1.08)	0	0.46	
OC use	Yes	1	0.87 (0.71-1.07)			0.82	2	1.01 (0.85-1.20)	50.9	0.15	0.07	2	0.93 (0.83-1.05)	0	0.33	0.36
	No	5	0.90 (0.79-1.01)	0	0.57		8	0.89 (0.83-0.95)	0	0.84		8	1.01 (0.93-1.09)	15.5	0.31	
Age at menarche	Yes	2	0.89 (0.78-1.02)	0	0.74	0.93	5	0.91 (0.78-1.05)	48.2	0.10	0.75	5	0.93 (0.85-1.02)	0	0.88	0.07
	No	4	0.88 (0.75-1.04)	0	0.42		5	0.90 (0.84-0.97)	0	0.81		5	1.04 (0.93-1.15)	26.4	0.25	
Age at menopause	Yes	3	0.87 (0.77-0.98)	0	0.66	0.54	2	0.80 (0.66-0.97)	0	0.73	0.51	4	0.93 (0.85-1.02)	0	0.81	0.10
	No	3	0.94 (0.77-1.16)	0	0.43		8	0.93 (0.87-1.00)	8.0	0.37		6	1.02 (0.92-1.13)	24.8	0.25	
Age at 1 <sup>st</sup> birth	Yes	2	0.89 (0.78-1.02)	0	0.74	0.93	4	0.98 (0.85-1.12)	36.0	0.20	0.21	4	0.90 (0.81-1.01)	0	0.93	0.07
	No	4	0.88 (0.75-1.04)	0	0.42		6	0.89 (0.83-0.95)	0	0.90		6	1.03 (0.95-1.11)	18.2	0.30	
Parity	Yes	3	0.89 (0.76-1.04)	15.6	0.31	1.00	4	0.98 (0.85-1.12)	36.0	0.20	0.09	4	0.92 (0.83-1.03)	0	0.75	0.16
	No	3	0.89 (0.76-1.04)	0	0.74		6	0.89 (0.83-0.95)	0	0.90		6	1.02 (0.93-1.12)	24.7	0.25	
Education	Yes	3	0.89 (0.76-1.04)	15.6	0.31	1.00	5	0.96 (0.87-1.05)	30.9	0.22	0.14	5	0.97 (0.87-1.08)	43.8	0.13	0.90
	No	3	0.89 (0.76-1.04)	0	0.74		5	0.85 (0.76-0.94)	0	0.89		5	0.98 (0.88-1.09)	0	0.44	
Alcohol	Yes	4	0.90 (0.80-1.00)	0	0.49	0.67	5	0.92 (0.83-1.03)	46.7	0.11	0.59	5	0.99 (0.90-1.08)	35.5	0.19	0.89
	No	2	0.83 (0.62-1.12)	0	0.56		5	0.89 (0.79-0.99)	0	0.76		5	0.97 (0.85-1.11)	13.7	0.33	

Smoking	Yes	3	0.83 (0.72-0.96)	0	0.82	0.38	4	0.95 (0.85-1.06)	45.5	0.14	0.26	4	1.00 (0.90-1.10)	41.6	0.16	0.58
	No	3	0.94 (0.81-1.09)	0	0.46		6	0.87 (0.78-0.96)	0	0.75		6	0.96 (0.87-1.06)	0	0.44	
Body mass index, weight, WHR	Yes	4	0.90 (0.80-1.00)	0	0.49	0.67	5	0.95 (0.86-1.05)	38.4	0.17	0.19	5	0.97 (0.89-1.07)	43.6	0.13	0.88
	No	2	0.83 (0.62-1.12)	0	0.56		5	0.85 (0.76-0.95)	0	0.89		5	0.99 (0.87-1.11)	0	0.41	
Physical activity	Yes	2	0.84 (0.71-0.99)	0	0.54	0.41	3	0.97 (0.85-1.09)	57.3	0.10	0.18	3	0.99 (0.88-1.12)	59.8	0.08	0.53
	No	4	0.93 (0.81-1.06)	0	0.63		7	0.86 (0.78-0.95)	0	0.84		7	0.96 (0.87-1.05)	0	0.57	
Energy intake	Yes	3	0.87 (0.77-0.98)	0	0.66	0.54	7	0.93 (0.85-1.01)	30.1	0.20	0.48	7	0.97 (0.90-1.05)	25.0	0.24	0.52
	No	3	0.94 (0.77-1.16)	0	0.43		3	0.87 (0.76-0.99)	0	0.78		3	1.05 (0.85-1.28)	36.5	0.21	

*n* denotes the number of risk estimates, the number of studies used is higher in some analyses as one publication reported a combined estimate for two studies (ref. no 13). <sup>1</sup> P for heterogeneity within each subgroup, <sup>2</sup> P for heterogeneity between subgroups with meta-regression analysis, <sup>3</sup> P for heterogeneity between premenopausal and postmenopausal women (excluding studies with mixed menopausal status)

Figure 1. Flow-chart of study selection

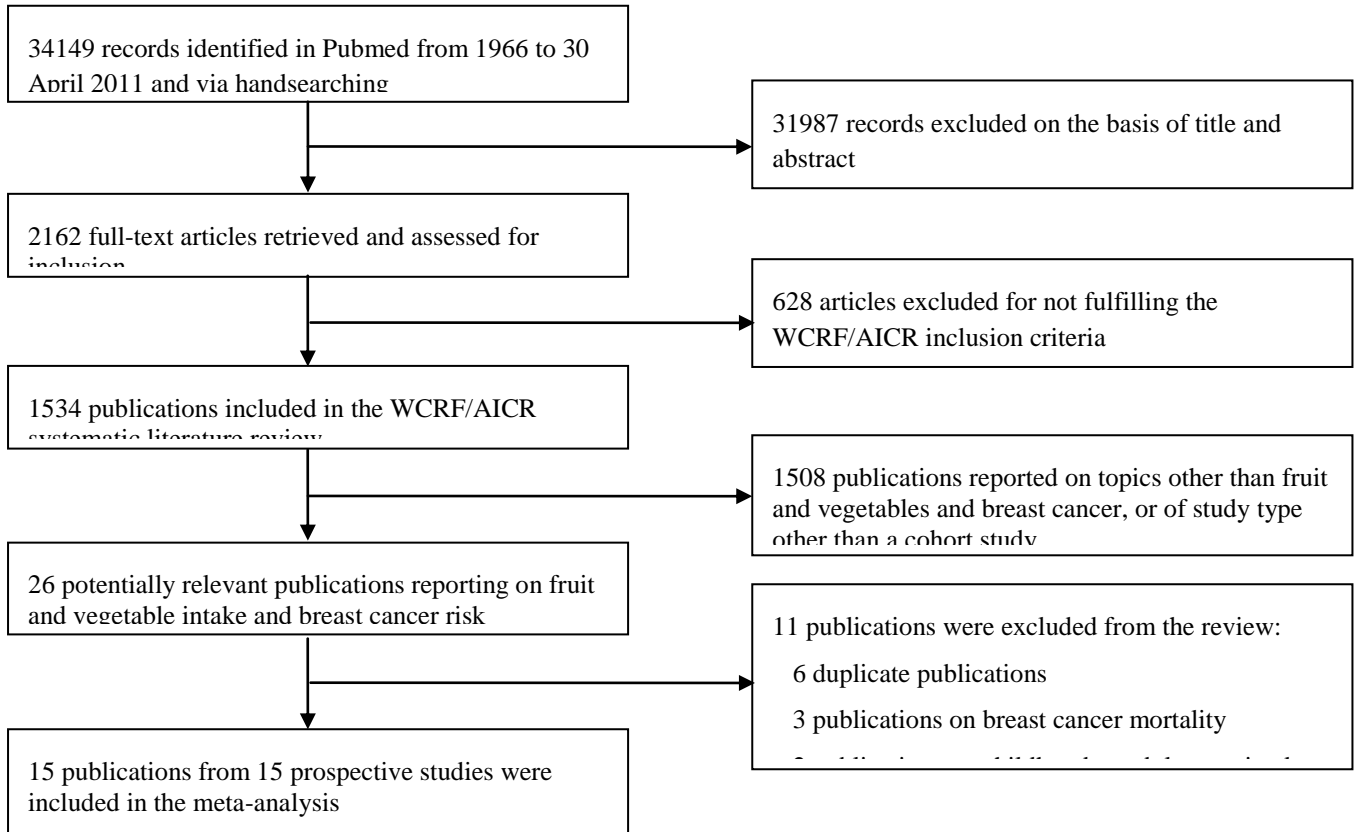
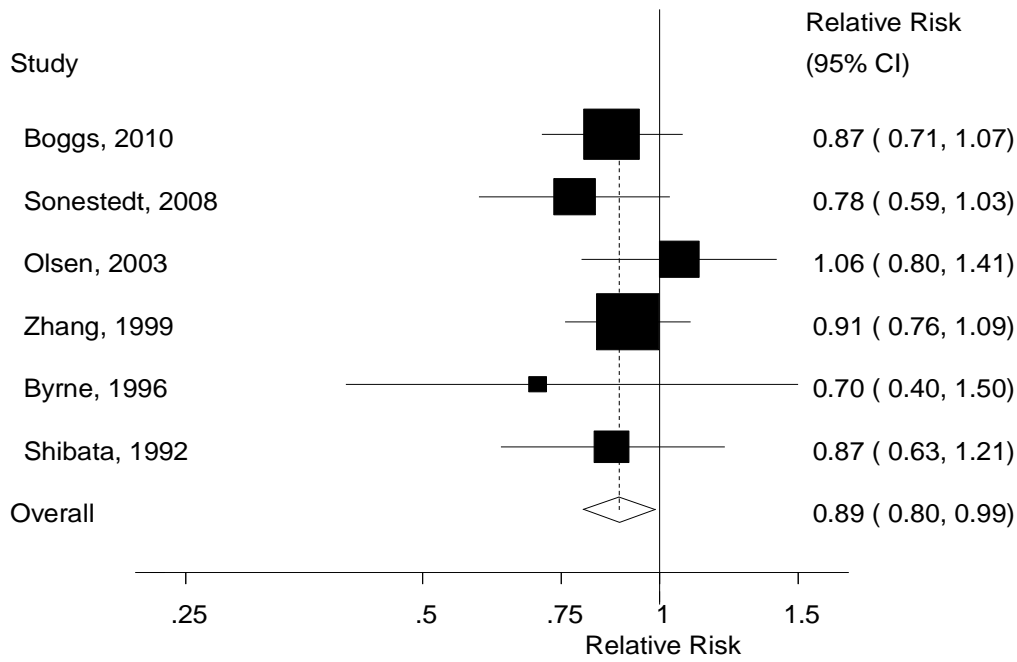


Figure 2. Fruits and vegetables and breast cancer

**A**

## Fruits and vegetables, high vs. low intake

**B**

## Fruits and vegetables, dose-response per 200 g/d

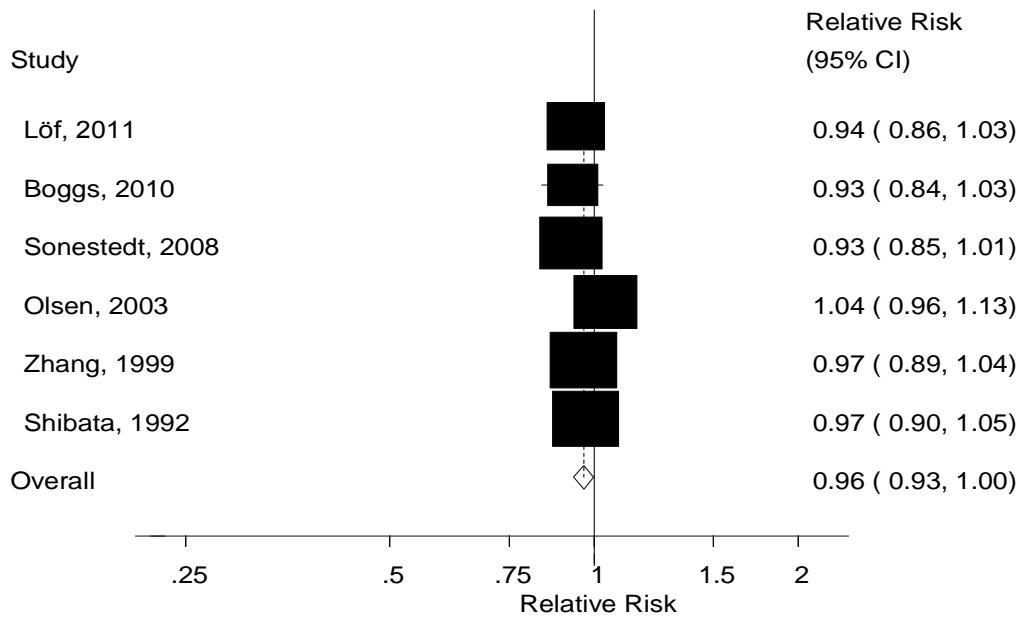


Figure 3. Fruits, vegetables and breast cancer, nonlinear dose-response

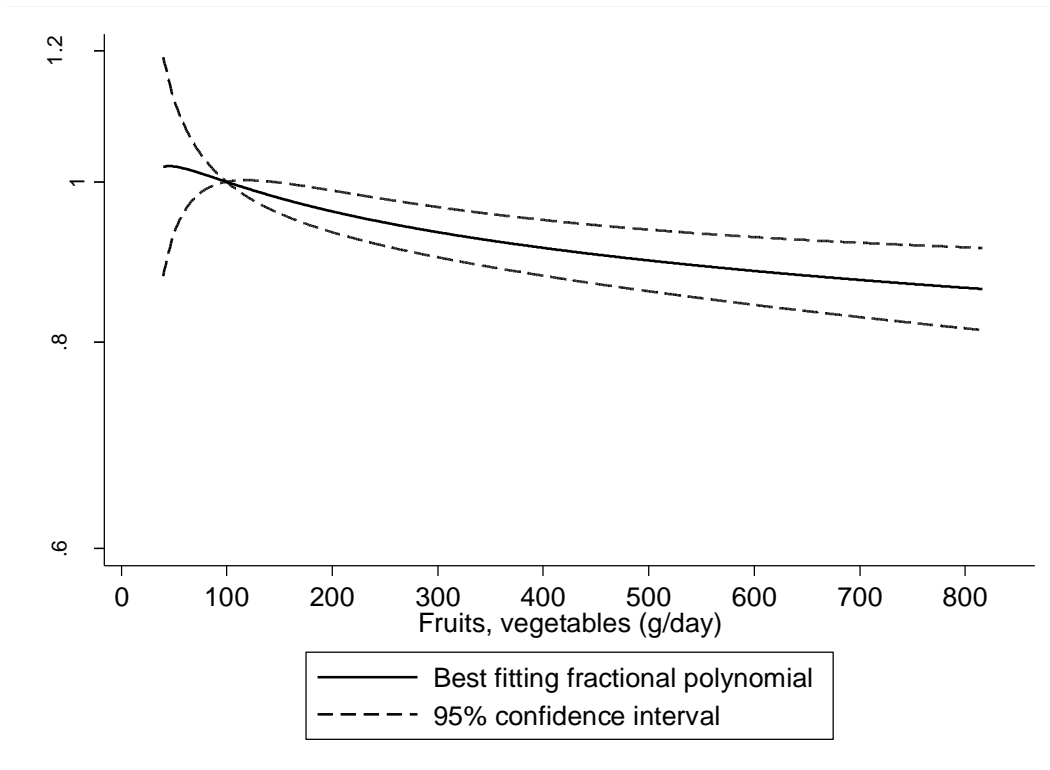




Figure 4. Fruits and breast cancer

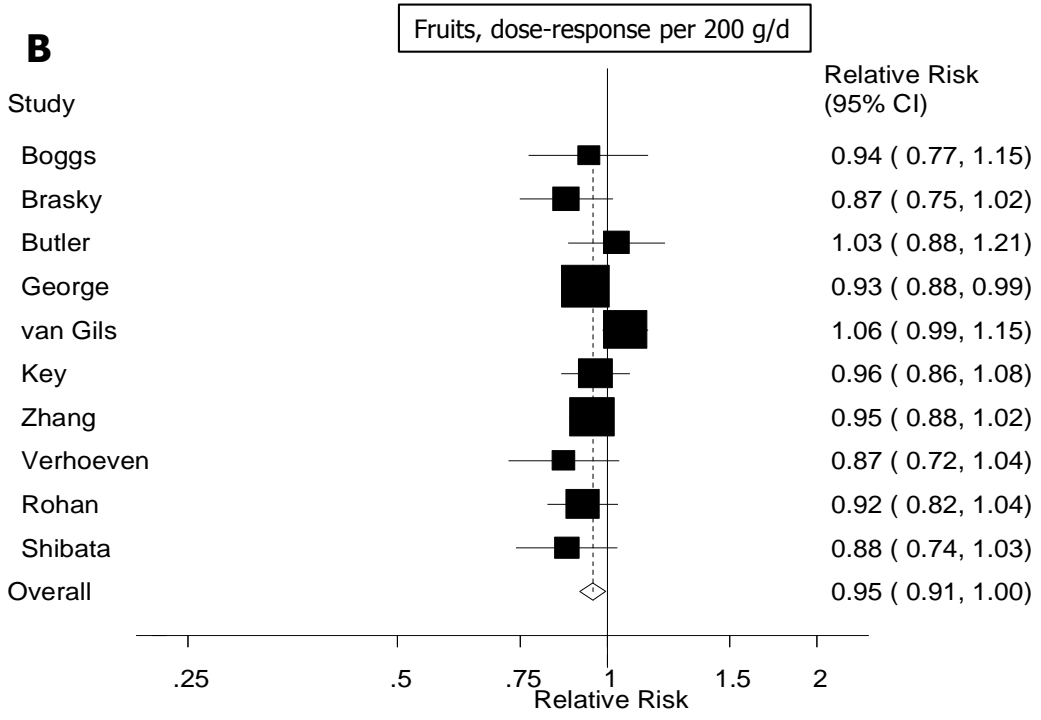
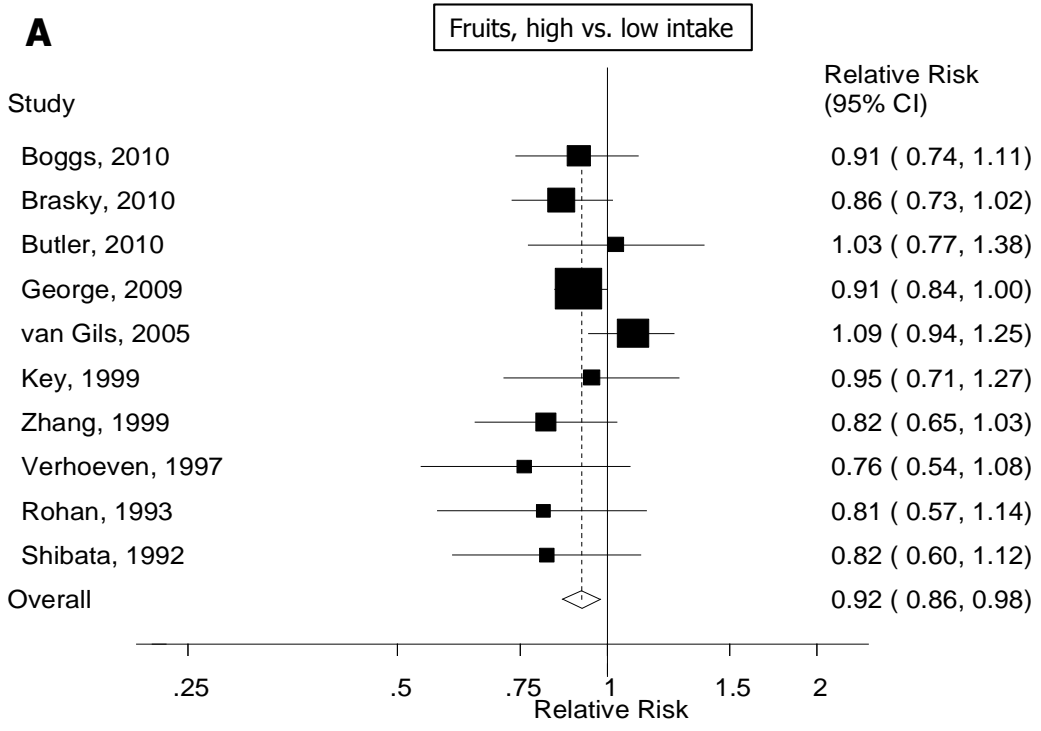


Figure 5. Fruits and vegetables and breast cancer, nonlinear dose-response analysis

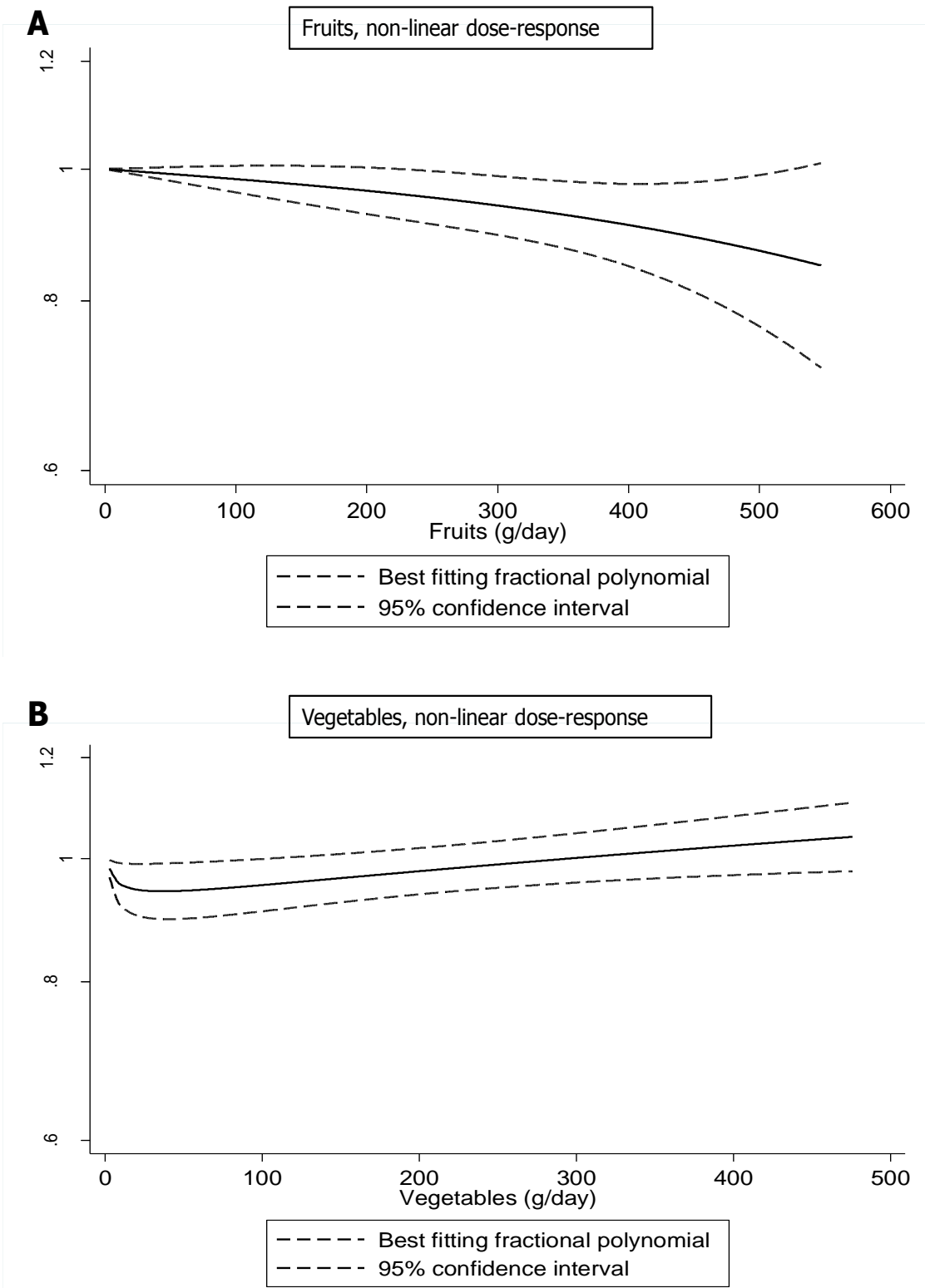


Figure 6. Vegetables and breast cancer

