

Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies.

Citation for published version (APA):

Smith-Warner, S. A., Spiegelman, D., Yaun, S., Adami, H., Beeson, W. L., van den Brandt, P. A., ... Hunter, D. J. (2001). Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. *JAMA-Journal of the American Medical Association*, 285, 769-776. <https://doi.org/10.1001/jama.285.6.769>

Document status and date:

Published: 01/01/2001

DOI:

[10.1001/jama.285.6.769](https://doi.org/10.1001/jama.285.6.769)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Download date: 04 Dec. 2019

Intake of Fruits and Vegetables and Risk of Breast Cancer

A Pooled Analysis of Cohort Studies

Stephanie A. Smith-Warner, PhD

Donna Spiegelman, ScD

Shiaw-Shyuan Yaun, MPH

Hans-Olov Adami, MD

W. Lawrence Beeson, DrPH

Piet A. van den Brandt, PhD

Aaron R. Folsom, MD

Gary E. Fraser, MB, ChB

Jo L. Freudenheim, PhD

R. Alexandra Goldbohm, PhD

Saxon Graham, PhD

Anthony B. Miller, MB, BCh

John D. Potter, MB, BS

Thomas E. Rohan, MB, BS

Frank E. Speizer, MD

Paolo Toniolo, MD

Walter C. Willett, MD

Alicja Wolk, DSc

Anne Zeleniuch-Jacquotte, MD

David J. Hunter, MB, BS

THE ASSOCIATION BETWEEN FRUIT and vegetable consumption and breast cancer risk has been examined in more than 25 case-control studies, but relatively few cohort studies.¹ A recent summary of 19 case-control and 3 cohort studies concluded that elevated fruit and vegetable consumption probably reduces breast cancer risk. Approximately half

For editorial comment see p 799.

Context Some epidemiologic studies suggest that elevated fruit and vegetable consumption is associated with a reduced risk of breast cancer. However, most have been case-control studies in which recall and selection bias may influence the results. Additionally, publication bias may have influenced the literature on associations for specific fruit and vegetable subgroups.

Objective To examine the association between breast cancer and total and specific fruit and vegetable group intakes using standardized exposure definitions.

Data Sources/Study Selection Eight prospective studies that had at least 200 incident breast cancer cases, assessed usual dietary intake, and completed a validation study of the diet assessment method or a closely related instrument were included in these analyses.

Data Extraction Using the primary data from each of the studies, we calculated study-specific relative risks (RRs) that were combined using a random-effects model.

Data Synthesis The studies included 7377 incident invasive breast cancer cases occurring among 351825 women whose diet was analyzed at baseline. For comparisons of the highest vs lowest quartiles of intake, weak, nonsignificant associations were observed for total fruits (pooled multivariate RR, 0.93; 95% confidence interval [CI], 0.86-1.00; *P* for trend=.08), total vegetables (RR, 0.96; 95% CI, 0.89-1.04; *P* for trend=.54), and total fruits and vegetables (RR, 0.93; 95% CI, 0.86-1.00; *P* for trend=.12). No additional benefit was apparent in comparisons of the highest and lowest deciles of intake. No associations were observed for green leafy vegetables, 8 botanical groups, and 17 specific fruits and vegetables.

Conclusion These results suggest that fruit and vegetable consumption during adulthood is not significantly associated with reduced breast cancer risk.

JAMA. 2001;285:769-776

www.jama.com

of the reported associations for all types of fruit and vegetable groups combined showed at least a 25% reduction in breast cancer risk, whereas few associations showed more than a 50% elevation in risk.² A meta-analysis of 14 case-control and 3 cohort studies reported that breast cancer risk was reduced by 25% for vegetables (relative risk [RR], 0.75; 95% confidence interval [CI], 0.66-0.85) and by 6% for fruits (RR, 0.94; 95% CI, 0.79-1.11) for comparisons of high vs low consumption.³

Besides the 2 main groups, total fruits and total vegetables, associations for specific food groups or individual foods have been reported sporadically and the associations that have been reported may be subject to publication bias. To gain a better understanding of how total and specific fruit and vegetable

Author Affiliations are listed at the end of this article.

Corresponding Author and Reprints: Stephanie A. Smith-Warner, PhD, Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115.

intakes are associated with breast cancer risk, we examined these relationships in the Pooling Project of Prospective Studies of Diet and Cancer (referred to as the Pooling Project) that was established to evaluate associations between dietary factors and cancer risk using a standardized approach. Using the primary data from each of the cohort studies, we standardized exposure categories and covariate definitions across studies, controlled for other dietary and nondietary variables, and evaluated potential effect modification of dietary variables by nondietary risk factors.

METHODS

The Pooling Project has been described previously.^{4,5} The following inclusion criteria were formulated: (1) a published prospective study with at least 200 incident breast cancer cases; (2) assessment of usual dietary intake; and (3) a validation study of the diet assessment method or a closely related instrument. Eight studies⁶⁻¹³ were identified that met these criteria (TABLE 1). The Nurses' Health Study was divided into 2 studies because it had repeated assessments of dietary intake and a longer follow-up period than the other studies. The 1980-1986 follow-up period is referred to as Nurses' Health Study (a) and the 1986-1996 follow-up period is referred to as Nurses' Health Study (b). Following the underlying theory of survival data, blocks of person-time in dif-

ferent periods are statistically independent, regardless of the extent that they are derived from the same people,¹⁴ so pooling the estimates from these 2 periods is equivalent to using a single period but takes advantage of the enhanced exposure assessment in 1986 compared with 1980.

Dietary Assessment

Diet was measured at baseline in each study using a food frequency questionnaire designed for that particular study. The number of fruit and vegetable questions ranged from 9 in the Sweden Mammography Cohort to 54 in the Nurses' Health Study (b). Intake data were obtained for the foods listed on the food frequency questionnaire. Missing responses for items were coded as never consumed. To take into account the varying portion sizes among participants within some cohorts and between study populations, the food intake data were analyzed as grams consumed per day. For the Iowa Women's Health Study, Nurses' Health Study (a), and Nurses' Health Study (b), the frequency data for each food item were converted to grams per day using standard gram weights¹⁵ for the serving sizes listed on the questionnaire. For the Adventist Health Study and New York State Cohort, serving sizes were not mentioned on the food frequency questionnaire; thus, the most common serving size specified on the question-

naires in the other cohorts in the Pooling Project was used to estimate the portion consumed.

We examined fruits without juice (referred to as fruits); fruit juice; fruits and fruit juice (total fruits); vegetables and vegetable juice (total vegetables); and fruits, vegetables, and juice (total fruits and vegetables). In addition, several fruit and vegetable groups were evaluated based on botanical taxonomy.¹⁶ These groups were examined as a potential method of identifying groups of fruits and vegetables that may be rich sources of bioactive phytochemicals for which adequate food composition data are not available. We could not examine associations with the Liliaceae family because garlic, onions, and leeks were asked about on the questionnaires in only 2 studies. Associations also were examined for individual fruits and vegetables for which intake was assessed in at least 5 studies. The studies that were included in the analyses of the botanical groups and individual foods varied based on whether the relevant food(s) was included on their food frequency questionnaires. Potatoes and mature beans were not included in the total vegetable or total fruit and vegetable groups because of their high starch and protein content, respectively, compared with other fruits and vegetables.¹⁷ However, they were included in estimates of the relevant botanically defined groups.

Table 1. Characteristics of the Cohort Studies Included in the Pooled Analysis of Fruit and Vegetable Intake and Breast Cancer*

Study	Years of Follow-up	Baseline Cohort, No.	Age Range at Baseline, y	No. of Cases†	Total Fruits		Total Vegetables	
					No. of Questions	Median Intake, g/d	No. of Questions	Median Intake, g/d
Adventist Health Study ⁶	1976-1982	15 172	28-90	160	7	355	6	162
Canadian National Breast Screening Study ⁷	1982-1987	56 837	40-59	419	6	327	15	226
Iowa Women's Health Study ⁸	1986-1995	34 406	55-69	1130	15	342	31	196
Netherlands Cohort Study ⁹	1986-1992	62 412	55-69	937	12	206	25	164
New York State Cohort ¹⁰	1980-1987	18 475	50-93	367	8	297	23	189
New York University Women's Health Study ¹¹	1985-1994	14 006	34-65	385	11	293	17	198
Nurses' Health Study (a) ¹²	1980-1986	89 046	34-59	1023	6	284	13	155
Nurses' Health Study (b) ¹²	1986-1996	68 817	40-65	1638	21	336	33	262
Sweden Mammography Cohort ¹³	1987-1997	61 471	40-76	1318	4	164	5	77

*The total number of women in the baseline cohort is 351 825 and the total number of cases is 7377. As a result of additional exclusion criteria specifically applied for the Pooling Project analyses (see "Statistical Methods" for details) and expanded follow-up in some studies, the baseline cohort size and number of cases included in these analyses may differ from original study-specific publications.

†Cases indicate women diagnosed with invasive breast cancer.

Statistical Methods

For each data set, after applying the exclusion criteria used by that study, we excluded participants if they reported energy intakes greater or less than 3 SDs from the study-specific log-transformed mean energy intake of the baseline population or reported a history of cancer (except nonmelanoma skin cancer) at baseline.

To reduce computational burden with little loss of statistical efficiency,¹⁸ the Adventist Health Study, Iowa Women's Health Study, New York State Cohort, New York University Women's Health Study, Nurses' Health Study (a), Nurses' Health Study (b), and Sweden Mammography Cohort were each analyzed as nested case-control studies. For each participant diagnosed as having invasive breast cancer, 10 controls were randomly selected from the subset of participants who had the same year of birth and who were alive, were not known to have migrated from the study area, and had not been diagnosed as having breast cancer before the year in which the case was diagnosed. A nested case-control design also was used in the Canadian National Breast Screening Study; the investigators of that study selected 2 controls for each case.⁷ The Nether-

lands Cohort Study used a case-cohort design.¹⁹

For the nested case-control studies, incidence rate ratios were estimated by conditional logistic regression using SAS PROC PHREG²⁰; for the Netherlands Cohort Study, Epicure software was used.²¹ The RRs were adjusted for several breast cancer risk factors (TABLE 2). An indicator variable for missing responses for measured covariates within a study was created when applicable. Two-sided 95% CIs were calculated. We used the random-effects model developed by DerSimonian and Laird²² to combine the log RRs; the study-specific RRs were weighted by the inverse of their variance. We tested for heterogeneity among studies using the asymptotic DerSimonian and Laird Q statistic.²²

We analyzed the effects of fruits, fruit juice, total fruits (corresponding to fruits plus fruit juice), total vegetables, and total fruits and vegetables as continuous variables (increment of 100 g/d) and as quartiles. Study-specific quartiles were assigned based on the distributions of the control populations for the nested case-control data sets and the subcohort in the Netherlands Cohort Study. To calculate the *P* for trend across quartiles, participants were assigned the median value

of their quartile of intake and this variable was entered as a continuous term in the conditional logistic regression model. Intakes of botanical groups and individual foods were modelled as continuous variables (increment of 100 g/d).

Effect Modification

We evaluated whether menopausal status at follow-up modified the association between breast cancer risk and each food group or individual food. Because most studies collected information at baseline only, we assigned menopausal status at follow-up in each study to women who were premenopausal at baseline using an algorithm based on an analysis of 42531 Nurses' Health Study participants who were premenopausal in 1976 and remained premenopausal or had natural menopause by 1992 (see Smith-Warner et al⁵ for more details). Breast cancer cases and their age-matched controls whose age at follow-up was 51 years or younger were considered to be premenopausal, between 51 and 55 years were considered as having an uncertain menopausal status, and 55 years or older were considered to be postmenopausal. For these analyses, the Iowa Women's Health Study, New York State Cohort, and Neth-

Table 2. Study-Specific and Pooled Multivariate Relative Risks of Breast Cancer by Categories of Fruit and Vegetable Consumption*

Study‡	Relative Risk (95% Confidence Interval) for 100 g/d Intake Increment†				
	Total Fruits	Fruits	Fruit Juice	Total Vegetables	Total Fruits and Vegetables
Adventist Health Study	0.97 (0.87-1.08)	0.97 (0.85-1.11)	0.92 (0.78-1.10)	1.10 (0.88-1.38)	0.99 (0.91-1.09)
Canadian National Breast Screening Study	0.98 (0.92-1.05)	0.95 (0.87-1.04)	1.03 (0.92-1.16)	0.98 (0.89-1.07)	0.98 (0.94-1.03)
Iowa Women's Health Study	1.01 (0.98-1.04)	1.02 (0.98-1.06)	1.00 (0.96-1.05)	0.98 (0.93-1.03)	1.00 (0.98-1.02)
Netherlands Cohort Study	0.97 (0.91-1.04)	0.98 (0.91-1.05)	0.94 (0.79-1.12)	0.90 (0.81-1.00)	0.96 (0.91-1.01)
New York State Cohort	1.01 (0.94-1.08)	1.02 (0.94-1.11)	0.96 (0.82-1.14)	1.04 (0.93-1.15)	1.01 (0.96-1.06)
New York University Women's Health Study	1.00 (0.95-1.05)	0.98 (0.90-1.07)	1.00 (0.94-1.07)	0.97 (0.90-1.04)	0.99 (0.95-1.03)
Nurses' Health Study (a)	0.98 (0.95-1.02)	0.98 (0.93-1.02)	0.99 (0.94-1.04)	1.01 (0.95-1.07)	0.99 (0.96-1.02)
Nurses' Health Study (b)	0.98 (0.95-1.01)	0.97 (0.94-1.01)	0.98 (0.95-1.02)	1.01 (0.98-1.05)	0.99 (0.97-1.01)
Sweden Mammography Cohort	0.99 (0.94-1.03)	0.97 (0.92-1.02)	1.02 (0.94-1.12)	1.01 (0.93-1.11)	0.99 (0.96-1.03)
Pooled	0.99 (0.98-1.00)	0.99 (0.97-1.00)	0.99 (0.97-1.02)	1.00 (0.97-1.02)	0.99 (0.98-1.00)
<i>P</i> value					
Pooled relative risk	.14	.13	.54	.67	.18
Test for heterogeneity	.90	.77	.96	.50	.92

*Incident rate ratios were estimated using conditional logistic regression and were adjusted for age at menarche (≤ 11 , 12, 13, 14, ≥ 15 years), interaction between parity (0, 1-2, ≥ 3) and age at birth of first child (≤ 20 , 21-25, 26-30, ≥ 30 years), oral contraceptive use (ever, never), history of benign breast disease (no, yes), menopausal status at follow-up (premenopausal, postmenopausal, uncertain), postmenopausal hormone use (ever, never), family history of breast cancer (no, yes), smoking status (ever, never), education ($<$ high school graduation, high school graduation, $>$ high school graduation), body mass index (weight in kilograms divided by the square of the height in meters; continuous), body mass index-menopausal status interaction, height (< 1.60 , 1.60 to < 1.65 , 1.65 to < 1.70 , 1.70 to < 1.75 , ≥ 1.75 m), alcohol intake (0, < 15 , ≥ 15 g/d), and energy intake (continuous).

†Approximate weights for common servings of specific fruits and vegetables are provided in Table 6.

‡We calculated the study-specific relative risks.

erlands Cohort Study were excluded because these studies only included postmenopausal women. Participants with uncertain menopausal status also were excluded from these analyses.

We also examined whether associations with total fruit, total vegetable, and total fruit and vegetable intakes and breast cancer risk were modified by baseline measures of family history of breast cancer, age at menarche, parity, age at first birth, oral contraceptive use, hormone replacement therapy use, history of benign breast disease, body mass index (<21, 21 to <23, 23 to <25, 25 to <29, ≥29 kg/m²), height, smoking, education, total fat consumption (quintiles), and alcohol consumption. The potential effect modifiers were categorized using the same groups as specified in Table 2, unless otherwise noted. For each factor of interest, a cross-product term of the ordinal score for the level of each factor and intake of a specific food group or food expressed as a continuous variable was included in the multivariate model. Participants with missing values of the factor of interest were excluded from these analyses. The pooled *P* value for the test for effect modification was obtained using squared Wald statistics by pooling the study-specific interaction coefficients and dividing by the square of the SE of the pooled interaction term, and referring the resulting statistics to a χ^2 distribution with 1 *df*.

RESULTS

Reported fruit and vegetable intakes differed across studies and were posi-

tively correlated with the number of fruit and vegetable questions on the food frequency questionnaires (Spearman correlation coefficients comparing intakes with the number of questions were 0.41 for fruits and 0.70 for vegetables). Reported total fruit consumption was highest in the Adventist Health Study and total vegetable consumption was highest in the Nurses' Health Study (b) (Table 1).

Fruit, fruit juice, total fruit (fruit plus fruit juice), total vegetable, and total fruit and vegetable intakes were not associated with breast cancer risk when modeled as continuous variables (Table 2). These results were not substantially different from those obtained from models not including the additional covariates (results not shown). Despite the differences in the number of items included on the food frequency questionnaires and the absolute intakes across studies, no association was observed for any of the 5 groups in any study except for total vegetable consumption in the Netherlands Cohort Study. Similarly, the *P* for heterogeneity exceeded .40 for each food group, indicating that there was no statistically significant heterogeneity in the results across studies. Simultaneous adjustment for total fruit and total vegetable intakes on a continuous scale (results not shown) did not materially alter the results observed when each group was included in a separate model. There was no evidence of an interaction by menopausal status at follow-up for any of these groups (TABLE 3). Similar asso-

ciations were observed for total fruits, total vegetables, and total fruits and vegetables for postmenopausal breast cancer diagnosed prior to age 62 years compared with cancers diagnosed at 62 years and older (results not shown).

When fruit and vegetable intakes were modeled as quartiles, the RRs comparing the highest vs lowest quartiles for fruit, fruit juice, total fruit, total vegetable, and total fruit and vegetable intakes were compatible with a reduced risk; however, none of the associations was statistically significant (TABLE 4). In these analyses, reported median total fruit and vegetable intakes for quartile 1 ranged from 110 g/d in the Sweden Mammography Cohort to 331 g/d in the Nurses' Health Study (b) and for quartile 4 ranged from 462 g/d in the Sweden Mammography Cohort to 1007 g/d in the Nurses' Health Study (b).

To investigate whether there was an effect of very high fruit and vegetable consumption, we categorized total fruit, total vegetable, and total fruit and vegetable intakes into deciles. The RRs for the uppermost vs lowermost deciles of intake were 0.97 (95% CI, 0.87-1.10) for total fruits, 0.91 (95% CI, 0.81-1.02) for total vegetables, and 0.96 (95% CI, 0.83-1.10) for total fruits and vegetables. Additional adjustment for total fat consumption or saturated, mono-unsaturated, and polyunsaturated fat intakes separately did not materially change the continuous, quartile, or decile results for total fruit, total vegetable, and total fruit and vegetable intakes; however, the RRs for the

Table 3. Pooled Multivariate Relative Risks of Breast Cancer by Menopausal Status and Categories of Fruit and Vegetable Consumption*

	Premenopausal (n = 1052)†		Postmenopausal (n = 5447)†		<i>P</i> Value for Interaction by Menopausal Status‡
	RR (95% CI) for 100 g/d	<i>P</i> Value for Heterogeneity	RR (95% CI) for 100 g/d	<i>P</i> Value for Heterogeneity	
Total fruits	0.98 (0.94-1.02)	.83	0.99 (0.98-1.01)	.89	.80
Fruits	0.95 (0.90-1.00)	.95	1.00 (0.97-1.02)	.69	.53
Fruit juice	1.00 (0.95-1.06)	.91	0.99 (0.97-1.02)	.99	.85
Total vegetables	0.99 (0.93-1.06)	.34	1.00 (0.97-1.02)	.31	.54
Total fruits and vegetables	0.99 (0.96-1.02)	.78	1.00 (0.98-1.01)	.85	.57

*RR indicates relative risk; CI, confidence interval. Menopausal status at follow-up was assigned using an algorithm (see "Methods" for details). See asterisk footnote for Table 2, which describes how relative risks were adjusted. For both premenopausal and postmenopausal breast cancer, menopausal status and the body mass index–menopausal status interaction terms are not included in the model. For premenopausal breast cancer, postmenopausal hormone use also is not included.

†The values designate the number of cases.

‡The *P* value for effect modification by menopausal status was calculated using data for only those studies including premenopausal and postmenopausal women at baseline. The Netherlands Cohort Study, Iowa Women's Health Study, and New York State Cohort were excluded from these analyses.

Table 4. Pooled Multivariate Relative Risks of Breast Cancer According to Quartiles of Fruit and Vegetable Consumption*

	Pooled Relative Risk (95% Confidence Interval)				P Value	
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Heterogeneity for Quartile 4	Trend
Total fruits	1.00	0.94 (0.87-1.01)	0.92 (0.86-0.99)	0.93 (0.86-1.00)	.94	.08
Fruits	1.00	0.98 (0.90-1.07)	0.95 (0.88-1.02)	0.93 (0.84-1.02)	.15	.08
Fruit juice	1.00	0.96 (0.87-1.06)	1.00 (0.92-1.08)	0.93 (0.86-1.00)	.64	.27
Total vegetables	1.00	0.99 (0.90-1.08)	0.97 (0.90-1.05)	0.96 (0.89-1.04)	.73	.54
Total fruits and vegetables	1.00	0.94 (0.88-1.01)	0.92 (0.86-0.99)	0.93 (0.86-1.00)	.99	.12

*See asterisk footnote for Table 2, which describes how relative risks were adjusted.

highest vs lowest quartile of total fruit and total fruit and vegetable consumption were marginally significant ($P = .04$) in the analyses that controlled for total fat intake. For these 3 groups, excluding the 1125 cases diagnosed during the first year of follow-up did not substantially change the continuous results, but did attenuate the quartile and decile results (results not shown).

Green leafy vegetable consumption (ie, spinach, lettuce, mustard/collard greens, kale) was not associated with breast cancer risk (RR, 0.99 for a 100-g/d increment, 95% CI, 0.92-1.06). The Rosaceae family was the only botanical group for which an inverse association was suggested (TABLE 5). Intakes of Compositae, Cruciferae, Cucurbitaceae, Leguminosae, Rutaceae, Solanaceae, and Umbelliferae were not associated with breast cancer risk. Likewise, none of the specific fruits or vegetables examined was significantly associated with breast cancer risk (TABLE 6). Menopausal status at follow-up did not modify the associations for green leafy vegetables, the botanical groups, or the specific fruits and vegetables evaluated (results not shown).

We evaluated whether associations for total fruit, total vegetable, and total fruit and vegetable intakes were modified by several breast cancer risk factors. The only significant pooled interactions occurred for height and total fruit intakes, for oral contraceptive use and total fruit intakes, and for oral contraceptive use and total fruit and vegetable consumption. The RR for a 100-g/d increment of total fruit consumption was 1.01 (95% CI, 0.99-1.04) for women with heights less than 160 cm and 0.96

Table 5. Pooled Multivariate Relative Risks of Breast Cancer by Consumption of Botanically Defined Fruit and Vegetable Groups*

Botanical Group	Example Foods	Relative Risk (95% Confidence Interval)	P Value for Heterogeneity
Compositae	Lettuce, endive	0.93 (0.84-1.02)†	.83
Cruciferae	Broccoli, cabbage	0.96 (0.87-1.06)‡	.95
Cucurbitaceae	Melons, squash	1.03 (0.88-1.21)§	.02
Leguminosae	Beans, peas	0.97 (0.87-1.08)	.36
Rosaceae	Apples, peaches	0.97 (0.94-1.00)‡	.72
Rutaceae	Grapefruits, oranges	0.99 (0.97-1.01)	.98
Solanaceae	Potatoes, tomatoes	1.02 (0.99-1.05)	.75
Umbelliferae	Carrots, celery	0.97 (0.87-1.09)‡	.46

*The values are based on a 100-g/d intake increment. See asterisk footnote for Table 2, which describes how relative risks were adjusted.

†The Nurses' Health Study (a) was not included in this analysis.

‡The Adventist Health Study was not included in this analysis.

§The Adventist Health Study, Canadian National Breast Screening Study, and Sweden Mammography Cohort were not included in this analysis.

(95% CI, 0.88-1.04) for women with heights of 175 cm or more; however, the relationship was not monotonic across the 5 height categories (P for interaction = .01). For the analyses evaluating whether oral contraceptive use modified the association with total fruit consumption, the RR for a 100-g/d increment of total fruit consumption was 0.97 (95% CI, 0.95-0.99) for participants who had never used oral contraceptives and 1.01 (95% CI, 0.97-1.04) for participants who reported ever using oral contraceptives (P for interaction = .05). Likewise, the RR for a 100-g/d increment of total fruit and vegetable consumption was 0.98 (95% CI, 0.97-1.00) for participants who had never used oral contraceptives and 1.01 (95% CI, 0.99-1.02) for participants who reported ever using oral contraceptives (P for interaction = .02).

COMMENT

These results suggest that fruit and vegetable consumption is not associated

with breast cancer risk when analyzed as total fruits and vegetables, fruits, fruit juice, total fruits, total vegetables, green leafy vegetables, 8 botanically defined fruit and vegetable groups, or 17 specific fruits and vegetables. Our results are similar to those of the 2 cohort studies not included in the Pooling Project, which reported weak, nonsignificant associations for various fruit and vegetable groups.^{23,24} However, a recent summary² of associations between several fruit and vegetable groups and breast cancer risk from 19 case-control and 3 cohort studies was more suggestive of an inverse association than our results. Overall, of the 70 risk estimates reported in the summary, 53% of the estimates showed at least a 25% reduction in breast cancer risk for the highest vs lowest consumers; whereas only 4% of the associations showed a 50% or more elevation in risk. The evidence was more consistent for vegetables than fruits. Identifying whether specific types of fruits and vegetables

vs overall exposure to fruits and vegetables have more cancer preventive potential is difficult because of the multitude of fruit and vegetable categories that have been reported. Besides the total fruit and total vegetable groups, few fruit and vegetable food groups have been reported consistently and reviews of published results are likely to be subject to publication bias.^{1,2} Furthermore, different analytic approaches have been used across studies even when the same exposures have been examined, which makes summarizing the data difficult. In contrast, in the Pooling Project, common food group and covariate definitions were applied across studies, uniform comparisons were made, and summary estimates were generated for those comparisons. Another potential explanation for the discrepancy could be related to differences in study design. The ma-

majority of studies in the summaries of the published literature were case-control studies, which are susceptible to recall and selection bias. Our analyses used data from prospective cohort studies that are less susceptible to these biases. Further clarification of the association between fruit and vegetable consumption and breast cancer risk may be forthcoming from ongoing diet intervention trials.

One of the advantages of the Pooling Project is the large sample size and, therefore, the enhanced statistical power to examine potential interactions with dietary factors. Several studies have evaluated whether the association between fruit and vegetable consumption is modified by menopausal status^{7,12,25-32} or by age group.³²⁻³⁴ Although 3 studies have suggested that the association with fruit and vegetable consumption is stronger for pre-

menopausal compared with postmenopausal breast cancer,^{12,31,34} most studies have found no evidence of an interaction by menopausal status.^{7,25-30,32,33} Like these studies, we also found no evidence of an interaction by menopausal status for any of the fruit and vegetable groups examined; however, we had limited power to evaluate associations in premenopausal women. Of the remaining interactions tested, only 3 were statistically significant and these were probably due to chance as they were not hypothesized a priori.

The number of fruit and vegetable questions included on the food frequency questionnaires varied over 4-fold across the studies. As reported previously,³⁵ reported fruit and vegetable servings increased with the number of fruit and vegetable items on the questionnaires. As a result, differences in estimates of absolute fruit and vegetable consumption across the studies in the Pooling Project may be due to differences in questionnaire design, as well as differences in true intakes. Therefore, we did not calculate risk estimates for categories of intakes that were defined using identical absolute cut points across the individual studies. Instead, we formed study-specific quartiles and pooled the RRs for each quartile. This type of analysis would reduce our ability to detect an association if breast cancer risk was lower only above a threshold of intake, and if only a subset of the studies had a substantial number of women consuming above this threshold. However, we observed little evidence that the risk estimates for comparisons of the highest vs lowest quartiles, or even deciles, of intakes was different among the studies. Furthermore, for most groupings, a slight reduction in risk was evident for the second compared with the lowest quartile, with little additional reduction in risk in comparisons of the third or fourth quartiles with the lowest quartile. This again suggests that while very low intakes may be adversely associated with breast cancer risk, very high intakes are not likely to be associated with a large reduction in risk.

Table 6. Pooled Multivariate Relative Risks of Breast Cancer for Specific Fruits and Vegetables*

Foods	Portion Size (Weight, g)†	Relative Risk (95% Confidence Interval)	P Value for Heterogeneity
Fruits			
Apples, pears	1 (138)	0.97 (0.93-1.01)‡	.54
Bananas	1 (114)	1.00 (0.93-1.08)‡	.30
Oranges, tangerines	1 (121)	0.98 (0.92-1.05)‡§##††	.94
Peaches, apricots, plums, nectarines	1 (87)	1.00 (0.91-1.09)‡ ††	.59
Vegetables			
Broccoli	1/2 cup (78)	0.86 (0.72-1.02)‡ ††	>.99
Brussels sprouts	1/2 cup (30)	0.67 (0.35-1.27)‡##*††	.12
Cabbage	1/2 cup (75)	1.05 (0.85-1.29)‡§**	.97
Carrots	1/2 cup (78)	0.95 (0.81-1.12)‡††	.70
Corn	1/2 cup (82)	1.25 (0.99-1.58)‡ ¶††	>.99
Lettuce, salad	1 cup (56)	0.93 (0.84-1.02)**	.83
Peas, lima beans	1/2 cup (80)	1.03 (0.78-1.37)‡ ##††	.26
Potatoes			
Total		1.03 (0.98-1.08)‡	.50
Baked, boiled, or mashed	1 (202)	1.02 (0.97-1.08)‡¶	.30
Fried	10 pieces (50)	1.00 (0.76-1.33)‡¶	.90
Spinach	1/2 cup cooked	0.61 (0.33-1.15)‡§***††	.02
String beans	1/2 cup (62)	0.85 (0.66-1.09)‡¶##††	.25
Tomatoes	1 (123)	1.04 (0.96-1.12)##**	.31

*The values are based on a 100-g/d intake increment. See asterisk footnote for Table 2, which describes how relative risks were adjusted.

†Based on Pennington, 1998.¹⁷

‡The Adventist Health Study was not included in the analysis.

§The Canadian National Breast Screening Study was not included in the analysis.

||The Netherlands Cohort Study was not included in the analysis.

¶The New York State Cohort was not included in the analysis.

#The New York University Women's Health Study was not included in the analysis.

**The Nurses' Health Study (a) was not included in the analysis.

††The Sweden Mammography Cohort was not included in the analysis.

We could only analyze most fruit and vegetable subgroups and individual foods as continuous variables, rather than as quartiles, because intakes within a study tended to be described in a limited number of discrete categories. Another limitation due to differences in questionnaire design is that the number of studies included in the fruit and vegetable subgroup analyses varied depending on whether the foods comprising a particular subgroup were asked on a study's questionnaire. Consequently, the power to examine associations for some subgroups and specific foods is more limited compared with that for analyses of the main fruit and vegetable groups.

In conclusion, our results suggest that fruit and vegetable consumption during adulthood is not significantly associated with breast cancer risk. Breast cancer risk was only 3% to 9% lower in women in the highest decile of fruit or vegetable consumption compared with the lowest decile. We did not identify any fruit and vegetable subgroups or specific fruits or vegetables that had stronger and statistically significant associations with breast cancer risk compared with the associations observed for total fruit and total vegetable consumption. Although fruits and vegetables may offer protection against other types of cancer² and heart disease,^{36,37} other types of interventions are needed to reduce the risk of breast cancer.

Author Affiliations: Departments of Nutrition (Drs Smith-Warner and Willett and Ms Yaun), Epidemiology (Drs Spiegelman, Willett, and Hunter), Biostatistics (Dr Spiegelman), and Environmental Health (Dr Speizer), Harvard School of Public Health, Harvard Center for Cancer Prevention (Drs Willett and Hunter), Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (Drs Speizer, Willett, and Hunter), Boston, Mass; Department of Medical Epidemiology, Karolinska Institutet, Stockholm, Sweden (Drs Adami and Wolk); Center for Health Research, Loma Linda University School of Medicine, Loma Linda, Calif (Drs Beeson and Fraser); Department of Epidemiology, Maastricht University, Maastricht, the Netherlands (Dr van den Brandt); Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis (Dr Folsom); Department of Social and Preventive Medicine, State University of New York, Buffalo (Drs Freudenheim and Graham); Department of Epidemiology, TNO Nutrition and Food Research Institute, Zeist, the Netherlands (Dr Goldbohm); Division of Clinical Epidemiology, Deutsches Krebsforschungszentrum, Heidelberg, Germany (Dr Miller); Cancer Prevention Research Program, Fred

Hutchinson Cancer Research Center, Seattle, Wash (Dr Potter); Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY (Dr Rohan); Department of Obstetrics and Gynecology, New York University School of Medicine, New York, NY (Dr Toniolo); and Nelson Institute of Environmental Medicine and Kaplan Cancer Center, New York University School of Medicine, New York (Dr Zeleniuch-Jacquotte).

Author Contributions: Dr Smith-Warner participated in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and supervised conduct of the study.

Dr Spiegelman participated in study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, provided statistical expertise, obtained funding, and supervised conduct of the study.

Ms Yaun participated in acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and provided statistical expertise.

Drs Adami and Miller participated in acquisition of data, critical revision of the manuscript for important intellectual content, obtained funding, and provided administrative, technical, or material support.

Dr Beeson participated in acquisition of data, critical revision of the manuscript for important intellectual content, and provided administrative, technical, or material support.

Dr van den Brandt participated in study concept and design, acquisition of data, analysis and interpretation of data, and provided critical revision of the manuscript for important intellectual content.

Drs Folsom, Wolk, and Zeleniuch-Jacquotte participated in acquisition of data and critical revision of the manuscript for important intellectual content.

Dr Fraser participated in acquisition of data, critical revision of the manuscript for important intellectual content, and provided statistical expertise.

Dr Freudenheim participated in analysis and interpretation of data and critical revision of the manuscript for important intellectual content.

Dr Goldbohm participated in study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and supervised conduct of the study.

Dr Graham participated in study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, obtained funding, provided administrative, technical, or material support, and supervised conduct of the study.

Dr Potter participated in study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and supervised conduct of the study.

Dr Rohan participated in study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and provided statistical expertise.

Dr Speizer participated in acquisition of data, critical revision of the manuscript for important intellectual content, obtained funding, provided administrative, technical, or material support, and supervised conduct of the study.

Dr Toniolo participated in acquisition of data, critical revision of the manuscript for important intellectual content, and supervised conduct of the study.

Dr Willett participated in study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, provided statistical expertise, obtained funding, provided administrative, technical, or material support, and supervised conduct of the study.

Dr Hunter participated in study concept and design, acquisition of data, analysis and interpretation of data,

critical revision of the manuscript for important intellectual content, provided statistical expertise, obtained funding, and supervised conduct of the study.

Funding/Support: This work was supported by research grant NIH CA55075, a grant from the Wallace Genetic Foundation Inc, and a Cancer Research Foundation of America/American Society of Preventive Oncology Research Fellowship.

Acknowledgment: We thank Karen Corsano, LMS, for computer support.

REFERENCES

1. Smith-Warner SA, Giovannucci E. Fruit and vegetable intake and cancer. In: Heber D, Blackburn GL, Go VLW, eds. *Nutritional Oncology*. Boston, Mass: Academic Press; 1999:153-183.
2. World Cancer Research Fund, American Institute for Cancer Research Expert Panel. *Food, Nutrition and the Prevention of Cancer: A Global Perspective*. Washington, DC: American Institute for Cancer Research; 1997.
3. Gandini S, Merzenich H, Robertson C, Boyle P. Meta-analysis of studies on breast cancer risk and diet: the role of fruit and vegetable consumption and the intake of associated micronutrients. *Eur J Cancer*. 2000; 36:636-646.
4. Hunter DJ, Spiegelman D, Adami H-O, et al. Cohort studies of fat intake and the risk of breast cancer: a pooled analysis. *N Engl J Med*. 1996;334:356-361.
5. Smith-Warner SA, Spiegelman D, Yaun S-S, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA*. 1998;279:535-540.
6. Mills PK, Beeson WL, Phillips RL, Fraser GE. Dietary habits and breast cancer incidence among Seventh-Day Adventists. *Cancer*. 1989;64:582-590.
7. Rohan TE, Howe GR, Friedenreich CM, Jain M, Miller AB. Dietary fiber, vitamins A, C, and E, and risk of breast cancer: a cohort study. *Cancer Causes Control*. 1993;4:29-37.
8. Kushi LH, Fee RM, Sellers TA, Zheng W, Folsom AR. Intake of vitamin A, C, and E and postmenopausal breast cancer. *Am J Epidemiol*. 1996;144:165-174.
9. Verhoeven DT, Assen N, Goldbohm RA, et al. Vitamins C and E, retinol, beta-carotene and dietary fibre in relation to breast cancer risk: a prospective cohort study. *Br J Cancer*. 1997;75:149-155.
10. Graham S, Zielezny M, Marshall J, et al. Diet in the epidemiology of postmenopausal breast cancer in the New York State Cohort. *Am J Epidemiol*. 1992; 136:1327-1337.
11. Toniolo P, Riboli E, Shore RE, Pasternack BS. Consumption of meat, animal products, protein, and fat and risk of breast cancer: a prospective cohort study in New York. *Epidemiology*. 1994;5:391-397.
12. Zhang S, Hunter DJ, Forman MR, et al. Dietary carotenoids, and vitamins A, C, and E and risk of breast cancer. *J Natl Cancer Inst*. 1999;91:547-556.
13. Wolk A, Bergström R, Hunter D, et al. A prospective study of association of monounsaturated fat and other types of fat with risk of breast cancer. *Arch Intern Med*. 1998;158:41-45.
14. Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 1998.
15. US Department of Agriculture, Agricultural Research Service. *USDA Nutrient Database for Standard Reference, Release 11*. Washington, DC: US Dept of Agriculture, Agricultural Research Service; 1996.
16. Smith SA, Campbell DR, Elmer PJ, Martini MC, Slavin JL, Potter JD. The University of Minnesota Cancer Prevention Research Unit vegetable and fruit classification scheme (United States). *Cancer Causes Control*. 1995;6:292-302.
17. Pennington JAT. *Bowes and Church's Food Values of Portions Commonly Used*. 17th ed. New York, NY: Lippincott-Raven; 1998.

18. Langholz B, Thomas DC. Nested case-control and case-cohort methods of sampling from a cohort: a critical comparison. *Am J Epidemiol*. 1990;131:169-176.
19. Prentice RL. A case-cohort design for epidemiologic cohort studies and disease prevention trials. *Biometrika*. 1986;73:1-11.
20. SAS/STAT Software: The PHREG Procedure: Preliminary Documentation. Cary, NC: SAS Institute; 1991.
21. EPICURE User's Guide: The PEANUTS Program. Seattle, Wash: Microsoft; 1993.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
23. Shibata A, Paganini-Hill A, Ross RK, Henderson BE. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. *Br J Cancer*. 1992;66:673-679.
24. Key TJA, Thorogood M, Appleby PN, Burr ML. Dietary habits and mortality in 11,000 vegetarians and health conscious people: results of a 17 year follow up. *BMJ*. 1996;313:775-779.
25. Kato I, Miura S, Kasumi F, et al. A case-control study of breast cancer among Japanese women: with special reference to family history and reproductive and dietary factors. *Breast Cancer Res Treat*. 1992; 24:51-59.
26. Hislop TG, Coldman AJ, Elwood JM, Brauer G, Kan L. Childhood and recent eating patterns and risk of breast cancer. *Cancer Detect Prev*. 1986;9:47-58.
27. Trichopoulou A, Katsouyanni K, Stuver S, et al. Consumption of olive oil and specific food groups in relation to breast cancer risk in Greece. *J Natl Cancer Inst*. 1995;87:110-116.
28. Hirose K, Tajima K, Hamajima N, et al. A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. *Jpn J Cancer Res*. 1995;86:146-154.
29. Longnecker MP, Newcomb PA, Mittendorf R, Greenberg ER, Willett WC. Intake of carrots, spinach, and supplements containing vitamin A in relation to risk of breast cancer. *Cancer Epidemiol Biomarkers Prev*. 1997;6:887-892.
30. Katsouyanni K, Trichopoulos D, Boyle P, et al. Diet and breast cancer: a case-control study in Greece. *Intl J Cancer*. 1986;38:815-820.
31. Braga C, La Vecchia C, Negri E, Franceschi S, Parpinel M. Intake of selected foods and nutrients and breast cancer risk: an age- and menopause-specific analysis. *Nutr Cancer*. 1997;28:258-263.
32. Franceschi S, Favero A, La Vecchia C, et al. Influence of food groups and food diversity on breast cancer risk in Italy. *Intl J Cancer*. 1995;63:785-789.
33. Graham S, Marshall J, Mettlin C, Rzepka T, Nemoto T, Byers T. Diet in the epidemiology of breast cancer. *Am J Epidemiol*. 1982;116:68-75.
34. Holmberg L, Ohlander EM, Byers T, et al. Diet and breast cancer risk: results from a population-based, case-control study in Sweden. *Arch Intern Med*. 1994; 154:1805-1811.
35. Krebs-Smith SM, Heimendinger J, Subar AF, Patterson BH, Pivonka E. Using food frequency questionnaires to estimate fruit and vegetable intake: association between the number of questions and total intakes. *J Nutr Educ*. 1995;27:80-85.
36. Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. *Intl J Epidemiol*. 1997; 26:1-13.
37. Law MR, Morris JK. By how much does fruit and vegetable consumption reduce the risk of ischaemic heart disease? *Eur J Clin Nutr*. 1998;52:549-556.

Remember, then, that it [science] is the guide of action; that the truth which it arrives at is not that which we can ideally contemplate without error, but that which we may act upon without fear; and you cannot fail to see that scientific thought is not an accompaniment or condition of human progress, but human progress itself.

—William Kingdon Clifford (1845-1879)