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# Fruits and Vegetables and Ovarian Cancer Risk in a Pooled Analysis of 12 Cohort Studies

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## Abstract

**Because fruits and vegetables are rich in bioactive compounds with potential cancer-preventive actions, increased consumption may reduce the risk of ovarian cancer. Evidence on the association between fruit and vegetable intake and ovarian cancer risk has not been consistent. We analyzed and pooled the primary data from 12 prospective studies in North America and Europe. Fruit and vegetable intake was measured at baseline in each study using a validated food-frequency questionnaire. To summarize the association between fruit and vegetable intake and ovarian cancer, study-specific relative risks (RR) were estimated using the Cox proportional hazards model, and then combined using a random-effects model. Among 560,441 women, 2,130 cases of invasive epithelial ovarian cancer occurred during a maximum follow-up of 7 to 22 years across studies. Total fruit intake was not associated with ovarian cancer risk—the pooled multivariate RR for the highest versus the lowest quartile of intake was 1.06 [95% confidence interval (95% CI), 0.92-1.21; *P* value, test for trend = 0.73; *P* value, test for between-studies heterogeneity = 0.74]. Similarly, results for total vegetable intake indicated no significant association (pooled multivariate RR, 0.90; 95% CI, 0.78-1.04, for the highest versus the lowest quartile; *P* value, test for trend = 0.06; *P* value, test for between-studies heterogeneity = 0.31). Intakes of botanically defined fruit and vegetable groups and individual fruits and vegetables were also not associated with ovarian cancer risk. Associations for total fruits and vegetables were similar for different histologic types. These results suggest that fruit and vegetable consumption in adulthood has no important association with the risk of ovarian cancer.** (Cancer Epidemiol Biomarkers Prev 2005; 14(9):2160–7)

## Introduction

Among women worldwide, ovarian cancer is the sixth most frequently diagnosed cancer and the seventh most common cause of cancer death (1). Survival from ovarian cancer is poor as the disease is usually diagnosed at advanced stages (2-4). Identifying preventive factors offers an approach to reducing the morbidity and mortality due to the disease. Reproductive factors, such as increasing parity, oral contraceptive use, increasing duration of lactation, and tubal ligation, have been most consistently associated with a decreased risk of ovarian cancer (5-7). However, most of these factors are not easily modifiable in middle life.

Fruits and vegetables are rich in potential cancer-preventive agents (8) and, thus, their consumption may be protective for ovarian cancer. A collaborative evaluation by the IARC of the published literature through early 2003 concluded from the eight previously published case-control and cohort studies that vegetable intake possibly reduces the risk of ovarian cancer (9). This conclusion has been supported by some (10, 11), although not all (12, 13), recent studies. On the other hand, the inconsistent findings among the six studies of fruit intake and ovarian cancer precluded a conclusion by the IARC (9) and an association with fruit intake has not been observed in subsequent studies (10-14). Similarly, results for specific fruit and vegetable groups, such as legumes or cruciferous vegetables, and individual foods, when reported, have not been consistent (12, 13, 15-21).

Only four of the previous studies of fruits and vegetables and ovarian cancer used a prospective design (11, 13, 22, 23) where information on diet and other risk factors was obtained before the development of ovarian cancer and, thus, was less subject to differential misclassification than in case-control designs. The inverse associations observed in the prospective

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studies were not as strong as those seen in the case-control studies and only one was statistically significant (11); however, statistical power in the cohort studies may have been limited due to the relatively small numbers of ovarian cancer cases in these studies, ranging from 139 to 301. To maximize the statistical power to detect small but potentially important associations, we examined intakes of total and specific fruits and vegetables in relation to the risk of ovarian cancer in the Pooling Project of Prospective Studies of Diet and Cancer (Pooling Project). Using the primary data from 12 cohort studies (11, 13, 22-31), including the four previously published cohort studies (11, 13, 22, 23), we used standardized definitions of fruit and vegetable intakes and covariate categories across studies and conducted multivariate analyses for the risk of invasive epithelial ovarian cancer overall, by specific histologic types and among particular population subgroups.

## Materials and Methods

**Study Population.** The Pooling Project has been described previously (32). The 12 prospective studies (11, 13, 22-31) included in the ovarian cancer analyses were conducted in North America and Europe and met the following predefined criteria: at least 50 incident invasive epithelial ovarian cancer cases; an assessment of usual diet; and a validation study of the diet assessment method or a closely related instrument. The cases occurring and person-time experienced during follow-up in the Nurses' Health Study was considered as two different cohorts [1980-1986, Nurses' Health Study (a); 1986-2000, Nurses' Health Study (b)] so that the more detailed dietary assessment conducted in 1986 could be utilized. According to the underlying theory of survival analysis, blocks of person-time in different time periods are asymptotically uncorrelated, regardless of the extent to which they are derived from the same people (33). Thus, pooling estimates from these two time periods is a statistically valid alternative to using a single time period.

For each study, the exclusion criteria used by that study were applied, after which we excluded participants who reported a history of any cancer (except nonmelanoma skin cancer) at baseline, had had a bilateral oophorectomy at baseline, or reported energy intakes >3 SDs from the study-specific $\log_e$-transformed mean energy intake of the baseline population. Exclusions based on bilateral oophorectomy were not made in the Adventist Health Study and the New York State Cohort because this information was not collected in these studies.

Incident invasive epithelial ovarian cancer cases were identified in each study using follow-up questionnaires with subsequent medical record review (23, 30, 31), linkage with a cancer registry (11, 13, 22, 26, 28), or both (24, 25, 27, 29). Mortality registries served as an additional source of incident cases in some studies (22, 23, 25, 27-31). Nonepithelial and borderline ovarian cancers were not identified in all studies and, thus, were not included in these analyses. Invasive epithelial ovarian cancers were further classified by histology according to the International Classification of Diseases for Oncology morphology codes (34) or the histologic classification provided by the original study investigators.

**Dietary Assessment.** A self-administered food-frequency questionnaire was used at baseline in each study to assess usual consumption of specific food items during the past year. The number of fruit and vegetable questionnaire items ranged from 9 in the Swedish Mammography Cohort to 54 in the Nurses' Health Study (b). The food intake data were analyzed in units of grams per day (g/d) to account for study-specific differences in serving sizes. We examined three main food groups: fruits, vegetables, and juices (total fruits and vegetables); fruits and fruit juices (total fruits); and vegetables and vegetable juices (total vegetables). Food group intakes were calculated by summing the intakes of specific foods included in that food group. Potatoes and mature beans were not classified as vegetables because of their high starch and protein content, respectively, compared with other vegetables. We also examined fruits and vegetables grouped according to botanical taxonomy (35) to evaluate potentially rich sources of particular bioactive compounds. In addition, we examined individual fruits and vegetables for which intake was assessed in at least seven studies.

The validity of the food-frequency questionnaires used in each cohort study in the Pooling Project or closely related instruments have been evaluated (36-42). Given that the validity of total fruits and total vegetables was evaluated only in the Netherlands Cohort Study (Spearman correlation coefficient = 0.60 for total fruits and 0.38 for total vegetables; ref. 40) and the Cancer Prevention Study II Nutrition Cohort (Pearson correlation coefficient = 0.62 for total fruits and 0.52 for total vegetables; ref. 37), we were not able to correct for measurement error in dietary assessment. For dietary vitamin C intake, a nutrient concentrated in fruits and vegetables (43), the Spearman or energy-adjusted deattenuated Pearson correlation coefficients between intakes from the food-frequency questionnaire and the reference method ranged from 0.3 to 0.8 across the studies. In the Nurses' Health Study, the median correlation for intakes of individual fruits and vegetables estimated from the food-frequency questionnaire and multiple dietary records was ~0.3 (44).

**Statistical Analysis.** For each study, relative risks (RR) and their associated 95% confidence intervals (95% CI) were calculated by fitting the Cox proportional hazards model (45) using SAS PROC PHREG (46), except for the Canadian National Breast Screening Study and Netherlands Cohort Study, which were analyzed as case-cohort studies (47) using Epicure software (48). Person-years of follow-up were calculated from the date of the baseline questionnaire until the date of ovarian cancer diagnosis, death, or end of follow-up, whichever came first. Age and calendar time were adjusted for by stratifying on age at baseline (in years) and the year the baseline questionnaire was returned. Multivariate models included terms for total energy intake, smoking habits, physical activity, body mass index, parity, age at menarche, oral contraceptive use, menopausal status, and postmenopausal hormone use. These variables were assessed at baseline in each study by self-administered questionnaires and categorized in a consistent manner across studies in our analysis. In the multivariate analyses, an indicator variable for missing responses was created for covariates, if applicable. The proportion of missing values generally was <8% in each study that measured the covariate. Summary RRs were calculated by combining study-specific $\log_e$ RRs, weighted by the inverse of their variance, using a random-effects model (49). The presence of heterogeneity between studies was tested for using the $Q$ statistic (49, 50). All statistical tests were two sided.

The associations between ovarian cancer and total fruits, total vegetables, and total fruits and vegetables were analyzed as continuous measures as well as according to quartiles and deciles of consumption. Study-specific quartiles and deciles were assigned based on the distributions in the subcohort in the case-cohort studies and in the baseline cohort for the remaining studies. We also analyzed associations for these food groups using cut points based on identical absolute intakes across studies. To calculate the $P$ value for the test for trend across categories of intake, participants were assigned the median value of their category and this variable was entered as a continuous term in the regression model.

Meta-regression analyses (51) were used to evaluate whether the number of fruit and vegetable questions included on each food-frequency questionnaire and the median follow-up time

in each study may have contributed to variation in RRs between studies. We also evaluated whether the associations for total fruits, total vegetables, and total fruits and vegetables varied by levels of previously identified risk factors for ovarian cancer. To do this, we first calculated the pooled RRs stratified by levels of these risk factors and then tested the null hypothesis of no effect modification using a Wald test. In addition, we examined associations separately for the main histologic types of epithelial ovarian cancer (serous, endometrioid, and mucinous) and tested for differences in the RRs by histologic type using a Wald test (52).

## Results

During a maximum follow-up of 7 to 22 years across the 12 studies included in this analysis, 2,130 epithelial ovarian cancer cases occurred among 560,441 women (Table 1). Total fruit and vegetable intake was lowest among women in the Swedish Mammography Cohort (mean = 252 g/d) and greatest among women in the Nurses' Health Study (b) (mean = 600 g/d). Intakes were positively correlated with the number of fruit and vegetable questions on the food-frequency questionnaires (Spearman correlation coefficients were 0.38 for total fruits and 0.78 for total vegetables).

Overall, total fruit, total vegetable, and total fruit and vegetable intakes were not associated with ovarian cancer risk (Table 2). Pooled multivariate and age-adjusted RRs were very similar for all three food groups. Simultaneous inclusion of total fruits and total vegetables in the same model did not appreciably change the RRs compared with analysis of each group separately (results not shown). RRs for total fruits not including fruit juices were similar with RRs for total fruits (results not shown). Across the studies, a statistically significant inverse association comparing the highest versus the lowest quartiles of intake was observed only in the Adventist Health Study for total vegetables (Fig. 1). Similarly, a statistically significant test for trend was observed only in the Adventist Health Study for analyses of total vegetables.

The tests for heterogeneity between studies in the highest quartile were not statistically significant for any food group (Table 2). Because intakes of fruits and vegetables were positively correlated with the number of fruit and vegetable questions, we examined whether study-specific RRs varied with the number of questions using meta-regression and observed no evidence of heterogeneity due to the varying number of questions across studies ($P$ = 0.26 for total fruits, 0.32 for total vegetables, and 0.43 for total fruits and vegetables). Because follow-up times varied across studies, we also examined whether study-specific RRs varied with median follow-up time and found no evidence of heterogeneity due to differences in follow-up time ($P$ = 0.38 for total fruits, 0.41 for total vegetables, and 0.34 for total fruits and vegetables). Similarly, RRs did not appreciably differ by period of follow-up. The pooled multivariate RRs (95% CI) comparing the highest versus the lowest quartiles of intake were 1.11 (0.89-1.37) for total fruits and 0.88 (0.71-1.09) for total vegetables for cases that occurred within the first 5 years, and 1.03 (0.84-1.26) for total fruits and 0.93 (0.77-1.11) for total vegetables for cases that occurred ≥5 years after baseline.

RRs were not substantially changed when we excluded cases that were diagnosed within the first 2 years of follow-up (number of cases excluded = 235; results not shown). In addition, RRs did not greatly differ when we stratified by age at diagnosis ($P$ = 0.17 for total fruits and 0.36 for total vegetables for the test for interaction by age in the highest quartile). For women diagnosed with ovarian cancer before the age of 63 ($n$ = 900 cases), the pooled multivariate RRs (95% CI) comparing the highest versus the lowest quartiles of intake were 1.20 (0.97-1.47) for total fruits and 0.96 (0.78-1.19) for total vegetables, whereas for women diagnosed at ages ≥63 ($n$ = 1,229), the corresponding RRs (95%CI) were 0.98 (0.78-1.21) for total fruits and 0.84 (0.70-1.00) for total vegetables. Associations for total fruits, total vegetables, and total fruits and vegetables among women who were postmenopausal at baseline ($n$ = 1,398 cases, excludes the Nurses' Health Study II because 99% of the women were premenopausal at baseline and the New York State Cohort because information on menopausal status was not available)

**Table 1. Characteristics of the cohort studies included in the pooled analysis of fruit and vegetable intake and ovarian cancer**

| Study | Follow-up years | Baseline cohort size* | Number of cases† | Baseline age range (y) | Total fruits | | Total vegetables | |
|---|---|---|---|---|---|---|---|---|
| | | | | | No. questions | Median intake (10-90%), g/d‡ | No. questions | Median intake (10-90%), g/d‡ |
| Adventist Health Study | 1976-1988 | 18,402 | 53 | 28-90 | 7 | 355 (133-654) | 6 | 162 (74-269) |
| Breast Cancer Detection Demonstration Project | 1987-1999 | 32,885 | 142 | 40-93 | 5 | 174 (34-388) | 10 | 127 (48-273) |
| Canadian National Breast Screening Study | 1980-2000 | 56,837 | 223 | 40-59 | 6 | 311 (110-576) | 15 | 219 (101-433) |
| Cancer Prevention Study II Nutrition Cohort | 1992-2001 | 61,202 | 278 | 50-74 | 7 | 195 (52-397) | 10 | 147 (62-303) |
| Iowa Women's Health Study | 1986-2001 | 28,486 | 208 | 55-69 | 15 | 339 (131-624) | 31 | 196 (92-382) |
| The Netherlands Cohort Study | 1986-1995 | 62,412 | 208 | 55-69 | 12 | 206 (82-388) | 25 | 163 (88-293) |
| New York State Cohort | 1980-1987 | 22,550 | 77 | 50-93 | 8 | 289 (86-539) | 23 | 188 (72-364) |
| New York University Women's Health Study | 1985-1998 | 12,401 | 65 | 34-65 | 11 | 288 (93-595) | 17 | 199 (75-423) |
| Nurses' Health Study (a) | 1980-1986 | 80,195 | 120 | 34-59 | 6 | 271 (72-556) | 13 | 149 (68-290) |
| Nurses' Health Study (b) | 1986-2002 | 59,538§ | 315 | 40-65 | 21 | 327 (114-640) | 33 | 258 (129-468) |
| Nurses' Health Study II | 1991-2000 | 91,502 | 52 | 27-44 | 15 | 223 (68-508) | 28 | 206 (95-399) |
| Swedish Mammography Cohort | 1987-2004 | 61,103 | 285‖ | 40-74 | 4 | 166 (45-372) | 5 | 77 (28-158) |
| Women's Health Study | 1993-2004 | 32,466 | 104 | 45-89 | 15 | 265 (86-537) | 28 | 235 (111-449) |

*Cohort sizes after applying study-specific exclusion criteria and then excluding women with log$_e$-transformed energy intake values >3 SDs from the study-specific mean, with previous cancer diagnoses (other than nonmelanoma skin cancer) and who had previously had a bilateral oophorectomy (except in the Adventist Health Study and the New York State Cohort where this information was not collected); the Canadian National Breast Screening Study and the Netherlands Cohort Study are analyzed as case-cohort studies so their baseline cohort size does not reflect the above exclusions; total cohort size is 560,441.

†Total number of cases is 2,130.

‡The approximate weight in grams for common servings of specific fruits and vegetables are provided in Table 4.

§Nurses' Health Study (b) is not included as part of total cohort size because they are included in Nurses' Health Study (a).

‖There were two cases missing information on both total fruits and total vegetables.

**Table 2. Pooled RR (95% CI) of epithelial ovarian cancer for quartiles of fruit and vegetable intake**

| | Quartile of intake | | | | *P* value, test for trend | *P* value, test for between-studies heterogeneity in quartile 4 |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | | |
| Total fruits | | | | | | |
| No. cases | 486 | 547 | 545 | 552 | | |
| Age-adjusted | 1.00 | 1.09 (0.96-1.23) | 1.06 (0.91-1.24) | 1.06 (0.94-1.20) | 0.56 | 0.54 |
| Multivariate* | 1.00 | 1.07 (0.94-1.21) | 1.05 (0.90-1.24) | 1.06 (0.92-1.21) | 0.73 | 0.74 |
| Total vegetables | | | | | | |
| No. cases | 531 | 576 | 523 | 499 | | |
| Age-adjusted | 1.00 | 1.08 (0.96-1.22) | 0.97 (0.86-1.10) | 0.92 (0.81-1.04) | 0.09 | 0.48 |
| Multivariate* | 1.00 | 1.07 (0.95-1.21) | 0.96 (0.85-1.09) | 0.90 (0.78-1.04) | 0.06 | 0.31 |
| Total fruits and vegetables | | | | | | |
| No. cases | 498 | 564 | 541 | 527 | | |
| Age-adjusted | 1.00 | 1.10 (0.97-1.24) | 1.03 (0.91-1.17) | 1.00 (0.88-1.14) | 0.62 | 0.44 |
| Multivariate* | 1.00 | 1.09 (0.96-1.24) | 1.02 (0.90-1.16) | 0.99 (0.86-1.14) | 0.46 | 0.54 |

*Adjusted for parity (0, 1, 2, 3+), oral contraceptive use (never, ever), menopausal status and postmenopausal hormone use (premenopausal, unknown menopausal status, postmenopausal never use, postmenopausal past use, postmenopausal current use), age at menarche (<13, 13, 14+ years), body mass index (<23, 23 to <25, 25 to <30, 30+ kg/m$^2$), physical activity (low, medium, high), smoking status (never, past, current), and total energy intake (kcal/d, continuous); age in years and year of questionnaire return were included as stratification variables.

were similar to that observed among women who were premenopausal at baseline and at follow-up ($n$ = 153 cases; results not shown), where menopausal status at follow-up was determined using a previously described algorithm (53). The Adventist Health Study, Breast Cancer Detection Demonstration Project, Cancer Prevention Study II Nutrition Cohort, Iowa Women's Health Study, the Netherlands Cohort Study, New York State Cohort, and Swedish Mammography Cohort were excluded from the analyses of premenopausal women because these studies either did not include premenopausal women, had very few premenopausal cases, or did not have information on menopausal status. Results from analyses restricted to nonusers of multivitamin supplements ($n$ = 1,018 cases; the Canadian National Breast Screening Study and Swedish Mammography Cohort were excluded from these analyses because they did not have baseline supplement use data) were similar to that seen among the whole study population (results not shown).

When fruit and vegetable intakes were modeled as continuous variables, the results were consistent with the findings from the quartile analyses. For an increment in intake of 100 g/d, which is ~1 serving per day, the pooled multivariate RRs (95% CI) were 1.00 (0.97-1.02) for total fruits, 0.98 (0.94-1.01) for total vegetables, and 0.99 (0.97-1.01) for total fruits and vegetables. Similarly, when we compared the highest versus the lowest deciles of consumption (results not shown) and when fruit and vegetable intake categories were

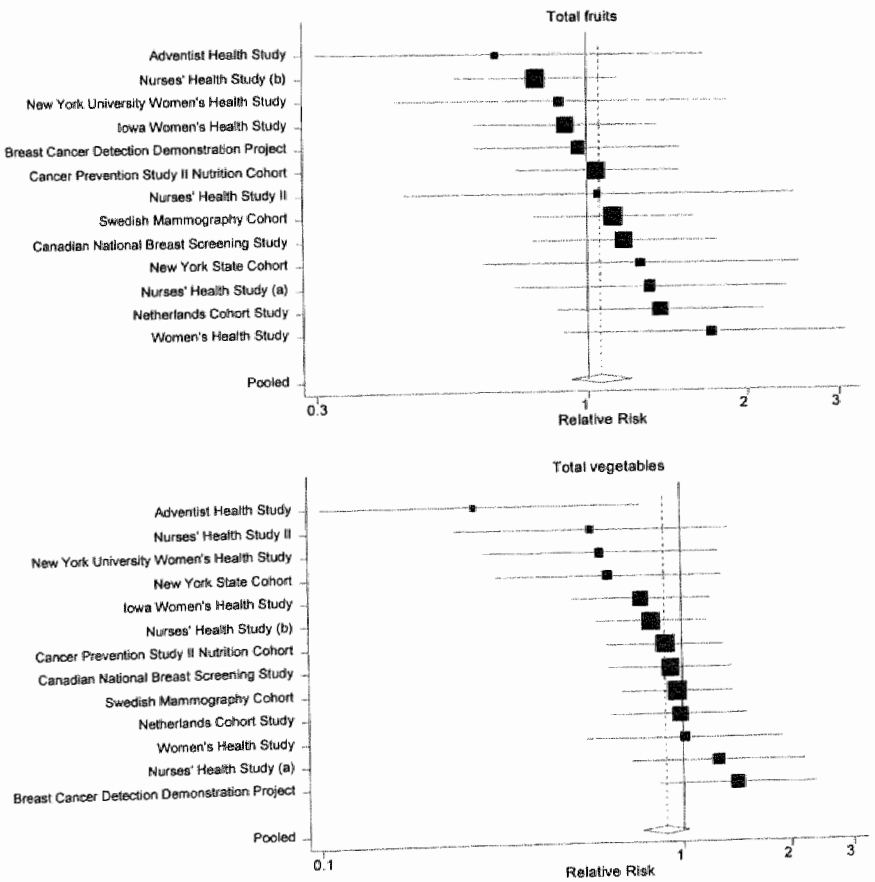


**Figure 1.** Study-specific and pooled multivariate RR and 95% CI of ovarian cancer and intake of total fruits and total vegetables, quartile 4 versus quartile 1. The black square and horizontal lines correspond to the study-specific multivariate RR and 95% CI, respectively. The area of the black square reflects the study-specific weight (inverse of the variance). The diamond represents the pooled multivariate RR and 95% CI. Multivariate model included terms as listed in footnote for Table 2.

**Table 3. Pooled RR (95% CI) of epithelial ovarian cancer for categories of intake of fruits and vegetables**

| | Category of intake | | | | | *P* value, test for trend | *P* value, test for between-studies heterogeneity in highest category |
|---|---|---|---|---|---|---|---|
| Total fruits | | | | | | | |
| Intake category (g/d) | <100 | 100-<200 | 200-<300 | 300-<400 | 400+ | | |
| Median intake (g/d) | 57.9 | 151.0 | 247.3 | 344.8 | 515.9 | | |
| No. cases | 293 | 477 | 517 | 358 | 485 | | |
| Age-adjusted | 0.96 (0.82-1.11) | 1.00 | 1.08 (0.95-1.22) | 1.00 (0.86-1.16) | 1.03 (0.89-1.19) | 0.37 | 0.56 |
| Multivariate* | 0.95 (0.81-1.10) | 1.00 | 1.07 (0.94-1.21) | 0.99 (0.85-1.15) | 1.02 (0.88-1.19) | 0.43 | 0.78 |
| Total vegetables | | | | | | | |
| Intake category (g/d) | <100 | 100-<200 | 200-<300 | 300-<400 | 400+ † | | |
| Median intake (g/d) | 68.9 | 146.5 | 241.6 | 339.4 | 481.1 | | |
| No. cases | 492 | 808 | 467 | 214 | 148 | | |
| Age-adjusted | 0.97 (0.86-1.10) | 1.00 | 0.92 (0.79-1.06) | 0.97 (0.82-1.14) | 0.92 (0.74-1.13) | 0.29 | 0.34 |
| Multivariate* | 0.98 (0.86-1.11) | 1.00 | 0.91 (0.78-1.06) | 0.96 (0.82-1.13) | 0.87 (0.71-1.07) | 0.18 | 0.51 |
| Total fruits and vegetables | | | | | | | |
| Intake category (g/d) | <200 | 200-<400 | 400-<600 | 600-<800 | 800+ | | |
| Median intake (g/d) | 143.8 | 304.6 | 489.6 | 681.5 | 958.1 | | |
| No. cases | 255 | 688 | 588 | 352 | 247 | | |
| Age-adjusted | 0.95 (0.78-1.15) | 1.00 | 0.96 (0.85-1.08) | 1.02 (0.88-1.18) | 0.99 (0.81-1.20) | 0.87 | 0.27 |
| Multivariate* | 0.95 (0.77-1.17) | 1.00 | 0.95 (0.84-1.07) | 1.00 (0.86-1.17) | 0.95 (0.79-1.15) | 0.64 | 0.41 |

*Adjusted for parity (0, 1, 2, 3+), oral contraceptive use (never, ever), menopausal status and postmenopausal hormone use (premenopausal, unknown menopausal status, postmenopausal never use, postmenopausal past use, postmenopausal current use), age at menarche (<13, 13, 14+ years), body mass index (<23, 23 to<25, 25 to<30, 30+ kg/m$^2$), physical activity (low, medium, high), smoking status (never, past, current) and total energy intake (kcal/d, continuous); age in years and year of questionnaire return were included as stratification variables.

†The Adventist Health Study and Swedish Mammography Cohort did not include any cases with vegetable intakes exceeding 400 g/d and were excluded from this category.

defined using identical absolute intake cut points (Table 3), the results for total fruits, total vegetables, and total fruits and vegetables were consistent with no association.

When we evaluated fruits and vegetables grouped according to botanical definitions (35), we found no statistically significant associations. The pooled multivariate RRs (95% CI) for a 100 g/d increment in intake were as follows: 0.86 (0.74-1.01) for *Compositae*; 0.95 (0.82-1.11) for *Cruciferae*; 1.07 (0.83-1.37) for Cucurbitaceae; 0.90 (0.75-1.09) for Leguminosae; 1.02 (0.96-1.07) for Rosaceae; 0.99 (0.95-1.03) for Rutaceae; 0.94 (0.87-1.03) for Solanacea; and 0.96 (0.77-1.18) for Umbelliferae. Statistically significant between-studies heterogeneity was observed only for Solanacea (study-specific RRs ranged from 0.22 to 1.08; *P* value for between-studies heterogeneity = 0.03). We observed a marginally significant association with the consumption of green leafy vegetables (pooled multivariate RR, 0.88; 95% CI 0.76-1.00, for a 100 g/d increment; *P* value for between-studies heterogeneity = 0.55). In the analyses of individual fruits and vegetables, there were no statistically significant associations with ovarian cancer risk observed (Table 4).

The RRs for ovarian cancer associated with the consumption of total fruits, total vegetables, and total fruits and vegetables (results not shown) were not modified by parity: ≤1 versus ≥2 (*P* value for interaction = 0.79 for total fruits, 0.30 for total vegetables, and 0.36 for total fruits and vegetables); oral contraceptive use: ever versus never (*P* value for interaction = 0.64 for total fruits, 0.43 for total vegetables, and 0.34 for total fruits and vegetables); postmenopausal hormone use among postmenopausal women: never versus past versus current use (*P* value for interaction = 0.28 for total fruits, 0.77 for total vegetables, and 0.47 for total fruits and vegetables); smoking status: never versus past versus current smoker (*P* value for interaction = 0.87 for total fruits, 0.25 for total vegetables, and 0.85 for total fruits and vegetables); or alcohol consumption: drinker versus nondrinker (*P* value for interaction = 0.68 for total fruits, 0.66 for total vegetables, and 0.64 for total fruits and vegetables). Associations for serous, endometrioid, and mucinous ovarian cancers were not significantly different from each other for total fruit, total vegetable, and total fruit and vegetable intakes (Table 5).

## Discussion

In this pooled analysis, the consumption of fruits and vegetables was not associated with the risk of invasive epithelial ovarian cancer. For total fruits, total vegetables, and total fruits and vegetables, the results were consistent whether examined according to continuous intake measures, study-specific quantiles, or categories based on identical absolute intakes. We found no statistical evidence of heterogeneity among studies in these analyses. The results did not differ appreciably among the various subgroups that were examined or by histologic type of ovarian cancer. Furthermore, analyses of botanically defined fruit and vegetable groups and individual fruits and vegetables did not reveal any associations with ovarian cancer risk.

The four previous prospective studies that have examined fruit and vegetable consumption and ovarian cancer risk are included in this pooled analysis (11, 13, 22, 23), and only a limited number of previous case-control studies have been conducted (10, 12, 14, 16, 18, 20, 21, 54, 55). The findings from these case-control studies have not strongly supported an inverse association between fruit intake and ovarian cancer (10, 12, 14, 16, 20, 21, 54, 55). Statistically significant associations have been observed in only two studies where the magnitude of the association for the comparison of the highest versus the lowest intakes were similar but in opposite directions (20, 21). In contrast, analyses of vegetable consumption have shown significant (10, 18, 20) and nonsignificant (12, 16, 54) inverse associations, with reduced risks ranging from 20% to 75% for comparisons of the highest versus the lowest intakes. Analyses of specific botanical groups and green leafy vegetables have been limited and their results have been inconsistent (12, 15-21, 55, 56). The only specific food item that has been examined in more than one study is carrots (12, 17, 19), where a statistically significant inverse association was seen in one investigation (17).

Likewise, our findings do not lend support to an inverse association with the consumption of total fruits, several botanical groups, green leafy vegetables, or the individual fruits and vegetables evaluated. However, contrary to previous studies, total vegetable consumption was also not associated with a statistically significant decreased risk in our analyses. A

statistically significant inverse association with total vegetable intake was observed only in the Adventist Health Study; however, this was based on a small number of women ($n = 53$) with ovarian cancer. Our study focused on invasive epithelial ovarian cancers, similar to most previous studies. In addition, the distribution of ovarian cancer risk factors, such as nulliparity and never use of oral contraceptives, among the Pooling Project cohorts were similar in range to that seen among past studies.

The main difference between our pooled analysis and previous case-control investigations of fruit and vegetable consumption and ovarian cancer risk is that our analyses were based on prospective cohort studies where diet was measured before the development of disease. Studies that have examined the potential for differential misclassification of fruit and vegetable intake in retrospective studies of cancer suggest that the likelihood of recall bias is generally not high except when study participants have changed their diet, particularly if the diet change was related to disease (9). Because prediagnostic abdominal pain and gastrointestinal upset have been reported in 50% to 70% of women with ovarian cancer (57-59), it is plausible that dietary habits may change before diagnosis. Thus, the stronger inverse association observed in the case-control studies compared with our study may reflect recall bias. If abdominal or gastrointestinal symptoms lead to a greater reduction in vegetable compared with fruit consumption, this may explain why the results for total fruits were not affected similarly. In addition, selection bias may have contributed to the inverse associations in previous case-control studies where participation rates among controls were not high if the controls that participated in these studies had healthier lifestyles, such as consuming more vegetables, than the underlying base population.

Potential limitations of our study include that we used only baseline dietary information, which may be subject to greater misclassification compared with diet information that utilizes data from multiple questionnaires throughout follow-up. However, given that the latency period for ovarian cancer is probably decades, the baseline diet is more likely to reflect the relevant exposure of past diet, particularly if prediagnostic changes may have occurred among cases. On the other hand, if fruit and vegetable intake before adulthood is more pertinent, as was suggested in the Nurses' Health Study (23), then our analysis of adult diet may not have appropriately captured the relevant exposure period. Furthermore, because measurement error in the assessment of fruit and vegetable intakes cannot be ruled out, it is possible that a modest but important inverse association was missed in our analysis.

To examine the association between fruit and vegetable consumption and ovarian cancer risk, we modeled intakes as continuous variables, study-specific quantiles and categories in which cut points were defined by identical absolute intakes across studies. With the study-specific quantile approach, true differences in population intakes are not taken into account, which may result in misclassification of exposure when pooling the results. On the other hand, misclassification could also occur in the analyses of absolute intake categories because intakes of fruits and vegetables may differ across studies due to differences in questionnaire design. As has been shown

**Table 4. Pooled RR (95% CI) of epithelial ovarian cancer for specific fruits and vegetables**

| Food item | No. cases | Serving size | | RR (95% CI)* | | *P* value, test for between-studies heterogeneity for multivariate RR |
|---|---|---|---|---|---|---|
| | | Quantity | Weight (g) | Age-adjusted | Multivariate† | |
| Fruits | | | | | | |
| Apples, pears, applesauce‡ | 2,066 | 1 or 1/2 cup | 138 | 1.04 (0.94-1.14) | 1.03 (0.93-1.13) | 0.77 |
| Bananas‡,§,‖ | 1,634 | 1 | 114 | 1.08 (0.92-1.26) | 1.04 (0.90-1.20) | 0.46 |
| Cantaloupe‡,¶,**,††,‡‡,§§ | 1,149 | 1/4 melon | 134 | 1.59 (0.76-3.36) | 1.55 (0.77-3.10) | 0.05 |
| Grapefruit‡,¶,‡‡,§§,‖‖ | 1,370 | 1/2 fruit | 120 | 1.01 (0.88-1.15) | 1.00 (0.87-1.15) | >0.99 |
| Oranges‡,¶,§§,‖‖ | 1,490 | 1 | 131 | 0.99 (0.84-1.16) | 0.98 (0.83-1.15) | 0.61 |
| Peaches‡,§,‖,**,§§ | 1,156 | 1 or 1/2 cup | 87 | 1.01 (0.86-1.18) | 1.00 (0.85-1.17) | 0.79 |
| Fruit juices | 2,095 | 6 oz | 190 | 0.98 (0.90-1.07) | 0.99 (0.92-1.06) | 0.42 |
| Vegetables | | | | | | |
| Broccoli‡,**,§§ | 1,581 | 1/2 cup | 78 | 0.91 (0.69-1.20) | 0.89 (0.68-1.17) | 0.04 |
| Brussels sprouts‡,§,‖,‡‡,§§,‖‖ | 1,183 | 1/2 cup | 78 | 1.08 (0.66-1.76) | 1.01 (0.61-1.67) | 0.43 |
| Cabbage‡,¶,‡‡ | 1,704 | 1/2 cup | 68 | 1.00 (0.76-1.32) | 1.01 (0.76-1.33) | 0.76 |
| Carrots‡,§,§§ | 1,645 | 1/2 cup | 57 | 1.05 (0.90-1.23) | 1.02 (0.86-1.20) | 0.41 |
| Lettuce, salad‡‡ | 1,996 | 1 cup | 56 | 0.94 (0.86-1.02) | 0.93 (0.85-1.02) | 0.58 |
| Peas, lima beans‡,§,‖,**,§§,‖‖ | 1,092 | 1/2 cup | 80 | 1.18 (0.85-1.64) | 1.17 (0.83-1.64) | 0.95 |
| String beans‡,§,‖,††,§§ | 1,289 | 1/2 cup | 68 | 0.82 (0.52-1.28) | 0.82 (0.52-1.30) | 0.02 |
| Spinach‡ | 2,049 | 1/2 cup | 73 | 1.03 (0.86-1.25) | 1.01 (0.83-1.23) | 0.61 |
| Tomatoes, tomato juice | 2,109 | 1 or 4 oz juice | 122 | 0.92 (0.79-1.08) | 0.91 (0.77-1.07) | 0.01 |
| Yams, sweet potatoes‡,¶,**,††,§§ | 1,278 | 1/2 cup | 128 | 1.06 (0.47-2.36) | 1.08 (0.48-2.42) | 0.41 |
| Mature beans and lentils | 2,111 | 1/2 cup | 131 | 0.84 (0.57-1.24) | 0.83 (0.57-1.22) | 0.49 |
| Potatoes‡,¶¶ | 2,068 | 1 or 1 cup | 202 | 0.97 (0.81-1.16) | 0.97 (0.81-1.15) | 0.66 |

*The relative risks are for a daily increment of the gram weight corresponding to ~1 serving as indicated in the table.
†Adjusted for parity (0, 1, 2, 3+), oral contraceptive use (never, ever), menopausal status and postmenopausal hormone use (premenopausal, unknown menopausal status, postmenopausal never use, postmenopausal past use, postmenopausal current use), age at menarche (<13, 13, 14+ years), body mass index (<23, 23 to<25, 25 to<30, 30+ kg/m$^2$), physical activity (low, medium, high), smoking status (never, past, current), and total energy intake (kcal/d, continuous); age in years and year of questionnaire return were included as stratification variables.
‡The Adventist Health Study was excluded.
§The Breast Cancer Detection Demonstration Project was excluded.
‖The Cancer Prevention Study II Nutrition Cohort was excluded.
¶The Canadian National Breast Screening Study was excluded.
**The Netherlands Cohort Study was excluded.
††The New York State Cohort Study was excluded.
‡‡The Nurses' Health Study (a) was excluded.
§§The Swedish Mammography Cohort was excluded.
‖‖The New York University Women's Health Study was excluded.
¶¶Potatoes, not including French fried potatoes or chips.

**Table 5. Pooled RR (95% CI) of epithelial ovarian cancer for fruit and vegetable intake by histologic type**

| Food group | RR (95% CI)* | | *P* value, test for between-studies heterogeneity for multivariate RR | *P* value, test for differences by serous, endometrioid, and mucinous histologic types† |
|---|---|---|---|---|
| | Age-adjusted | Multivariate‡ | | |
| Total fruits | | | | |
| All histologic types | 1.00 (0.98-1.03) | 1.00 (0.97-1.02) | 0.51 | |
| Serous | 1.01 (0.97-1.04) | 1.01 (0.97-1.04) | 0.67 | |
| Endometrioid§ | 1.01 (0.95-1.08) | 1.01 (0.94-1.08) | 0.79 | 0.81 |
| Mucinous‖ | 1.03 (0.92-1.14) | 1.03 (0.93-1.14) | 0.38 | |
| Total vegetables | | | | |
| All histologic types | 0.98 (0.94-1.02) | 0.98 (0.94-1.01) | 0.40 | |
| Serous | 0.98 (0.93-1.04) | 0.98 (0.91-1.05) | 0.16 | |
| Endometrioid§ | 1.03 (0.94-1.14) | 1.06 (0.96-1.18) | 0.60 | 0.16 |
| Mucinous‖ | 1.09 (0.95-1.24) | 1.10 (0.94-1.27) | 0.41 | |
| Total fruits and vegetables | | | | |
| All histologic types | 1.00 (0.98-1.02) | 0.99 (0.97-1.01) | 0.31 | |
| Serous | 1.00 (0.97-1.03) | 1.00 (0.97-1.03) | 0.18 | |
| Endometrioid§ | 1.01 (0.96-1.06) | 1.02 (0.96-1.07) | 0.73 | 0.53 |
| Mucinous‖ | 1.03 (0.95-1.11) | 1.03 (0.96-1.11) | 0.48 | |

NOTE: Adventist Health Study was not included in analyses by histologic type due to very few cases; in total, there were 2,130 cases of which there were 1,025 serous, 261 endometrioid, and 122 mucinous cases; 141 cases were missing histology information.

*Relative risks for a 100 g/d increment.

†Test based on multivariate models of only those studies included in the analyses of all 3 of serous, endometrioid and mucinous.

‡Adjusted for parity (0, 1, 2, 3+), oral contraceptive use (never, ever), menopausal status and postmenopausal hormone use (premenopausal, unknown menopausal status, postmenopausal never use, postmenopausal past use, postmenopausal current use), age at menarche (<13, 13, 14+ years), body mass index (<23, 23 to<25, 25 to<30, 30+ kg/m$^2$), physical activity (low, medium, high), smoking status (never, past, current) and total energy intake (kcal/d, continuous); age in years and year of questionnaire return were included as stratification variables.

§New York State Cohort and New York University Women's Health Study were excluded from endometrioid analyses due to very few cases.

‖Breast Cancer Detection Demonstration Project, New York State Cohort, New York University Women's Health Study, Nurses' Health Study II, and Women's Health Study were excluded from mucinous analyses due to very few cases.

previously (60), we found that the number of fruit and vegetable questionnaire items was positively correlated with intakes. Nonetheless, our results were consistent regardless of how fruit and vegetable consumption was analyzed. Because not all individual fruit and vegetable items were common to all studies, our analyses of individual foods did not always include all 12 studies; thus, our evaluation of individual fruits and vegetables was not as comprehensive as our analyses of total fruits and total vegetables. However, analyses of individual fruits and vegetables are quantitatively comparable.

Another limitation in our analysis is that incomplete control for confounding may have been present in some studies, because data on all covariates were not available for all studies. However, age-adjusted and multivariate results were not substantially different even in the studies that had complete covariate information, suggesting that confounding by these ovarian cancer risk factors was not strong. We were not able to adjust for tubal ligation, lactation duration, or family history of ovarian cancer because this information was not available for most cohorts. Ovarian cancers that are linked to family history generally occur at young ages (61). Among the cases that were included in our analyses, 12% were diagnosed at ages ≤50 years and ~5% were ≤45 years, suggesting that the potential for confounding by family history may not have been substantial.

Strengths of this study include that 12 cohorts from North America and Europe with a wide range of fruit and vegetable consumption were prospectively examined. By conducting a pooled analysis, we were able to define fruit and vegetable intakes, as well as other covariates, in a standardized manner across studies and, thus, minimize heterogeneity between studies due to differences in exposure and covariate definitions. Also, our study included over 2,000 cases of invasive epithelial ovarian cancer and, thus, had greater statistical power to analyze these associations compared with the previous case-control and individual cohort studies. The large number of cases also provided the opportunity to investigate potential differences in risk according to the main histologic types of ovarian cancer, which has not previously been examined in relation with fruit and vegetable consumption. In addition, we were able to evaluate whether associations with fruit and vegetable intake varied by levels of other ovarian cancer risk factors, which has only been examined in one other study of 1,031 cases (18). In that study, associations were generally not found to vary greatly across levels of several risk factors.

In summary, our results do not provide evidence that the consumption of fruits and vegetables during adulthood is associated with the risk of ovarian cancer. Our findings were consistent regardless of how fruit and vegetable intakes were defined and among the different subgroups of the study populations that were examined. These findings may not generalize to fruit and vegetable intakes at an earlier time in life. Nevertheless, generous fruit and vegetable consumption remains important because of benefits that have been observed for other chronic diseases, including cardiovascular disease (62, 63), obesity (64), and some other cancers (9).

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