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Fruit and vegetable consumption and breast cancer incidence: Repeated measures over 30 years of follow-up

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Abstract

We evaluated the relation of fruit and vegetable consumption, including specific fruits and vegetables, with incident breast cancer characterized by menopausal status, hormone receptor status, and molecular subtypes. Fruit and vegetable consumption, cumulatively averaged across repeated, validated questionnaires, was examined in relation to risk of invasive breast cancer among 182,145 women initially aged 27–59y in the Nurses' Health Study (NHS, 1980–2012) and NHSII (1991–2013). Cox proportional hazards regression, adjusted for known risk factors, was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), and assessed tumors by hormone receptor status and molecular subtypes. We prospectively documented 10,911 invasive breast cancer cases. Greater intake of total fruits and vegetables, especially cruciferous and yellow/orange vegetables, was associated with significantly lower breast cancer risk (>5.5 versus 2.5 servings/day HR=0.89, 95% CI=0.83–0.96; $P_{trend}=0.006$). Intake of total vegetables was especially associated with lower risk of estrogen receptor negative tumors (HR per 2 additional servings/day as a continuous variable=0.84, 95% CI=0.77–0.93; $P_{heterogeneity}=0.02$). Among molecular subtypes, higher intake of total fruits and vegetables (HR per 2 additional servings/day as a continuous variable) was most strongly associated with lower risk of human epidermal growth factor receptor 2 (HER2)-enriched (HR=0.79, 95% CI=0.67–0.93), basal-like (HR=0.84, 95% CI=0.72–0.97), and luminal A (HR=0.94, 95% CI=0.89–0.99), but not with luminal B tumors ($P_{heterogeneity}=0.03$). In conclusion, our findings support that higher intake of fruits and vegetables, and specifically cruciferous and yellow/orange vegetables, may reduce the risk of breast cancer, especially those that are more likely to be aggressive tumors.

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No potential conflicts of interest were disclosed.

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Introduction

Worldwide, breast cancer is the most common cancer in women and the second leading cause of cancer death, with variation in incidence around the world.¹ Breast cancer is a heterogeneous disease representing multiple tumor types with specific pathological features and biological behaviors, different responses to therapeutics, and variable survival.² Fruits and vegetables are rich in potentially anti-carcinogenic nutrients including fiber, vitamins C and E, carotenoids, and other bioactive substances,^{3–5} and higher intakes have been hypothesized to reduce cancer risk. Despite inconsistencies across individual studies of breast cancer risk,^{6–20} inverse associations with intake of vegetables, but not fruits, were observed in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.¹⁹ In contrast, higher intake of fruits was associated with lower risk of breast cancer in a meta-analysis including 15 prospective cohort studies.²¹ Evidence of associations by estrogen receptor (ER) status and molecular subtypes of breast cancer is sparse, with inconsistent results.^{10, 12, 15, 17, 19, 20, 22} In a large pooled analysis of 20 studies²⁰ as well as the EPIC cohort,¹⁹ total vegetable consumption was particularly associated with ER-negative, but not ER-positive tumors. In our prior analysis in the Nurses' Health Study (NHS), healthier dietary patterns were suggestively associated with a lower risk of human epidermal growth factor receptor 2 (HER2)-enriched breast cancer, and this appeared to be due to high consumption of fruit.²² Given that fruits and vegetables vary widely in nutrients, examination of specific fruit and vegetable subgroups is also important; however, little is known about the relationship with breast cancer.^{11, 15, 17, 20, 23} In some studies, inverse associations have been observed with ER-negative tumors, including apples/pears, peaches/nectarines, strawberries, and lettuce in the pooled study,²⁰ and berries and peaches/nectarines in the NHS.²³ In a previous publication among younger women in the NHSII, we observed a suggested but non-significant inverse association between pre-menopausal total fruit consumption and incident breast cancer.²⁴ Although prior assessments were suggestive, they were limited in power, particularly for specific fruits and vegetables, as well as aggressive subtypes of breast cancer.

Pooling data from the NHS and NHSII cohorts allowed us to evaluate the relation of fruit and vegetable consumption, including specific fruits and vegetables, with incident breast cancer in a large group of women with up to nine assessments of diet and a large number of breast cancer cases characterized by menopausal status, hormone receptor status, and molecular subtypes.

SUBJECTS AND METHODS

Study Population

As ongoing prospective cohort studies of US female registered nurses, the NHS started in 1976 with 121,700 women aged 30–55 years, and the NHSII began in 1989 with 116,429 women aged 25–42 years. Participants first completed semi-quantitative food frequency questionnaires (SFFQ) beginning in 1980 (NHS, n=98,047) or 1991 (NHSII, n=97,813). Participants were excluded for implausible total energy intake (<600 or >3500 kcal/day), cancer diagnosis (except non-melanoma skin cancer) before the baseline questionnaire, or having left blank >10 items (NHS) or >70 items (NHSII) on the baseline SFFQ, or left blank

all fruit and/or vegetable items, leaving 88,301 women in the NHS and 93,844 women in the NHSII for analysis. The cumulative follow-up rates exceed 95% in both cohorts. This study was approved by the Institutional Review Board at Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health. Consent was implied by the return of completed questionnaires.

Dietary Assessment

In the NHS, participants completed a 61-item SFFQ in 1980, followed by SFFQs expanded to 116–130 items in 1984, 1986, and every four years thereafter. In the NHSII, in 1991 and every four years thereafter, dietary intake was measured with a ~130-item SFFQ (questionnaires available at <http://www.nurseshealthstudy.org/participants/questionnaires>). Questions included the frequency of consumption for a specified serving of each food item in nine categories from “never or less than once/month” through “6 or more times/day.” The validity of the SFFQ has been documented by comparison with more detailed methods^{25–27} and biomarkers of intake.²⁶ Intake of fruits and vegetables in these cohorts has been associated with lower risk of other diseases, including diabetes²⁸ and coronary heart disease.²⁹

In the 1980 SFFQ, we calculated total fruit consumption by summing the consumption of five individual fruits including apples/pears, oranges, peaches/plums/apricots, bananas, and other fruits. Total vegetable consumption was calculated by summing the consumption of ten individual vegetable items including green beans, broccoli, cabbage/cauliflower/Brussels sprouts, carrots, corn, spinach/other greens, peas/lima beans, winter squash, sweet potatoes, and tomatoes/tomato juice. Ten individual fruits were asked consistently since 1984 in the NHS and 1991 in the NHSII: grapes/raisins, peaches/plums/apricots, prunes, bananas, cantaloupe/melon, apples/pears, oranges, grapefruits, strawberries, and blueberries (Appendix Table 1). We calculated total fruit intake (not including juices) by summing the intake amounts of all individual fruits that were asked consistently or sporadically during follow-up. Individual vegetables have also been reported in the Appendix Table 1. We consistently asked about most of them in SFFQs, except mushroom, onion, beet, alfalfa sprouts, and sauerkraut, which we inquired about sporadically. Individual items were summed to create total vegetables (not including potatoes) (Appendix Table 1). Total fruit juice intake was calculated by summing the intake levels of juices reported in SFFQs. We did not inquire about type or brand of fruit juices in the SFFQs. Five subgroups of vegetables included green leafy vegetables, yellow/orange vegetables, tomatoes, cruciferous vegetables, and other vegetables. Fruits and vegetables were also grouped by the content of vitamin C (40 mg/100g), α -carotene (3000 mcg/100g), β -carotene (3000 mcg/100g), and lutein (10 mg/100g).^{29–32}

Identification of Breast Cancer Cases and Molecular Subtypes of Breast Cancer

Cases of breast cancer were identified on biennial follow-up questionnaires; the National Death Index was searched for nonresponders. Participants (or next of kin) were asked for permission to obtain relevant hospital records and pathology reports. Because accuracy was high for self-reporting (99%), breast cancer diagnoses (n=883) without medical records were included in the analysis. We collected breast cancer tissue for approximately 70% of cases

and constructed tumor microarrays (TMA) to assess tumor characteristics by immunohistochemistry; details are described elsewhere.^{22, 33, 34} Immunohistochemical staining, with results read manually by a study pathologist, was performed for ER, progesterone receptor (PR), HER2, cytokeratin 5/6 (CK5/6), and epidermal growth factor receptor (EGFR). ER, PR, and HER2 status for cases without TMAs was extracted from medical records. Molecular subtypes were defined according to ER, PR, HER2, CK5/6, and EGFR status in combination with histologic grade: Luminal A (ER-positive and/or PR-positive, and HER2-negative with grade 1 or 2); luminal B (ER-positive, and/or PR-positive, and HER2-positive; or ER-positive, and/or PR-positive, and HER2-negative with grade 3); HER2-enriched (ER-negative, PR-negative, and HER2-positive); basal-like (ER-negative, PR-negative, HER2-negative, and CK5/6-positive and/or EGFR-positive); unclassified tumors lacked expression for all five markers.

Assessment of other variables

Data on potential breast cancer risk factors were obtained from the biennial questionnaires, including age, weight, history of benign breast disease, family history of breast cancer, smoking, ages at menarche, menopause, and first birth, parity, menopausal status, postmenopausal hormone use, oral contraceptive use, alcohol consumption, and physical activity, updated with the most recent information, if available. Body mass index (BMI) at age 18 and height were obtained from the baseline questionnaire. Weight change since age 18 was calculated at each questionnaire cycle.

Statistical Analysis

Data from the NHS and NHSII were pooled. Participants contributed person-years from the date of return of the baseline SFFQ (NHS, 1980; NHSII, 1991) to the date of any cancer diagnosis except non-melanoma skin cancer, death, or end of follow-up (NHS, June 1, 2012; NHSII, June 1, 2013), whichever occurred first. To minimize within-person variation and reduce measurement error in exposures, we calculated the cumulative average of dietary intake by averaging repeated measures through follow-up. We categorized total and subgroups of fruits and vegetables in five groups based on the frequency of intake. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) in the pooled data, using the lowest category of intake as the reference. Models stratified by age in months, calendar year of the current questionnaire cycle, and cohort. Multivariable models included the covariates described above and energy intake (kcal/day). We replaced missing covariate data with carried-forward method for continuous variables and missing indicator method for categorical variables. Linear trend was examined by modeling the median value for fruit/vegetable categories as a continuous variable. We also evaluated the association between each two servings per week of individual fruit, vegetable, and fruit juice consumption. For this analysis, because some of the fruit, vegetable, and fruit juice items (including grapes/raisins, blueberries, strawberries, grapefruits, prunes, cantaloupe/melon, apple juice, other juice, lettuce, cauliflower, kale/mustard greens/chard, Brussels sprouts, eggplant/zucchini, celery, and mixed vegetables) were not asked in 1980 SFFQ, the follow-up started from 1984. In secondary analyses, we additionally adjusted for dietary fiber, animal fat, and a modified alternate healthy eating index (AHEI) score that excluded fruits and vegetables.

To assess potential differences in the relation between intakes of fruits and vegetables, and incident breast cancer by BMI at age 18, family history of breast cancer, history of benign breast disease, and smoking status, cross-product terms were added to the multivariable model and evaluated with a likelihood ratio test. To examine differential associations of fruit and vegetable consumption with breast cancer risk by hormone receptor status and molecular subtypes, we used proportional hazards regression models with a data duplication method for competing risks.³⁵ To take advantage of repeated diet assessments in these cohorts and evaluate the latency between fruit and vegetable consumption and breast cancer incidence, analyses were performed using varying lag times. For example, in the NHS for the 0–4 year latency interval, fruit and vegetable consumption in 1980 was related to breast cancer risk between the 1980 and 1984 follow-up period; consumption in 1984 was related to risk between 1984 and 1986; consumption in 1986 was related to risk between 1986 and 1990, and so on. For the 4–8 year latency interval, fruit and vegetable consumption in 1980 was related to breast cancer risk between 1984 and 1986; consumption in 1984 was related to risk between 1986 and 1990, and so on.³⁶ To evaluate the difference between HRs for fruit or vegetable items, we evaluated the P-value for heterogeneity with the Q statistic.^{37,38} To examine whether the associations with breast cancer risk were heterogeneous among individual fruits, two fully-adjusted models were fitted: one with total fruit consumption and the other with total fruit consumption plus consumption of individual fruits excluding apples (which had the most similar association as the total fruit consumption) to avoid over-fitting. The same analyses were done for total and individual vegetables, excluding carrots (which had the most similar association as the total vegetable consumption). The likelihood ratio test tested whether the model including individual fruits or vegetables had better fit than total fruit or total vegetable consumption only. We also performed a multivariable stepwise Cox proportional hazards analysis to select the independent fruit and vegetable items. All *P*-values were two-sided. SAS version 9.3 (SAS Institute, Inc., Cary NC) was used for all analyses.

Results

Total fruit and vegetable Consumption and Dietary and Lifestyle Factors

Over 4,309,000 person-years of follow up (mean follow-up time=23.7 years), 10,911 invasive cases of breast cancer were documented. In both cohorts, higher total fruit and vegetable consumption was associated with lower prevalence of smoking, lower animal fat consumption, higher level of physical activity, higher fiber consumption, and earlier age at menarche (Table 1). In the NHS, participants with higher intakes of fruits and vegetables consumed less alcohol, whereas in the NHSII this association was opposite. In the NHSII, higher consumption of total fruits and vegetables was associated with lower prevalence of oral contraceptive use.

Fruit and vegetable consumption and breast cancer incidence

Results from the age-adjusted models were generally similar to multivariable models, so only multivariable results are presented. Higher consumption of total fruits and vegetables was associated with lower breast cancer incidence (>5.5 vs. 2.5 servings/day; HR=0.89, 95% CI=0.83–0.96; *P*_{trend}=0.006) (Table 2). Total fruits and total vegetables, separately, were

both associated inversely with lower breast cancer incidence (>2.5 servings/day vs. 4 servings/week of fruits; HR=0.91, 95%CI=0.84–0.99; P_{trend} =0.08; >4.5 vs. 1.5 servings/day of vegetables; HR=0.91, 95%CI=0.84–1.00; P_{trend} =0.03). Fruit juice consumption was not associated with breast cancer risk.

Among subgroups of vegetables, green leafy vegetables (>1 servings/day vs. 2 servings/week; HR=0.93, 95%CI=0.87–0.99; P_{trend} =0.03), yellow/orange vegetables (>5 vs. 2 servings/week; HR=0.91, 95%CI=0.84–0.99; P_{trend} =0.004), and cruciferous vegetables (>5 vs. 2 servings/week; HR=0.90, 95%CI=0.84–0.96; P_{trend} =0.0002) were associated with lower breast cancer risk (Table 3). For yellow/orange and cruciferous vegetables combined, >4 vs. 2 servings/week of each was associated with a 17% lower risk of breast cancer (HR=0.83, 95%CI=0.76–0.91). With mutual adjustment for subgroups, the association with cruciferous vegetable consumption was not materially changed (>5 vs. 2 servings/week; HR=0.92, 95%CI=0.85–0.98; P_{trend} =0.008), however, the association for yellow/orange vegetables was attenuated (>5 vs. 2 servings/week; HR=0.94, 95%CI=0.86–1.03; P_{trend} =0.14). When examining subgroups of fruits and vegetables defined by micronutrient content, those rich in vitamin C (>1 servings/day vs. 2 servings/week; HR=0.89, 95%CI=0.82–0.95; P_{trend} =0.004), α -carotene (3 servings/week vs. <2 servings/month; HR=0.91, 95%CI=0.84–0.99; P_{trend} =0.02), and β -carotene (>1 servings/day vs. 2 servings/week; HR=0.87, 95%CI=0.80–0.94; P_{trend} =0.0004) were each inversely associated with breast cancer risk.

When examining individual fruits and vegetables, the associations appeared stronger per 2 servings/week of winter squash (HR=0.90, 95%CI=0.83–0.98), broccoli (HR=0.96, 95%CI=0.92–0.99), cabbage (HR=0.93, 95%CI=0.89–0.99), and cauliflower (HR=0.92, 95%CI=0.87–0.98), ($P_{Heterogeneity}$ =0.63 for individual fruits; $P_{Heterogeneity}$ =0.009 for individual vegetables) (Appendix Figure S1). The goodness of fit was not significantly improved by adding individual fruit consumption (except apples) to the model with total fruit consumption or adding individual vegetable consumption (except carrots) to the model with total vegetable consumption. Using stepwise selection analyses with individual fruits and vegetables (including apples/pears, oranges, broccoli, cabbage, cauliflower, carrots, winter squash, lettuce, eggplant/zucchini), carrots remained significant ($p<0.05$).

Fruit and vegetable consumption and breast cancer subtypes

In analyses by tumor hormone receptor status, higher consumption of fruits and vegetables was more strongly associated with ER-negative than ER-positive tumors (Table 4) (for example, per 2 servings/day of total fruit and vegetable intake, ER-negative, HR=0.88, 95%CI=0.83–0.94; $P_{heterogeneity}$ =0.02). Similar results were observed for ER-negative/PR-negative compared with ER-positive/PR-negative or ER-positive/PR-positive. Higher consumption of green leafy, yellow/orange, tomato and other vegetables, as well as fruits and vegetables rich in vitamin C, α -carotene, β -carotene and lutein was each associated with lower risk of ER-negative cancer. Higher consumption of cruciferous vegetables was associated with lower risk of both ER-positive and ER-negative breast cancer. In contrast, higher consumption of fruit juice was associated with higher risk of ER-negative breast cancer (data not shown).

When examining molecular subtypes of breast cancer, we found that each 2 servings/day of total fruit and vegetable consumption were most strongly associated with lower risk of HER2-enriched (HR=0.79, 95%CI=0.67–0.93), basal-like (HR=0.84, 95%CI=0.72–0.97), and luminal A (HR=0.94, 95%CI=0.89–0.99), compared with luminal B (HR=0.98, 95%CI=0.90–1.06) tumors ($P_{heterogeneity}=0.03$) (Table 4). Among subgroups, high intake of yellow/orange vegetables, tomato, fruits and vegetables rich in vitamin C, and fruits and vegetables rich in α -carotene was each associated with lower risk of HER2-enriched cancer (data not shown). High intake of cruciferous vegetables was associated with lower risk of luminal A (for each serving/day; HR=0.82, 95%CI=0.69–0.98) and basal-like tumors (for each serving/day; HR=0.58, 95%CI=0.36–0.93).

Examining individual fruits and vegetables with ER-negative breast cancer, higher intakes of blueberries, strawberries, lettuce, carrots, winter squash, broccoli, and cauliflower were associated with reduced risk (Figure 1). Using stepwise selection (including blueberries, strawberries, oranges, lettuce, carrots, winter squash, broccoli, cauliflower, celery), carrots and winter squash remained significant ($p<0.05$).

Subgroup Analyses

In separate evaluations of pre- and postmenopausal breast cancer, the associations between total fruit and vegetable consumption and subgroups of fruit and vegetable consumption produced similar HRs, although among premenopausal women, some of the associations were not significant due to the smaller sample size (Appendix Tables S2, S3). The associations between total fruit or total vegetable consumption and breast cancer incidence did not differ by BMI at age 18, smoking status, history of benign breast disease, and family history of breast cancer (p -interaction >0.05).

To evaluate the importance of timing of fruit and vegetable consumption in relation to breast cancer risk, we conducted analyses using only baseline dietary data (NHS, 1980; NHSII, 1991) without updating, as well as latency analyses assessing intake 0–4, 4–8, 8–12, 12–16, and 16–20 years prior to diagnosis. With baseline intake, total fruit and vegetable consumption was significantly associated with lower breast cancer risk (>5.5 vs. 2.5 servings/day; HR=0.91, 95%CI=0.85–0.98; $P_{trend}=0.009$), as was total vegetable consumption (>4.5 vs. 1.5 servings/day; HR=0.92, 95%CI=0.84–1.00; $P_{trend}=0.01$). However, baseline total fruit consumption was not associated with risk (>2.5 servings/day vs. 4 servings/week; HR=0.95, 95%CI=0.89–1.02; $P_{trend}=0.17$). In the time-lagged analyses, total fruit and vegetable consumption was associated with significantly decreased breast cancer risk 8–12 years after exposure, but not for shorter latency periods (Table 5). Total fruit consumption was more strongly associated with breast cancer risk for longer time lags, 12–16 years after exposure. Total vegetable consumption was associated with lower risk for 8–12 and 12–16 years after exposure. However, lower risk of ER-negative or ER-negative/PR-negative cancer was observed with high intake of total fruits and vegetables 4–8 years before breast cancer diagnosis (Appendix Table S4).

The association for total fruit and vegetable intake and breast cancer was attenuated after adjustment for fiber consumption, as a constituent of fruits and vegetables, (>5.5 vs. 2.5 servings/day; HR=0.92, 95%CI=0.83–1.01; $P_{trend}=0.21$). However, the associations

remained significant for cruciferous vegetables, and fruits and vegetables rich in β -carotene after additional adjustment for fiber consumption (Appendix Table S5). Additional adjustment for animal fat or AHEI did not change the results (Appendix Table S5). We observed similar finding for total fruit and vegetable intake where energy intake was included in the models as continuous variables (>5.5 vs. 2.5 servings/day; HR for total fruits and vegetables=0.90, 95%CI: 0.84–0.96; $P_{trend}=0.01$). In Appendix Table S6, the results were presented for NHS and NHSII separately. We did not observe significant heterogeneity between the two cohorts and total fruit and vegetable consumption was associated with lower risk of breast cancer in the NHS and NHSII.

Discussion

In this large analysis, pooling repeated measures from two large prospective cohorts, higher total fruit and vegetable consumption during adulthood was associated with a modest, statistically significant lower invasive breast cancer incidence, with the strongest associations for ER-negative, HER2-enriched, and basal-like tumors. The inverse associations appeared to be strongest for consumption eight or more years before diagnosis. Higher intakes of yellow/orange vegetables, cruciferous vegetables, green leafy vegetables as well as fruits and vegetables rich in vitamin C, α -carotene, and β -carotene were associated with lower breast cancer incidence. The associations differed significantly among individual vegetables: higher intakes of winter squash, broccoli, cabbage, and cauliflower were significantly associated with lower incidence of breast cancer.

Fruit and vegetable consumption has been hypothesized to reduce risk of breast cancer, but many studies have not observed associations. In a pooled analysis of 20 prospective cohort studies with 34,526 cases of breast cancer, including the NHS and NHSII,²⁰ consumption of total fruits and vegetables was not associated with overall risk of breast cancer, but vegetable consumption was inversely associated with risk of ER-negative/PR-negative tumors (highest vs. lowest quintile; HR=0.84, 95%CI=0.75–0.93; $P_{trend}=0.001$). Total vegetable consumption was associated with lower risk of overall breast cancer as well as ER-negative/PR-negative tumors in a recent EPIC study (10,197 breast cancer cases).¹⁹ A limitation of most of the studies was that diet was assessed with a single questionnaire at baseline, and in many studies, the follow-up was relatively short. Our latency analyses suggested weak associations with 0–8 year lags. Our results indicate that fruit and vegetable intake may be important eight or more years before diagnosis, which is consistent with an effect acting in the early stages of carcinogenesis. Our findings also strongly support a greater benefit of both total fruit and vegetable and total vegetable consumption for reduction of ER-negative breast cancer, which may be due to the dominant role of hormonal exposures in the etiology of ER-positive tumors. Consistent with our earlier NHS report included 792 ER-negative cases,²³ higher intake of strawberries and blueberries was associated with substantially lower risk of ER-negative tumors; as were observed for strawberries in the pooled analysis.²⁰ However, these foods were not included in many other studies.

In addition to analyses by ER/PR status, we observed significant heterogeneity in the association between fruit and vegetable consumption by tumor molecular subtypes, with

stronger associations with HER2-enriched and basal-like tumors, more aggressive forms of breast cancer with few identified preventive factors.³⁹ While these associations may reflect the ER-negative component of these subtypes, future studies are warranted to replicate the stronger associations we observed with HER2-enriched tumors to understand the role of HER2 in the underlying mechanisms. To our knowledge, the current study is the first to evaluate the risk of breast cancer by molecular subtype in relation to fruit and vegetable consumption.

With widely varying nutrient and phytochemical content of fruits and vegetables, we observed, as expected, heterogeneity in breast cancer association by individual items. Particularly notable was the inverse association with cruciferous vegetables including cauliflower, cabbage, and broccoli. Although associations with Brussels sprouts and kale/mustard greens/chard were not significant, the 95% CIs were wide given relatively low consumption and they were not assessed in early questionnaires. Cruciferous vegetables are hypothesized to prevent cancer given that they are rich sources of bioactive compounds including isothiocyanates and indoles that suppress mutagenic and carcinogenic activity in laboratory models.⁴⁰ In the large pooled analysis, cruciferous vegetable consumption was not significantly associated with lower breast cancer risk,⁴¹ but an inverse association was observed in the Black Women's Health Study.¹⁵

Consistent with our prior finding of reduced breast cancer risk with higher fiber intake,⁵ and the biologically plausible role of fiber in fruits and vegetables, the inverse association with total fruit and vegetable intake was attenuated with additional adjustment for fiber. However, the associations with cruciferous vegetables and β -carotene-rich fruits and vegetables were not attenuated with adjustment for fiber, suggesting other constituents of fruits and vegetables such as micronutrients that may also be important. For example, carotenoids have been hypothesized to reduce cancer risk through antioxidant or antiproliferative activity.⁴² This is consistent with prior studies where both dietary intake and circulating levels of carotenoids have been inversely associated with breast cancer, especially ER-negative tumors.^{4, 43, 44} Our results also support a role of vitamin C, which also may act as an antioxidant in reducing breast cancer risk.

Our use of pooled data from two, large, well-established cohorts with long-term follow-up, many repeated diet assessments, and a large number of cases, allowed the detection of modest reductions in risk, examination of specific fruits and vegetables, and assessment of breast cancer risk by hormone receptor status, molecular subtype, and menopausal status. While residual confounding cannot be excluded, the incorporation of updated, detailed data on lifestyle factors and other potential confounders had minimal effects on associations. Although the majority of participants were white educated females, the underlying biologic mechanisms were not likely to differ substantially by race.^{45,46} Type I error is possible given that we made multiple comparisons. However, the central finding of an inverse association with fruits and vegetables, particularly for ER-negative cases, was our primary hypothesis, and additional analyses supported these results.

In conclusion, our findings from two, large prospective cohorts support the hypothesis that total fruit and vegetable consumption are associated with lower breast cancer incidence,

particularly the more aggressive tumors including ER-negative, HER2-enriched, and basal-like. Yellow/orange and cruciferous vegetables appear to be particularly beneficial. Notably, these associations for cruciferous vegetables are independent of fiber intake. Finally, fruit and vegetable intake may be important in reducing tumor initiation given the importance of intake 8 or more years before diagnosis. Increased intake of fruits and vegetables has numerous health benefits, including the potential of reducing the breast cancer risk. Our findings support current guidelines for cancer prevention⁴⁷ that recommend a diet high in fruits and vegetables, and suggest the importance of translational studies to understand the underlying mechanisms with cancer incidence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Impact

Based on these results, high intake of fruits and vegetables may reduce the risk of breast cancer, especially aggressive tumors.

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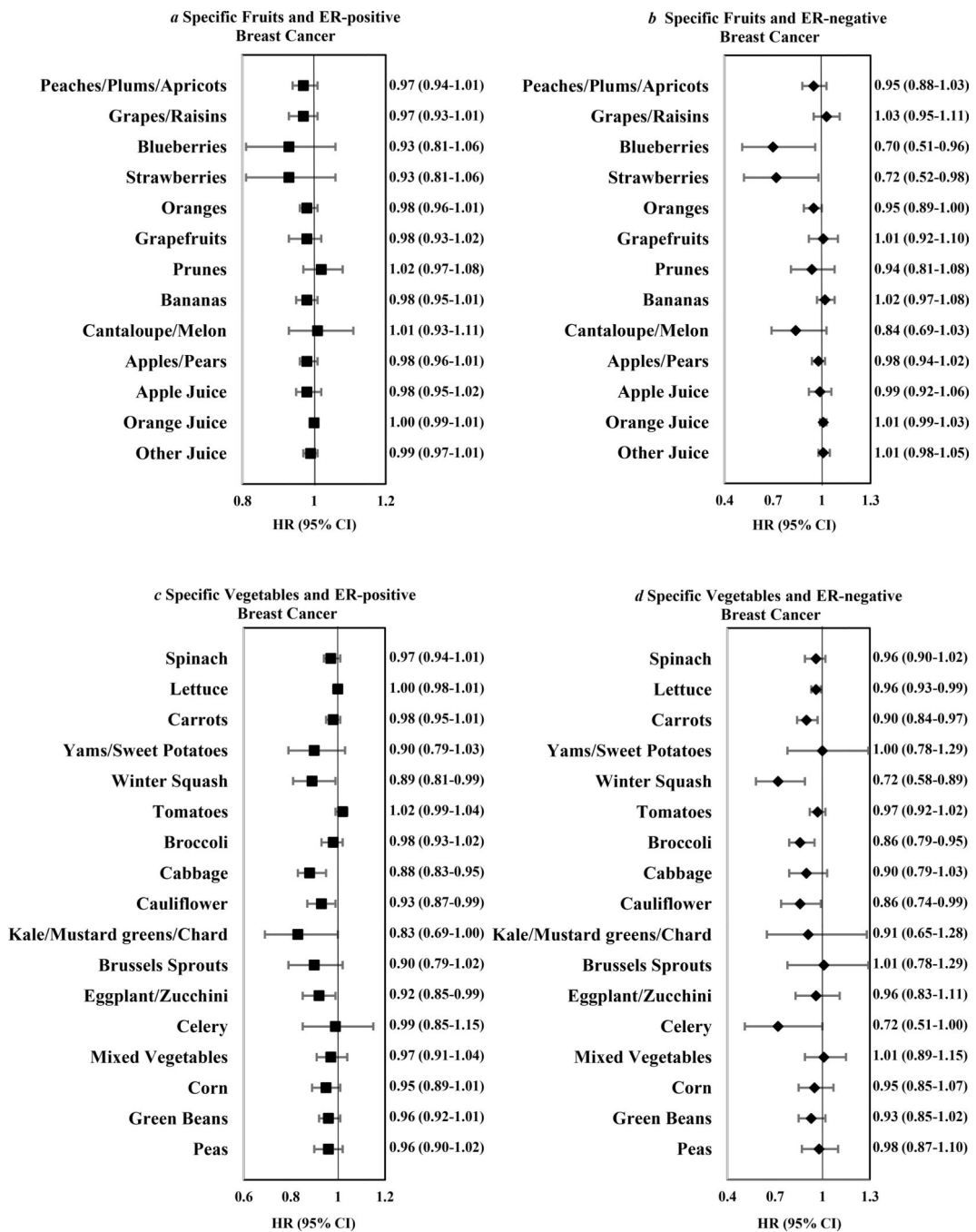


Figure 1. Multivariable hazard ratios and 95% confidence intervals for every 2 servings/week of specific fruits (a and b) and vegetables (c and d) in relation to ER positive cancers (7,464 cases) and ER negative cancers (1,794 cases) among 182,145 women in the Nurses’ Health Studies

Table 1

Age and age-standardized characteristics according to consumption of total fruits and vegetables among women enrolled in the Nurses' Health Study (n=88,301) in 1980 and Nurses' Health Study II (n=93,844) in 1991

	Nurses' Health Study						Nurses' Health Study II								
	2.5 servings/day	>2.5 to 3.5 servings/day	>3.5 to 4.5 servings/day	>4.5 to 5.5 servings/day	>5.5 servings/day	2.5 servings/day	>2.5 to 3.5 servings/day	>3.5 to 4.5 servings/day	>4.5 to 5.5 servings/day	>5.5 servings/day	2.5 servings/day	>2.5 to 3.5 servings/day	>3.5 to 4.5 servings/day	>4.5 to 5.5 servings/day	>5.5 servings/day
Number	32,287	21,429	15,096	8,868	10,621	27,479	20,989	17,355	11,647	16,374					
Mean															
Total fruit intake, servings/day	0.6	1.2	1.7	2.2	3.4	0.4	0.8	1.1	1.4	2.1					
Total vegetable intake, servings/day	1.1	1.8	2.3	2.7	3.8	1.3	2.2	2.8	3.5	5.2					
Fruit juice, servings/day	0.9	1.0	1.1	1.1	1.2	0.6	0.9	1.0	1.1	1.3					
Age, years	45.1	46.2	46.8	47.5	47.9	35.7	36.1	36.2	36.4	36.6					
BMI at age 18, kg/m ²	21.2	21.3	21.4	21.5	21.6	21.1	21.2	21.2	21.4	21.6					
Current BMI, kg/m ²	24.3	24.4	24.5	24.6	24.6	24.6	24.6	24.5	24.7	24.8					
Physical activity, MET-hrs/wk	11.4	13.5	15.4	16.8	18.7	15.5	18.7	21.2	24.2	29.8					
Alcohol consumption, g/day	7.2	6.3	5.8	5.8	5.4	2.9	3.1	3.2	3.2	3.3					
Total fiber intake, g/day	8.9	12.1	14.2	16.2	20.5	14.4	17.2	18.9	20.5	24.0					
Animal fat intake, % energy	30.8	29.6	28.7	27.7	25.4	18.7	17.9	17.3	16.8	15.5					
Total energy intake, kcal	1397	1545	1642	1745	1910	1490	1708	1849	1980	2200					
%															
Current smokers	36	28	25	22	21	16	12	11	10	10					
Ever used oral contraceptives	48	49	48	48	47	86	85	85	84	82					
Family history of breast cancer in mother or sisters	6	6	6	6	6	6	6	6	6	6					
History of benign breast disease	24	25	25	25	25	9	10	10	10	10					
Nulliparous	6	6	6	6	7	30	26	24	25	27					
Age at menarche <12 years	21	22	24	24	24	23	23	24	26	28					

Table 2

Hazard ratios and 95% confidence intervals of fruit and vegetable consumption in relation to incident invasive breast cancer (n=10,911 cases) in Nurses' Health Study and Nurses' Health Study II.

		Consumption Levels					<i>P</i> _{trend}
		>2.5 to 3.5 servings/day	>3.5 to 4.5 servings/day	>4.5 to 5.5 servings/day	>5.5 servings/day		
Total fruit and vegetable intake							
Amount of intake		2.5 servings/day	>3.5 to 4.5 servings/day	>4.5 to 5.5 servings/day	>5.5 servings/day		
No. of cases/person-years in NHS		1,292/457,076	1,683/542,469	1,324/376,169	1,544/453,806		
No. of cases/person-years in NHSII		722/450,298	693/405,921	516/281,609	608/363,466		
Model 1	1	0.97 (0.92–1.03)	0.99 (0.93–1.05)	1.00 (0.94–1.07)	0.94 (0.88–1.00)	0.11	
Model 2	1	0.94 (0.88–1.00)	0.94 (0.88–1.00)	0.95 (0.89–1.02)	0.89 (0.83–0.96)	0.006	
Total fruit intake							
Amount of intake		4 servings/week	>4 to 6 servings/week	>6 servings/week to 1.5 servings/day	>1.5 to 2.5 servings/day	>2.5 servings/day	
No. of cases/person-years in NHS		1,023/365,517	963/298,599	2,311/718,399	2,400/682,790	914/289,822	
No. of cases/person-years in NHSII		802/497,615	583/337,772	1,061/612,398	677/391,529	177/114,632	
Model 1	1	1.02 (0.96–1.10)	0.98 (0.92–1.04)	0.98 (0.92–1.04)	1.01 (0.95–1.07)	0.91 (0.85–0.99)	
Model 2	1	1.00 (0.94–1.07)	1.00 (0.94–1.07)	0.95 (0.90–1.01)	0.99 (0.93–1.05)	0.91 (0.84–0.99)	
Total vegetable intake							
Amount of intake		1.5 servings/day	>1.5 to 2.5 servings/day	>2.5 to 3.5 servings/day	>3.5 to 4.5 servings/day	>4.5 servings/day	
No. of cases/person-years in NHS		1,155/421,021	2,547/815,680	2,282/651,837	1,034/299,308	593/167,280	
No. of cases/person-years in NHSII		483/308,753	1,034/610,319	898/518,716	487/287,107	398/229,049	
Model 1	1	0.98 (0.92–1.04)	0.98 (0.92–1.04)	1.01 (0.95–1.07)	0.96 (0.89–1.03)	0.98 (0.90–1.06)	
Model 2	1	0.93 (0.88–0.99)	0.93 (0.88–0.99)	0.94 (0.88–1.00)	0.89 (0.82–0.96)	0.91 (0.84–1.00)	
Fruit juice Intake							
Amount of intake		1 serving/week	>1 to 4 servings/week	>4 to 6 servings/week	>6 servings/week to 1.5 servings/day	>1.5 servings/day	

Table 3

Hazard ratios and 95% confidence intervals of subgroups of fruit and vegetable consumption in relation to incident invasive breast cancer (n=10,911 cases) in Nurses' Health Study and Nurses' Health Study II.

		Consumption Levels						<i>P_{trend}</i>
Green leafy vegetable intake								
Amount of intake	2 servings/week	>2 to 4 servings/week	>4 to 6 servings/week	>6 servings/week to 1 serving/day	>1 servings/day			
No. of cases/person-years in NHS	1,500/567,610	2,163/659,719	1,848/534,085	723/213,002	1,367/372,934			
No. of cases/person-years in NHSII	604/403,641	870/538,425	757/415,130	284/177,224	785/419,358			
Model 1	1	1.02 (0.96–1.08)	1.02 (0.96–1.09)	1.02 (0.94–1.10)	1.04 (0.98–1.11)		0.28	
Model 2	1	0.95 (0.90–1.01)	0.93 (0.87–0.99)	0.92 (0.85–0.99)	0.93 (0.87–0.99)		0.03	
Yellow/orange vegetable intake								
Amount of intake	2 servings/week	>2 to 3 servings/week	>3 to 4 servings/week	>4 to 5 servings/week	>5 servings/week			
No. of cases/person-years in NHS	4,108/1,305,886	1,657/470,261	931/293,064	457/129,100	458/156,630			
No. of cases/person-years in NHSII	1,953/1,188,668	631/352,322	361/191,770	154/104,970	201/116,123			
Model 1	1	1.00 (0.95–1.05)	0.96 (0.91–1.02)	0.94 (0.87–1.02)	0.90 (0.83–0.98)		0.007	
Model 2	1	0.98 (0.93–1.03)	0.95 (0.89–1.01)	0.93 (0.85–1.01)	0.91 (0.84–0.99)		0.004	
Tomato intake								
Amount of intake	2 servings/week	>2 to 4 servings/week	>4 to 6 servings/week	>6 servings/week to 1 serving/day	>1 servings/day			
No. of cases/person-years in NHS	1,675/595,564	3,132/950,188	1,815/518,863	498/157,262	479/128,381			
No. of cases/person-years in NHSII	750/511,096	1,197/658,061	794/456,451	202/115,244	357/212,870			
Model 1	1	1.05 (1.00–1.11)	1.07 (1.01–1.13)	1.05 (0.96–1.14)	1.11 (1.02–1.20)		0.009	
Model 2	1	1.02 (0.97–1.07)	1.03 (0.97–1.09)	1.02 (0.93–1.11)	1.06 (0.98–1.15)		0.21	
Cruciferous vegetable intake								
Amount of intake	2 servings/week	>2 to 3 servings/week	>3 to 4 servings/week	>4 to 5 servings/week	>5 servings/week			
No. of cases/person-years in NHS	3,030/1,024,004	1,729/476,923	1,190/364,159	705/192,392	955/297,017			
No. of cases/person-years in NHSII	1,458/880,950	681/385,353	466/262,993	281/161,688	414/262,876			
Model 1	1	1.01 (0.96–1.06)	0.95 (0.89–1.00)	0.97 (0.90–1.04)	0.91 (0.85–0.96)		0.0007	
Model 2	1	0.97 (0.92–1.02)	0.92 (0.87–0.98)	0.94 (0.87–1.01)	0.90 (0.84–0.96)		0.0002	

		Consumption Levels						<i>P_{trend}</i>
Green leafy vegetable intake								
Other vegetable intake								
Amount of intake	2 servings/week	>2 to 4 servings/week	>4 to 6 servings/week	>6 servings/week to 1 serving/day	>1 servings/day			
No. of cases/person-years in NHS	554/222,662	2,183/694,458	2,286/681,612	912/264,363	1,676/491,969			
No. of cases/person-years in NHSII	251/154,205	821/490,953	905/504,966	320/194,177	1,003/609,606			
Model 1	1	1.03 (0.96–1.12)	1.03 (0.95–1.11)	1.04 (0.95–1.13)	0.99 (0.91–1.07)		0.17	
Model 2	1	0.99 (0.92–1.07)	0.98 (0.90–1.06)	0.99 (0.90–1.08)	0.94 (0.86–1.02)		0.06	
Fruits and vegetables high in vitamin C								
Amount of intake	2 servings/week	>2 to 4 servings/week	>4 to 6 servings/week	>6 servings/week to 1 serving/day	>1 servings/day			
No. of cases/person-years in NHS	821/322,755	1,787/566,451	1,836/548,713	825/229,135	2,342/688,031			
No. of cases/person-years in NHSII	444/271,768	954/577,239	823/468,741	286/164,045	793/472,149			
Model 1	1	0.99 (0.92–1.06)	0.97 (0.91–1.04)	1.02 (0.94–1.10)	0.94 (0.88–1.00)		0.04	
Model 2	1	0.94 (0.87–1.00)	0.91 (0.85–0.97)	0.95 (0.87–1.03)	0.89 (0.82–0.95)		0.004	
Fruits and vegetables high in α-carotene								
Amount of intake	<2 servings/month	2 to <4 servings/month	1 to <2 servings/week	2 to <3 servings/week	3 servings/week			
No. of cases/person-years in NHS	665/191,717	2,070/649,455	2,586/802,189	1,123/316,909	1,162/391,617			
No. of cases/person-years in NHSII	451/284,886	889/529,046	1,033/599,456	471/266,650	456/273,655			
Model 1	1	0.95 (0.89–1.02)	0.94 (0.88–1.00)	0.92 (0.85–0.99)	0.91 (0.84–0.98)		0.01	
Model 2	1	0.95 (0.88–1.01)	0.92 (0.86–0.99)	0.89 (0.82–0.96)	0.91 (0.84–0.99)		0.02	
Fruits and vegetables high in β-carotene								
Amount of intake	2 servings/week	>2 to 4 servings/week	>4 to 6 servings/week	>6 servings/week to 1 serving/day	>1 servings/day			
No. of cases/person-years in NHS	736/301,972	1,381/455,777	1,697/508,135	851/241,899	2,946/847,277			
No. of cases/person-years in NHSII	249/173,435	612/379,126	696/414,291	324/186,699	1,419/800,339			
Model 1	1	1.01 (0.93–1.09)	1.00 (0.93–1.08)	1.04 (0.95–1.13)	1.00 (0.93–1.07)		0.66	
Model 2	1	0.94 (0.86–1.01)	0.90 (0.83–0.98)	0.92 (0.84–1.01)	0.87 (0.80–0.94)		0.0004	
Fruits and vegetables high in lutein								
Amount of intake	1 serving/month	>1 to 3 servings/month	>3 to 4 servings/month	>1 to 3 servings/week	>3 servings/week			

Green leafy vegetable intake		Consumption Levels			<i>P_{trend}</i>
No. of cases/person-years in NHS	797/254,275	1,944/581,492	1,410/457,320	2,820/820,986	630/233,258
No. of cases/person-years in NHSII	861/565,092	1,084/622,253	492/299,831	723/389,612	140/76,717
Model 1	1	1.04 (0.98–1.11)	1.03 (0.97–1.11)	1.04 (0.98–1.10)	0.98 (0.89–1.07)
Model 2	1	1.01 (0.95–1.07)	1.00 (0.93–1.07)	0.97 (0.92–1.04)	0.94 (0.86–1.03)

Model 1 stratified by cohort, calendar year, and age in months.

Model 2 stratified by cohort, calendar year, and age in months and adjusted for family history of breast cancer (yes, no), history of benign breast disease (yes, no), height (<1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, and 1.75 meters), BMI at age 18 years (<18.5, 18.5 to <20, 20 to <22.5, 22.5 to <25, 25.0 to <30, 30.0 kg/m²), weight change since age 18 (continuous), smoking (never, past, current 1 to 14/day, current 15 to 24/day, current 25/day), physical activity (quintiles of MET-hr per week, missing), oral contraceptive use (never, < 2 years, 2 to <5 years, 5 to <10 years, 10 years), alcohol intake (g/day, quintiles), total energy intake (kcal/day, quintiles), age at menarche (<12, 12, 13, 14, >14 years), parity and age at first birth (nulliparous, parity 2 and age at first birth <25 years, parity 2 and age at first birth 25 to <30 years, parity 3 to 4 and age at first birth <25 years, parity 3 to 4 and age at first birth 25 to <30 years, parity 3 to 4 and age at first birth >30 years, parity 5 and age at first birth <25 years, parity 5 and age at first birth 25 years), and menopausal status, age at menopause, and postmenopausal hormone use (premenopausal, postmenopausal and age at menopause<50 years and never postmenopausal hormone use, postmenopausal and age at menopause<50 years and past postmenopausal hormone use, postmenopausal and age at menopause<50 years and current postmenopausal hormone use, postmenopausal and age at menopause 50 years and never postmenopausal hormone use, postmenopausal and age at menopause 50 years and current postmenopausal hormone use, postmenopausal and age at menopause 50 years and past postmenopausal hormone use, missing).

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parity 5 and age at first birth <25 years, parity 5 and age at first birth 25 years), and menopausal status, age at menopause, and postmenopausal hormone use (premenopausal, postmenopausal and age at menopause<50 years and never postmenopausal hormone use, postmenopausal and age at menopause<50 years and current postmenopausal hormone use, postmenopausal and age at menopause 50 years and never postmenopausal hormone use, postmenopausal and age at menopause 50 years and past postmenopausal hormone use, postmenopausal and age at menopause 50 years and current postmenopausal hormone use, missing).