

Citation:

Genkinger JM, Platz EA, Hoffman SC, Comstock GW, Helzlsouer KJ. Fruit, vegetable, and antioxidant intake and all-cause, cancer, and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. *Am J Epidemiol*. 2004; 160(12): 1223-1233.

PubMed ID: [15583375](#)

Study Design:

Prospective cohort study.

Class:

B - [Click here](#) for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To assess the relationship of fruit and vegetable and dietary ascorbic acid, beta-carotene and alpha-tocopherol intake with all-cause mortality, cardiovascular disease (CVD) mortality and cancer mortality in the community-based CLUE cohort studies in Washington County, MD, and to determine whether these associations differ by cigarette smoking and body mass index (BMI).

Inclusion Criteria:

- 8,394 residents of Washington County, MD, who donated blood in 1974 and 1989
- Volunteers of two cohort studies (CLUE I and CLUE II), Odyssey Cohort participants
- Participants (N=6,563) who adequately completed modified short Block Food Frequency Questionnaire (FFQ).

Exclusion Criteria:

- Inadequate completion of FFQ: reporting total caloric intake outside 800kcal to 5,000kcal range, more than half of items blank or reporting fewer than three foods per day
- Blood sample no longer available
- DNA amplification did not occur
- Results of genotyping were ambiguous
- Self-reported cancer, myocardial infarction, stroke or diabetes before 1989.

Description of Study Protocol:**Recruitment**

Two CLUE studies recruited participants with their campaign slogan, "Give Us a Clue to Cancer and Heart Disease".

Design

Prospective cohort.

Statistical Analysis

- Dietary antioxidant nutrient intake analyzed separately for men and women
 - Not energy-adjusted by residual method
 - Energy-adjusted by residual analysis.
- Distribution of intakes of fruits and vegetables, cruciferous vegetables and antioxidant nutrients was divided into fifths, separately for males and females, then pooled over sex, so that lowest fifth for males and females was combined
- Intakes of fruits and vegetables and cruciferous vegetables were categorized as less than 2.3 or greater than or equal to 2.3 (overall median) and 0.17 (overall median) servings per day, respectively
- Cox proportional hazards regression analysis was used to estimate hazard ratios for all-cause deaths, cancer deaths, and CVD deaths, adjusting for age.
- Three models used for antioxidant nutrient:
 - Age-adjusted with energy-adjusted antioxidant nutrient values from residual analysis
 - Multivariate with energy-adjusted antioxidant nutrient values from residual analysis
 - Antioxidant nutrient value not energy-adjusted.
- Estimates further adjusted for smoking status, cholesterol levels and BMI in multivariate analysis
- Ordinal terms for quintiles of fruit and vegetable, cruciferous vegetable and antioxidant nutrient intake were included to test for trend, and coefficients evaluated by Wald test
- Additional analyses compared bottom fifth with top four fifths; median values included in Cox proportional hazards regression analysis used to assess threshold effect
- Association between nutrient and mortality was stratified by sex, cigarette use and BMI.

Data Collection Summary:

Timing of Measurements

- Demographic characteristics and medical history collected in baseline questionnaires in 1974 and 1989. 1989 questionnaire asked current height and weight.
- Plasma cholesterol measured in 1989
- Follow-up questionnaires (1996, 1998, 2000) assessed history of cancer, CVD and other major illnesses and year diagnosed
- 61-item modified Block FFQ administered in 1989 to estimate diet during the previous year.

Dependent Variables

- All-cause mortality
- Cancer mortality
- CVD mortality.

Independent Variables

- Fruit and vegetable intake
- Cruciferous vegetable intake
- Dietary antioxidant nutrient intake.

Control Variables

- Age
- Sex
- Smoking status
- Cholesterol levels
- BMI.

Description of Actual Data Sample:

Initial N: 6,151 (2,276 men, 3,875 women)

Attrition (final N): 97% (final N=5,952)

Age: Ranged from 30 years to 93 years at start of follow-up in 1989. Mean age of each quintile ranged from 52.2 years to 59.4 years.

Ethnicity: 99% white

Other relevant demographics: 78% married, 13% current smokers

Anthropometrics: Percentage of participants in two categories of BMI [25 to 29.9 (overweight) or more than 30.0 (obese)] was similar across groups (ranges, 37.2% to 41.7% were overweight and 17.7% to 18.6% were obese)

Location: Washington County, MD.

Summary of Results:

All-Cause Mortality

- Fruit and vegetable intake
 - Participants in the top vs. bottom fifth had a lower risk (hazard ratio=0.58; 95% CI 0.47, 0.71; P-trend<0.0001). Association slightly attenuated after multivariate adjustment (hazard ratio=0.63; 95% CI 0.51, 0.78; P-trend=0.0004).
 - Because of possible threshold effect, top four fifths were combined and compared with lowest fifth of intake (hazard ratio=0.82; 95% CI 0.75, 0.90)
 - Similar estimates observed when juice intake included
 - When stratified according to smoking status, highest vs. lowest intake resulted in equally decreased risk among ever-smokers (hazard ratio=0.77; 95% CI: 0.63, 0.95) and never-smokers (hazard ratio=0.72; 95% CI: 0.55, 0.95).
- Cruciferous vegetable intake
 - Participants in highest vs. lowest fifth of intake had lower risk (hazard ratio=0.78; 95% CI: 0.64, 0.96; P-trend=0.13)
 - Top four fifths vs. lowest fifth (hazard ratio=0.32; 95% CI: 0.13, 0.80).
- Individual antioxidant nutrient intake
 - Highest vs. lowest intake of energy-adjusted beta-carotene intake (hazard ratio=0.81;

95% CI: 0.66, 1.00; P-trend=0.19) in multivariate models

- No association between top four fifths vs. lowest fifth in intake of vitamin C and E (data not shown)
 - Only slight differences in results found with and without energy adjustment
 - Similar estimates observed when supplement information included.

Cancer Mortality

- Fruit and vegetable intake
 - Highest vs. lowest fifth of intake had lower risk (hazard ratio=0.65; 95% CI: 0.45, 0.93; P-trend = 0.08)
 - Highest four fifths vs. lowest fifth of intake had lower risk (hazard ratio=0.85; 95% CI: 0.73, 0.99)
 - When stratified according to smoking status, highest vs. lowest intake resulted in decrease risk for both never-smokers (hazard ratio=0.69; 95% CI: 0.41, 1.17) and ever-smokers (hazard ratio=0.85; 95% CI: 0.60, 1.20), although this was not statistically significant.
- Cruciferous vegetable intake
 - No association found when comparing highest vs. lower risk
 - Highest four fifths vs. lowest fifth had lower risk (hazard ratio=0.25; 95% CI: 0.05, 1.14).
- Antioxidant nutrient intake
 - No statistically significant associations found when highest vs. lowest fifth compared for vitamins C and E or beta-carotene
 - No trends across fifths of intake observed.

Cardiovascular Disease Mortality

- Fruit and vegetable intake
 - Risk slightly lower for top vs. bottom fifth of intake (hazard ratio=0.76; 95% CI: 0.54, 1.06)
 - No association when comparing top four vs. bottom fifth intake.
 - No statistically significant association found when stratified according to smoking status.
- Cruciferous vegetable intake
 - Risk slightly lower for top vs. bottom fifth of intake (hazard ratio=0.89; 95% CI: 0.64, 1.25)
 - No association when comparing top four vs. bottom fifth intake.
- Antioxidant nutrient intake: No association found for vitamins C and E or beta-carotene.

Other Findings

- Those who ate more fruits and vegetables were older, more educated and less likely to have smoked.
- Those who ate the least fruits and vegetables were less likely to have been treated for hypercholesterolemia.
- Mean overall intakes of fruits, vegetables and cruciferous vegetables were 1.15, 1.53 and 0.25 servings per day, respectively.
- Mean dietary intakes of vitamin C, vitamin E and beta-carotene were 102.6mg per day, 8.4mg per day and 2,096mcg per day, and total (diet and supplement) intakes were 225.2mg per day, 20.8mg per day and 2,444mcg per day, respectively.
- Only 9% of participants consumed the recommended five or more servings per day of fruits

and vegetables.

- Risk of all-cause mortality (hazard ratio=0.80; 95% CI: 0.64, 1.00) and cancer mortality (hazard ratio=0.77; 95% CI: 0.51, 1.15) was lower in those who consumed five or more servings of fruits and vegetables per day vs. those who ate fewer
- No association for CVD mortality was found with eating five or more servings of fruits and vegetables per day.
- Evaluation of mortality risk in smokers vs. non-smokers.

Author Conclusion:

This study suggests that an increased fruit and vegetable intake can delay the risk of all-cause mortality, cancer mortality and CVD mortality. This provides further evidence to support the public health message to increase fruit and vegetable intakes. Whether the benefit from higher intake is due to antioxidant content is yet to be determined.

Reviewer Comments:

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

- | | | |
|----|---|-----|
| 1. | Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies) | Yes |
| 2. | Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about? | Yes |
| 3. | Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice? | Yes |
| 4. | Is the intervention or procedure feasible? (NA for some epidemiological studies) | Yes |

Validity Questions

- | | | |
|------|---|-----|
| 1. | Was the research question clearly stated? | Yes |
| 1.1. | Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified? | Yes |
| 1.2. | Was (were) the outcome(s) [dependent variable(s)] clearly indicated? | Yes |
| 1.3. | Were the target population and setting specified? | Yes |
| 2. | Was the selection of study subjects/patients free from bias? | Yes |

2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	Were study groups comparable?	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	Was method of handling withdrawals described?	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	Was blinding used to prevent introduction of bias?	???

5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	???
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	Yes
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	Were outcomes clearly defined and the measurements valid and reliable?	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes

7.7.	Were the measurements conducted consistently across groups?	Yes
8.	Was the statistical analysis appropriate for the study design and type of outcome indicators?	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	No
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	Are conclusions supported by results with biases and limitations taken into consideration?	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	Is bias due to study's funding or sponsorship unlikely?	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes

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