DOI:10.1093/jnci/dju314
First published online October 21, 2014
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ARTICLE

Diet Quality and Survival After Ovarian Cancer: Results From the Women's Health Initiative

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Manuscript received January 8, 2014; revised May 16, 2014; accepted August 21, 2014.

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Background Survival after an ovarian cancer diagnosis is poor. Given the high mortality in these patients, efforts to identify modifiable lifestyle behaviors that could influence survival are needed. Earlier evidence suggests a protective role for vegetables, but no prior studies have evaluated overall dietary quality and ovarian cancer survival. The purpose of this analysis was to evaluate the role of prediagnosis diet quality in ovarian cancer survival.

Methods We identified 636 centrally adjudicated cases of ovarian cancer within the Women's Health Initiative Observational Study or Clinical Trials of 161 808 postmenopausal women followed from 1995 to 2012. Dietary quality was assessed for the Healthy Eating Index (2005) using a food frequency questionnaire, covariables were obtained from standardized questionnaires, and adiposity was measured by clinic-based measurements of height, weight, and waist circumference. The association between diet quality and mortality was analyzed using Cox proportional hazards regression, adjusted for potential confounders, and stratified by waist circumference, physical activity level, and diabetes status. Tests of statistical significance were two-sided.

Results Overall, higher diet quality was associated with lower all-cause mortality after ovarian cancer (hazard ratio [HR] for highest vs lowest tertile = 0.73; 95% confidence interval [CI] = 0.55 to 0.97, P_{trend} = .03). The effect was strongest among women with waist circumference of 88 cm or less and with no history of diabetes (HR = 0.73, 95% CI = 0.54 to 0.98). Physical activity level did not modify the association between diet quality and survival.

Conclusion Our results suggest that overall higher prediagnosis diet quality may protect against mortality after ovarian cancer.

JNCI J Natl Cancer Inst (2014) 106(11): dju314 doi:10.1093/jnci/dju314

Ovarian cancer is the leading cause of gynecological cancer death in US women with an estimated 22 280 new cases and 15 500 deaths annually (1). Most cases are diagnosed at an advanced stage of disease, thus contributing to low survival rates (1). Efforts to identify prognostic factors for ovarian cancer are needed, and diet may provide a modifiable influence on survival (1).

The role of diet in the development of ovarian cancer is not clearly understood (2), and evidence in relation to survival after diagnosis is sparse. Only two prior observational studies have specifically evaluated prediagnostic diet and its association with survival after ovarian cancer diagnosis. A case-control study by Nagle et al. demonstrated a 25% greater survival in 609 Australian women previously treated for stage I–IV invasive epithelial ovarian cancer who consumed greater amounts of vegetables (3). Additionally, prediagnosis diet was evaluated in relation to ovarian cancer survival in an Illinois cohort of 341 ovarian cancer survivors with follow-up for seven to 11 years (4). Diets higher in vegetables and fruit and lower in meat were associated with longer survival (4). Dietary quality, summarized in a score that reflects the combined effects of cancer-associated food exposures (5,6), may be best suited to evaluate the influence of overall diet on cancer survival. Similar analyses evaluating the association between diet quality and risk of breast (7–9), colorectal (10), and pancreatic (11) cancer offer compelling support for this approach.

Here we present an analysis from a large sample of postmenopausal women enrolled in the Women's Health Initiative designed to test the hypothesis that the Healthy Eating Index (HEI)–2005, a measure of overall diet quality (12,13), is inversely associated with mortality after ovarian cancer. Additionally, we sought to determine if any associations between diet quality and mortality were modified by obesity, diabetes, or physical activity, factors that are included in current recommendations targeting survival after cancer (14,15).

Methods

Study Population

The study sample for this analysis includes postmenopausal women who enrolled in the Women's Health Initiative (WHI) Observational Study (OS) or Clinical Trials (CT) from 1993 through 1998 and had an adjudicated ovarian cancer diagnosis during the observational period. Details of the enrollment criteria have been previously published (16). Briefly, the OS and CT enrolled 93 676 and 68 132 (total 161 808) postmenopausal (age 50 to 79 years) women from 40 US clinical research centers. The study protocols for WHI were approved by the Institutional Review Boards at all clinical sites, and women provided written informed consent prior to participation.

In WHI, 732 women were diagnosed with invasive ovarian cancer during follow-up, at least 12 months after study enrollment, with at least one day of survival time (ie, not diagnosed only during autopsy). Cancer staging codes take into account the tumor site, size, multiplicity, depth of invasion, and extension to regional or distant tissues, involvement of regional lymph nodes, and distant metastases (http://seer.cancer.gov/archive/manuals/historic/ssm_1977.pdf). Of these, 726 had measurement of diet by food frequency questionnaire (FFQ) at least 12 months prior to diagnosis. Women were excluded from analysis for: history of any cancer except nonmelanoma skin cancer prior to baseline (n = 63), in situ disease (n = 6), unknown stage at diagnosis (n = 10), or missing physical activity data (n = 11). Of the remaining 636 women, 573 (90.1%) were diagnosed with invasive cancer, whereas 63 (9.9%) had borderline tumor behavior. In total, 354 (55.7%) died during the follow-up period, of which 305 (91.3%) deaths were specific to ovarian cancer. This analysis uses data for cancer outcomes through September 17, 2012.

Dietary Exposure Assessment

Dietary intake was measured from the WHI FFQ (17) using a standardized protocol at baseline for all women, again at year three for OS participants, and at year one for dietary modification CT participants. Follow-up FFQs were completed in years two through nine for a rotating proportion of dietary modification CT participants, such that a 33% randomly selected CT sample was asked to complete a follow-up FFQ at year two. A second random one-third of CT women was asked to complete at year three, and the final one-third was asked to complete the FFQ at year four. During year five, the rotation went back to the initial one-third, and the rotating cycle continued for years six through nine.

All FFQs were reviewed for completeness and quality prior to data analysis. FFQs were included in our analysis if the data were collected at least 12 months prior to ovarian cancer diagnosis and if reported energy intake was plausible (600–5000 kcal/day). Estimates of overall diet quality were calculated according to the HEI-2005, computed from MyPyramid Equivalents (12,13). The HEI was calculated from FFQ line items and related output variables for the following 12 dietary elements and assigned a point range, with a maximum total score of 100 points: 1) total fruit (includes 100% juice, 0–5 points), 2) whole fruit (not juice, 0–5 points), 3) total vegetables (0–5 points), 4) dark green and orange vegetables and legumes (legumes counted as vegetables only after meat and beans standard is met, 0–5 points), 5) total grains (0–5 points), 6) whole grains (0–5 points), 7) milk (includes all milk products and soy beverages, 0–10 points), 8) meat and beans (0–10 points), 9) oils (includes nonhydrogenated vegetable oils and oils in fish, nuts, and seeds, 0–10 points), 10) saturated fat (0–10 points), 11) sodium (0–10 points), and 12) calories from solid fats, alcoholic beverages, and added sugars (0–20 points). For women with any repeat FFQ after baseline (35.2% completed a single FFQ, 32.6% completed two FFQs, and the remainder completed three to five FFQs), the average of all HEI scores measured at least 12 months prior to ovarian cancer diagnosis was used as a composite measure of diet quality.

Other Covariates

Baseline height and weight were measured in WHI clinics by trained personnel to the nearest tenth of a centimeter or kilogram, respectively, using standardized protocols with a wall-mounted stadiometer and balance beam or digital scale. Body mass index (BMI) (weight[kg]/height[m^2]) was calculated from these measurements. Potential effect modifiers included waist circumference (WC) and prior diagnosis of diabetes, as these exposures have been associated with diet quality (18–20), and physical activity, which has been suggested to alter cancer prognosis (21,22). WC was measured at the umbilicus by trained study staff using standardized protocols. Recreational physical activity was assessed using standardized questions regarding frequency and duration of activities, including moderate-intensity activities (eg, cycling outdoors, swimming, and floor classes) as well as vigorous-intensity activities (eg, jogging/running, aerobics, and tennis). Frequency was reported in days/times per week; duration was reported categorically with responses ranging from less than 20 min to 60 min and greater. Reported moderate and strenuous activities were analyzed as Metabolic Equivalent of Tasks (METs)–hr/week and categorized as none (0), greater than 0 to less than 9 MET-hr/week (below recommended activity level), 9 to less than 15 MET-hr/week (at recommended activity levels), and 15 MET-hr/week or greater (above recommended activity level). Baseline BMI, WC, physical activity, diabetes, and cardiovascular disease (CVD) were used unless a repeat measure/report was available up until 12 months prior to ovarian cancer diagnosis. The 12-month cutoff was particularly important for WC in order to avoid elevated WC that could be associated with disease (23).

Ascertainment of Outcomes

Health outcomes were collected using standardized questionnaires mailed to participants annually. Details on the ascertainment of outcomes, including standardized operating procedures for local and central adjudication of cancer endpoints, have been described (24). Participant-reported cancer diagnoses were verified by medical records and reviewed by WHI physician adjudicators. Death of any cause was ascertained from proxy report, or vital status was determined through linkage with the National Death Index with cause of death coded according to the International Classification of Diseases (25). Ovarian cancer included all borderline and invasive ovarian cancers. Borderline tumor behavior was defined according to the Surveillance, Epidemiology, and End Results (SEER) Program coding definition as "neoplasm of uncertain and unknown behavior" (ie, a tumor whose behavior is uncertain whether benign

or malignant) (26). A sensitivity analysis that excluded borderline cases showed similar results (data not shown). Ovarian cancer-specific mortality was defined as death from ovarian cancer; overall mortality was defined as death from any cause, with 90% of deaths from ovarian cancer.

Statistical Analysis

Crude and age- and stage-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for participant attributes using Cox proportional hazards regression. Overall and ovarian cancer-specific mortality and their associations with diet quality were analyzed using Cox proportional hazards regression, adjusting for potential confounders identified in the previous analysis (characteristics associated with overall mortality after adjusting for age and stage, $P < .1$): age at ovarian cancer diagnosis (years, continuous), stage at diagnosis (localized, regional, distant), race/ethnicity (non-Hispanic white [NHW], Hispanic, black, other/unknown), diabetes (ever, yes, no), moderate-to-vigorous physical activity (0, > 0 to < 9, 9 to < 15, ≥ 15 MET-hr/week), waist circumference (≤ 88, > 88 cm), family history of ovarian cancer (yes, no, unknown), and trial arm assignment(s) for CT women. These variables were associated with both exposure (diet) and outcome (mortality), with the exception of stage and family history, which were not associated with diet but are consistently associated with ovarian cancer risk or mortality in the literature. The proportional hazards assumption in each Cox model was assessed using plots of log-minus-log survival with confirmation using Schoenfeld's test. In several models, age at diagnosis did not meet the proportional hazards assumption based on Schoenfeld's test. For these models, the results from the Cox model were confirmed treating age as a time-dependent covariable (thereby relaxing the constant hazard ratio assumption). Coefficients and *P* values from the two models were quite similar, so only the results from the Cox proportional hazards models are included in the paper.

Dietary exposure variables were modeled categorically (low, medium, and high, with specific cutoff values differing for each variable based on its distribution). The referent categories reflect the lowest score, indicating poor diet quality as measured by a particular HEI food group or total HEI score. Tests for trend were conducted by modeling each categorical dietary variable as ordinal, with the lowest category assigned a value of 1, middle category assigned a value of 2, and highest category assigned a value of 3. Interactions between diet quality (overall HEI score) and potential effect modifiers (WC, diabetes, and physical activity) were tested using likelihood ratio tests. Ethnic group differences were not evaluated in relation to HEI and mortality because of small sample size. All tests of statistical significance were two-sided with $\alpha = 0.05$. Statistical analyses were conducted using Stata 13.1 (StataCorp, College Station, TX).

Results

Women in this sample were diagnosed with ovarian cancer at a mean age of 62.9 years; 18.6%, 14.6%, and 66.8% had localized, regional, and distant disease, respectively. Common characteristics associated with ovarian cancer mortality included age, family history, and stage of disease (Table 1). After adjusting for age and stage, all-cause mortality was higher in black women compared with NHWs (HR = 1.78, 95% CI = 1.18 to 2.69). Women with a previous diagnosis of diabetes had statistically significantly higher risk of death (HR = 1.84, 95% CI = 1.31 to 2.60), as did those with WC greater than 88 cm (HR = 1.27, 95% CI = 1.02 to 1.58).

An overall higher-quality diet (HEI) was associated with 27% lower all-cause mortality after ovarian cancer diagnosis (HR for the highest vs lowest tertile = 0.73, 95% CI = 0.55 to 0.97, $P_{trend} = .03$) (Table 2). The association between HEI and ovarian cancer-specific mortality was similar but attenuated (HR for the highest vs lowest tertile = 0.75, 95% CI = 0.55 to 1.01, $P_{trend} = .06$). No specific HEI component score items, nor total energy intake, were statistically significantly associated with lower mortality. The association between HEI and mortality was stratified by WC above or below clinical guidelines for health risk (88 cm) and by history of diabetes (never, ever). Importantly, the lower mortality risk associated with high diet quality (HEI tertile 3) was present only in women with WC 88 cm or less (HR = 0.60, 95% CI = 0.42 to 0.85) or no prior history of diabetes (HR = 0.73, 95% CI = 0.54 to 0.98) (Figure 1). However, the difference in effect according to WC or diabetes group was not statistically significant (likelihood ratio test for interaction between HEI and WC or diabetes, $P = .15$ and .29, respectively). Understanding that combined healthy behaviors may optimize survival after cancer (27) and owing to an analysis from WHI suggesting that physical activity is associated with lower mortality after ovarian cancer (36), we also stratified the relationship between HEI and mortality by physical activity level; the association was not appreciably different in women achieving greater than or equal to 9 vs less than 9 MET-hr/week moderate to vigorous physical activity (HR for < 9 MET-hr/week for lowest vs highest tertile = 0.76, 95% CI = 0.54 to 1.07; HR for ≥ 9 MET-hr/week = 0.62, 95% CI = 0.36 to 1.06, likelihood ratio test $P = .80$).

Discussion

Our study is among the very few observational studies to evaluate the role of prediagnosis diet in mortality after a diagnosis of ovarian cancer. The most important finding was the marked 27% lower risk of mortality after ovarian cancer diagnosis in women who report higher overall dietary quality (tertile 3) compared with the lowest score (tertile 1). In this analysis, none of the individual dietary components was associated with mortality after ovarian cancer, suggesting that it is the overall dietary pattern that is relevant. No other publications have evaluated HEI in relation to ovarian cancer survival, although a few have suggested that diets higher in vegetables may be associated with better survival. A study by Nagle et al. suggested that higher total vegetable intake was associated with improved ovarian cancer survival (3), and a study of 341 cases and matched controls by Dolecek et al. (4) suggested that vegetables, in particular green and orange-yellow vegetables, were associated with 39% longer survival.

In stratified analysis, our results suggested that diet quality was not associated with survival after ovarian cancer in women with diabetes. Consistent with our findings, an earlier study of 341 ovarian cancer cases found that diabetes (not treated with metformin, a drug for hyperglycemia) was associated with higher mortality after ovarian cancer, such that women with a diagnosis of diabetes

Table 1. Age and stage at diagnosis, prediagnosis characteristics of ovarian cancer patients, and effects on all-cause mortality in the Women's Health Initiative (n = 636)

Characteristic	No. of deaths/total (%)	Crude HR (95% CI)	Adjusted* HR (95% CI)
Age at diagnosis, y			
< 60	27/57 (47.4)	1.00 (reference)	1.00 (reference)
60–69	141/271 (52.0)	1.42 (0.94 to 2.15)	0.94 (0.62 to 1.43)
70–79	146/245 (59.6)	2.07 (1.36 to 3.13)	1.33 (0.88 to 2.02)
≥ 80	40/63 (63.5)	3.29 (2.00 to 5.39)	2.16 (1.32 to 3.56)
Stage at diagnosis			
Localized	14/118 (11.9)	1.00 (reference)	1.00 (reference)
Regional	37/93 (39.8)	4.27 (2.27 to 8.04)	4.02 (2.14 to 7.58)
Distant	303/425 (71.3)	12.6 (7.19 to 22.0)	11.8 (6.76 to 20.7)
Race/ethnicity			
Non-Hispanic white	314/560 (56.1)	1.00 (reference)	1.00 (reference)
Black	25/40 (62.5)	1.47 (0.98 to 2.20)	1.78 (1.18 to 2.69)
Hispanic	6/18 (33.3)	0.66 (0.29 to 1.48)	0.63 (0.28 to 1.41)
Other/unknown	9/18 (50.0)	1.07 (0.55 to 2.08)	1.67 (0.86 to 3.26)
Education			
≤ High school	68/130 (52.3)	1.00 (reference)	1.00 (reference)
Some post-secondary	126/216 (58.3)	1.07 (0.79 to 1.43)	0.98 (0.73 to 1.32)
≥ College degree	157/284 (55.3)	1.00 (0.75 to 1.33)	0.96 (0.72 to 1.28)
Oral contraceptive use (ever)			
No	219/384 (57.0)	1.00 (reference)	1.00 (reference)
Yes	135/252 (53.6)	0.81 (0.66 to 1.01)	1.08 (0.85 to 1.37)
NSAID use (current)			
No	301/535 (56.3)	1.00 (reference)	1.00 (reference)
Yes	53/101 (52.5)	0.93 (0.69 to 1.24)	1.12 (0.83 to 1.50)
Smoking (current)			
No	331/599 (55.3)	1.00 (reference)	1.00 (reference)
Yes	23/36 (63.9)	1.13 (0.74 to 1.72)	1.19 (0.78 to 1.84)
Parity (n)			
0	40/84 (47.6)	1.00 (reference)	1.00 (reference)
1	27/48 (56.3)	1.27 (0.78 to 2.08)	1.17 (0.72 to 1.91)
2	89/168 (53.0)	1.16 (0.80 to 1.69)	0.99 (0.68 to 1.43)
3	85/149 (57.1)	1.23 (0.84 to 1.79)	0.94 (0.64 to 1.36)
4	52/98 (53.1)	1.01 (0.67 to 1.52)	0.81 (0.54 to 1.23)
≥ 5	60/87 (69.0)	1.64 (1.10 to 2.45)	1.11 (0.74 to 1.66)
Diabetes (ever)			
No	316/580 (54.5)	1.00 (reference)	1.00 (reference)
Yes	38/56 (67.9)	1.71 (1.22 to 2.39)	1.84 (1.31 to 2.60)
Body mass index, kg/m^2			
< 25	142/239 (59.4)	1.00 (reference)	1.00 (reference)
25–29.9	119/213 (55.9)	0.95 (0.75 to 1.22)	0.98 (0.77 to 1.25)
≥ 30	93/184 (50.5)	0.85 (0.65 to 1.10)	1.01 (0.78 to 1.31)
Waist circumference, cm			
≤ 88	219/387 (56.6)	1.00 (reference)	1.00 (reference)
> 88	135/249 (54.2)	1.07 (0.86 to 1.32)	1.27 (1.02 to 1.58)
Moderate-to-strenuous recreational physical activity, MET-hr/week			
0	161/274 (58.8)	1.00 (reference)	1.00 (reference)
> 0 – < 9	92/167 (55.1)	0.81 (0.62 to 1.04)	0.85 (0.66 to 1.10)
9 – < 15	40/86 (46.5)	0.70 (0.49 to 0.99)	0.75 (0.53 to 1.06)
≥ 15	61/109 (56.0)	0.84 (0.63 to 1.13)	0.82 (0.61 to 1.10)
Family history of ovarian cancer			
No	323/581 (55.6)	1.00 (reference)	1.00 (reference)
Yes	12/13 (92.3)	1.83 (1.03 to 3.25)	1.87 (1.05 to 3.33)
Unknown	19/42 (45.2)	0.72 (0.45 to 1.14)	0.76 (0.48 to 1.20)
Cardiovascular disease			
No	314/573 (54.8)	1.00 (reference)	1.00 (reference)
Yes	36/55 (65.5)	1.46 (1.04 to 2.07)	1.33 (0.94 to 1.90)

* All multivariable models were adjusted for age (continuous), and all models except for stage at diagnosis were adjusted for stage at diagnosis (localized, regional, distant). Missing data: education (n = 6), smoking (n = 1), parity (n = 2), cardiovascular disease (n = 8). CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent; NSAID = nonsteroidal anti-inflammatory drug.

Table 2. Associations between diet quality and mortality in ovarian cancer patients (n = 636)

Dietary energy or HEI score	Deaths, no. (%)	All-cause mortality HR (95% CI)*	Ovarian cancer-specific mortality HR (95% CI)*
Dietary energy			
Tertile 1 (≤ 1295 kcal/d)	118 (55.7)	1.00 (reference)	1.00 (reference)
Tertile 2	119 (56.1)	1.11 (0.85 to 1.44)	1.15 (0.87 to 1.53)
Tertile 3 (≥ 1719 kcal/d)	117 (55.2)	0.99 (0.76 to 1.30)	1.00 (0.75 to 1.35)
P_{trend}†		.98	.94
HEI total score			
Tertile 1 (≤ 66.0)	130 (61.3)	1.00 (reference)	1.00 (reference)
Tertile 2	110 (51.9)	0.71 (0.54 to 0.92)	0.68 (0.51 to 0.91)
Tertile 3 (≥ 74.3)	114 (53.8)	0.73 (0.55 to 0.97)	0.75 (0.55 to 1.01)
P_{trend}†		.03	.06
HEI 1: total fruit			
Low (< 2.5 points)	35 (58.3)	1.00 (reference)	1.00 (reference)
Medium (2.5 – < 5 points)	138 (55.4)	0.79 (0.53 to 1.17)	0.78 (0.51 to 1.19)
High (5 points)	181 (55.4)	0.82 (0.55 to 1.21)	0.84 (0.54 to 1.28)
P_{trend}†		.58	.77
HEI 2: whole fruit			
Low (< 2.5 points)	39 (57.4)	1.00 (reference)	1.00 (reference)
Medium (2.5 – < 5 points)	104 (54.7)	1.29 (0.88 to 1.89)	1.27 (0.84 to 1.92)
High (5 points)	211 (55.8)	1.19 (0.82 to 1.71)	1.20 (0.81 to 1.77)
P_{trend}†		.61	.58
HEI 3: total vegetables			
Low (< 2.5 points)	40 (64.5)	1.00 (reference)	1.00 (reference)
Medium (2.5 – < 5 points)	211 (53.3)	0.62 (0.43 to 0.89)	0.66 (0.44 to 1.01)
High (5 points)	103 (57.9)	0.70 (0.47 to 1.04)	0.76 (0.48 to 1.20)
P_{trend}†		.46	.78
HEI 4: dark green and orange vegetables, legumes			
Low (< 2.5 points)	188 (55.8)	1.00 (reference)	1.00 (reference)
Medium (2.5 – < 5 points)	142 (54.6)	0.97 (0.77 to 1.22)	0.97 (0.75 to 1.24)
High (5 points)	24 (61.5)	1.10 (0.71 to 1.72)	1.17 (0.74 to 1.87)
P_{trend}†		.91	.79
HEI 5: total grains			
Low (< 2.5 points)	19 (82.6)	1.00 (reference)	1.00 (reference)
Medium (2.5 – < 5 points)	232 (55.2)	0.88 (0.54 to 1.44)	0.97 (0.55 to 1.71)
High (5 points)	103 (53.4)	0.83 (0.49 to 1.38)	0.95 (0.52 to 1.71)
P_{trend}†		.44	.83
HEI 6: whole grains			
Low (< 2.5 points)	187 (52.4)	1.00 (reference)	1.00 (reference)
Medium (2.5 – < 5 points)	149 (60.1)	1.03 (0.83 to 1.29)	1.03 (0.81 to 1.31)
High (5 points)	18 (58.1)	0.84 (0.50 to 1.41)	0.89 (0.51 to 1.57)
P_{trend}†		.84	.96
HEI 7: milk			
Low (< 7.5 points)	183 (54.0)	1.00 (reference)	1.00 (reference)
Medium (7.5 – < 10 points)	105 (59.7)	1.12 (0.87 to 1.43)	1.15 (0.88 to 1.50)
High (10 points)	66 (54.6)	1.04 (0.77 to 1.40)	1.13 (0.82 to 1.54)
P_{trend}†		.66	.37
HEI 8: meat and beans			
Low (< 7.5 points)	55 (57.9)	1.00 (reference)	1.00 (reference)
Medium (7.5 – < 10 points)	126 (51.9)	0.76 (0.54 to 1.07)	0.77 (0.54 to 1.11)
High (10 points)	173 (58.1)	0.88 (0.64 to 1.20)	0.83 (0.59 to 1.17)
P_{trend}†		.83	.55
HEI 9: oils			
Low (< 7.5 points)	193 (57.3)	1.00 (reference)	1.00 (reference)
Medium (7.5 – < 10 points)	113 (57.1)	1.02 (0.80 to 1.30)	0.97 (0.75 to 1.27)
High (10 points)	48 (47.5)	0.80 (0.57 to 1.11)	0.82 (0.57 to 1.16)
P_{trend}†		.27	.30
HEI 10: saturated fat			
Low (< 7.5 points)	193 (56.6)	1.00 (reference)	1.00 (reference)
Medium (7.5 – < 10 points)	127 (54.0)	0.95 (0.74 to 1.21)	0.92 (0.70 to 1.21)
High (10 points)	34 (56.7)	0.96 (0.65 to 1.43)	1.11 (0.73 to 1.68)
P_{trend}†		.74	.93

(*Table continues*)

Table 2 (Continued).

Dietary energy or HEI score	Deaths, no. (%)	All-cause mortality HR (95% CI)*	Ovarian cancer-specific mortality HR (95% CI)*
HEI 11: sodium			
Low (0 points)	28 (52.8)	1.00 (reference)	1.00 (reference)
Medium (> 0 – < 2.5 points)	126 (58.9)	0.99 (0.65 to 1.52)	1.16 (0.71 to 1.89)
High (2.5 – 10 points)	200 (54.2)	1.00 (0.66 to 1.51)	1.14 (0.71 to 1.85)
P_{trend}†		.97	.75
HEI 12: calories from solid fat, alcohol, and added sugar (SoFAAS)			
Low (< 15 points)	162 (56.5)	1.00 (reference)	1.00 (reference)
Medium (15 – < 20 points)	150 (55.2)	0.92 (0.73 to 1.17)	0.99 (0.77 to 1.27)
High (20 points)	42 (54.6)	0.99 (0.68 to 1.43)	0.93 (0.61 to 1.41)
P_{trend}†		.71	.78

* Adjusted for age at diagnosis (continuous), stage at diagnosis (localized, regional, distant), race/ethnicity (non-Hispanic white, black, Hispanic, other/unknown), diabetes, physical activity (0, > 0 to < 9, 9 to < 15, ≥ 15 metabolic equivalent of tasks–hr/week), total energy intake (quintiles), waist circumference (≤ 88, > 88 cm), family history of ovarian cancer (no, yes, unknown), and clinical trial arms. CI = confidence interval; HEI = Healthy Eating Index; HR = hazard ratio.

† P_{trend} values are two-sided and were calculated using Cox proportional hazards regression, modeling each categorical dietary variable as ordinal, with the lowest category assigned a value of 1, middle category assigned a value of 2, and highest category assigned a value of 3.

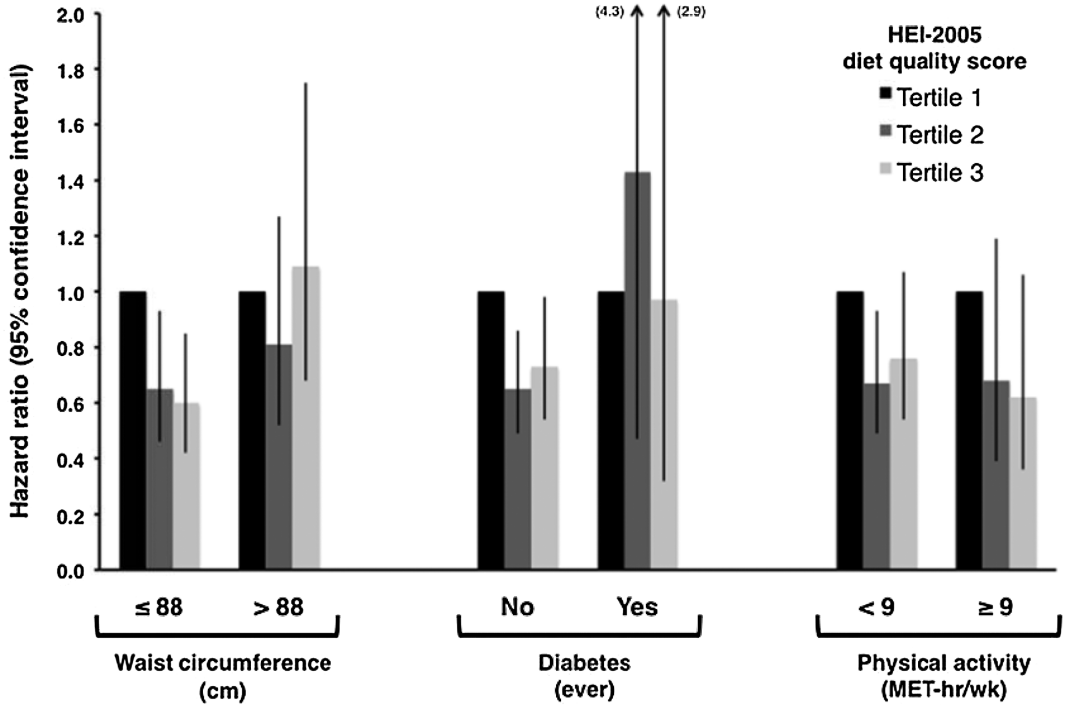

Figure 1. Association between Healthy Eating Index (HEI)–2005 diet quality score, in tertiles, and all-cause mortality among 636 ovarian cancer survivors, stratified by waist circumference, diabetes, and moderate-to-strenuous recreational physical activity. Cox proportional hazards regression models were adjusted for age at diagnosis, stage at diagnosis, race/ethnicity (non-Hispanic white, black, Hispanic, other/unknown), diabetes, physical activity (0, > 0 to < 9, 9 to < 15, ≥ 15 metabolic equivalent of tasks–hr/week), total energy intake (quintiles), waist circumference (≤ 88, > 88 cm), family history of ovarian cancer (no, yes, unknown), and clinical trial arms. HEI = Healthy Eating Index; MET = metabolic equivalent of tasks.

exhibited a 23% five-year survival rate compared with 37% in women without diabetes (28). Also, a 2011 study that included 570 healthy women and 72 women with diabetes previously treated for ovarian cancer demonstrated that median survival for those with diabetes was 1503 days vs 2464 days for those without (HR = 2.04, $P < .01$) (29). Our results are indirectly supported by evidence from a case-control analysis (72 case patients, 143 matched control patients) that showed metformin was associated with greater survival after ovarian cancer (30). Importantly, mechanistic studies have suggested that metformin augments the cytotoxicity of carboplatin (31) and cell growth (32) in ovarian cancer cell culture studies.

Additionally, we found that high HEI was associated with a 40% lower risk of mortality in women with WC at or below the recommended clinical cutpoint of ≤ 88 cm, but not in women with WC greater than 88 cm. WC is consistently associated with diabetes risk (33) and insulin resistance, a clinical condition known to contribute to the pathogenesis of cancer, but perhaps not specific to ovarian cancer or survival after diagnosis, for which data are lacking (34). The therapeutic targeting of insulin and insulin-like growth

factors to modify ovarian cancer survival has been proposed (35). Abdominal bloating/expansion has been associated with ovarian cancer risk (23), so elevated WC could reflect disease; however, we excluded all WC measurements within 12 months of diagnosis, limiting the likelihood that greater WC was disease-specific and not an indicator of visceral adiposity.

Several studies have evaluated the relationship between obesity and survival after ovarian cancer. A recent analysis in WHI suggested that higher BMI (> 30 kg/m^2) may be associated with lower overall mortality after ovarian cancer (36), as did findings from a review by Protani (37); however, these associations are not consistent (38,39). Ours is the first to relate WC to mortality after ovarian cancer, although central adiposity has been evaluated in relation to risk of ovarian cancer with mixed findings (40,41).

Few studies have evaluated prediagnosis physical activity in relation to ovarian cancer survival. The prospective cohort study by Moorman et al. demonstrated a modest 31% lower mortality in nonobese women who reported more than 2 hr/week regular physical activity (HR = 0.69, 95% CI = 0.47 to 1.00); overall HR for the entire sample was not statistically significant (42). A recent WHI analysis by Zhou et al. also suggested higher survival after ovarian cancer in women reporting higher vigorous physical activity (36).

There are limitations to our analysis. First, it is possible that diet, waist circumference, and physical activity changed with diagnosis and between diagnosis and study endpoints, given the potential for ovarian cancer treatment to change food tolerance and/or a woman's effort to increase healthy food selections, physical activity, or even body weight after a cancer diagnosis (43). We did not have adequate measures of these behaviors between diagnosis and death to evaluate postdiagnosis exposures. Second, we chose to use all available repeat measures of diet and covariables to better characterize these exposures. This may place greater weight on dietary behavior closer to diagnosis even with exclusion of data collected within 12 months of diagnosis. Third, our analysis is based on self-reported dietary intake using FFQ, an instrument that has known measurement error (44) and has been demonstrated to obscure the relationship between energy intake and cancer risk in the WHI (45). Fourth, our analysis lacked information regarding the optimal debulking of tumor burden during surgical therapy for ovarian cancer and specifics of chemotherapy, yet these factors would influence survival after diagnosis. Also, increased BMI, but not WC specifically, has been associated with risk of endometroid and mucinous tumors, subtypes that have a somewhat better survival than the serous subtype. However, a large number of cases with missing data on tumor subtype restricted a full evaluation of histology in interpreting our results. Finally, while we found a differential association between HEI and mortality in women with or without diabetes, CVD comorbidity was not associated with mortality. However, a recent analysis suggested that heart rate and venous thromboembolic events, specifics of which were not available for WHI, were associated with worse survival after ovarian cancer (46).

In summary, our results represent one of only a few published analyses regarding the role of prediagnosis diet on mortality after ovarian cancer. Here we demonstrate that self-reported dietary quality at least 12 months prior to diagnosis was associated with a statistically significant 27% lower risk of death after ovarian cancer. Benefits may be greater in women with WC ≤ 88 cm or without history of diabetes. A large (n = 1070) randomized, controlled trial is currently underway to test the hypothesis that dietary changes toward higher HEI, along with physical activity, adopted after treatment for stage II–IV ovarian cancer will improve progression-free survival (NCT 00719303). Whether changing diet to increase diet quality score after ovarian cancer diagnosis would offer improvements in mortality is yet to be determined.

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Funding

This work was supported by the National Heart, Lung, and Blood Institute, National Cancer Institute, National Institutes of Health, US Department of Health and Human Services (grant number P30 CA023074), through contracts (grants numbered HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C and CCSG-CA023074).

Notes

The study sponsors had no role in the design of the study, the collection, analysis, or interpretation of the data, the writing of the manuscript, nor the decision to submit the manuscript for publication.

The authors have no conflicts of interest to declare.

The authors wish to acknowledge the following individuals:

Manuscript development support: Nicole Bergier, University of Arizona

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, MD) Jacques Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, and Nancy Geller

Clinical Coordinating Center: Clinical Coordinating Center: (Fred Hutchinson Cancer

Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and CharlesKooperberg

Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical

School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University,

Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA)

Marcia L. Stefanick; (Ohio State University, Columbus, OH) Rebecca Jackson; (University

of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY)

Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher;

(University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Pittsburgh,

Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem,NC) Sally Shumaker

Women's Health Initiative Memory Study: (Wake Forest University School of Medicine,

Winston-Salem, NC) Sally Shumaker

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