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ARTICLE

Epidemiology

Association between dietary inflammatory potential and mortality after cancer diagnosis in the Women's Health Initiative

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BACKGROUND: Chronic inflammation is implicated in cancer prognosis and can be modulated by diet. We examined associations between post-diagnosis dietary inflammatory potential and mortality outcomes among post-menopausal women diagnosed with cancer in the Women's Health Initiative (WHI).

METHODS: Energy-adjusted dietary inflammatory index scores (E-DII) were calculated from dietary and supplemental intake data collected on the first food frequency questionnaire following the diagnosis of primary invasive cancer for 3434 women in the WHI. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for risk of death from any cause, cancer, cardiovascular disease (CVD) and other causes by post-diagnosis quartiles of E-DII. Subgroup analyses by cancer stage and grade were performed.

RESULTS: There were 1156 deaths after a median 13 years of follow-up from the date of a cancer diagnosis. In the multivariable-adjusted analyses, a more anti-inflammatory diet plus supplements after cancer diagnosis was associated with lower all-cause mortality, cancer mortality, CVD mortality and mortality from other causes with $HRs_{Q1vs.Q4}$ ranging from 0.47 to 0.68 (all *P*-trends < 0.05). Associations were stronger for cancers diagnosed at more distant stages or moderately differentiated grades.

CONCLUSION: A more anti-inflammatory diet plus supplements after a cancer diagnosis may improve survival for post-menopausal cancer survivors.

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BACKGROUND

The number of cancer survivors living in the United States (US) increases every year due to the ageing of the population and increased survival owing to improvements in early-detection approaches and treatment options for many types of cancer [1]. There are an estimated 16.9 million people (~52% females) with a history of cancer alive in the US as of January 2019, and this number is estimated to increase by at least 30% by 2030 [1]. Compared to individuals who have never been diagnosed with any cancer, cancer survivors are at increased risk of early mortality due to their cancer diagnosis, recurrence, second primary cancer, or comorbidities such as cardiovascular disease (CVD) [2].

Cancer patients are at increased likelihood of adopting lifestyle modifications after the cancer diagnosis, particularly improvements in dietary quality [3]. It is therefore important to determine whether and how diet after a cancer diagnosis is associated with cancer survival. Previous research has identified several a priori and *a posteriori* dietary patterns after a cancer diagnosis that were significantly associated with survival outcomes among cancer patients, indicating better overall dietary quality could lower mortality risk [2, 4–9]. However, these studies almost all focused on cancer survivors of a specific cancer type, such as colorectal or breast cancers, instead of overall cancer survivors who often share a tumour-induced microenvironment leading to common post-diagnosis risk factors [10]. Among the dietary patterns that have been examined post-diagnosis, the dietary inflammatory index (DII) is among the few that have been developed based on a specific disease mechanism, i.e. chronic inflammation, a critical biological substrate and regulator implicated in cancer progression and survivorship [11–15].

The DII is a literature-derived dietary index which assesses the inflammatory potential of the diet and has been constructed and validated with multiple inflammation biomarkers, including interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) in

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the Women's Health Initiative (WHI) [11, 16]. We previously reported lower CVD mortality risk among post-menopausal women diagnosed with invasive breast cancers and lower all-cause mortality among women diagnosed with colorectal cancers in the WHI who consumed a more anti-inflammatory diet [2, 17]. In the current study, we examined post-diagnosis dietary inflammatory potential in relation to mortality outcomes, including all-cause mortality, cancer mortality, CVD mortality and mortality from other causes, among all cancer patients diagnosed in the WHI. The larger sample size of all cancer patients increased power as compared to our previous analyses of breast or colorectal cancer survivors [2, 17] and allowed for the examination of associations stratified by cancer stage and grade at diagnosis. We hypothesised that a more anti-inflammatory diet post-cancer diagnosis would be associated with lower mortality risk.

METHODS

Study population

The WHI, a large and complex national clinical study, was initially established to explore the causes of some of the most common diseases among post-menopausal women. Details of the study design have been published elsewhere [18, 19]. Briefly, between 1993 and 1998, a total of 161,808 women aged 50–79 years were enroled from 40 clinical centres across the US to one or multiple randomised clinical trials (CT) or to the Observational Study (OS). The CTs investigated the health effects of post-menopausal hormone therapy, dietary modification (DM), or calcium and vitamin D supplement. The initial WHI study ended in 2005, and follow-up of all women who consented continued in the WHI Extension Study I (2005–2010) and II (2010–2015). Only participants in the WHI-DM and WHI-OS completed multiple food frequency questionnaires (FFQs) during follow-up. Therefore, the present analysis focused on women from the WHI-DM and WHI-OS who were diagnosed with at least one invasive cancer confirmed by pathology report [20] during follow-up and who completed a FFQ after diagnosis of first invasive cancer, which was also regarded as an individual's first primary cancer (overall = 4428; WHI-DM = 2493; WHI-OS = 1935). Of these, we excluded 187 women (104 from WHI-DM and 83 from WHI-OS) who had daily energy intake out of the range of 600–5000 kcals/day [2], and women who survived less than 6 months after diagnosis to meet Cox proportional hazard assumption ($n = 23$). We further excluded subjects with missing data on covariates, including cancer grade ($n = 26$), cancer stage ($n = 179$), educational level ($n = 26$), physical activity ($n = 304$), smoking status ($n = 57$), body mass index (BMI) ($n = 28$) and income ($n = 164$), for a final sample size of 3434 women in the analysis. We listed the number and percentage of cancer survivors by cancer type included in the current analysis in Supplemental Table 1. The WHI protocol was approved by the Institutional Review Boards at the Clinical Coordinating Center (CCC) at the Fred Hutchinson Cancer Research Center (Seattle, WA) and at each of the participating Clinical Centers. All participants provided written informed consent in accordance with the U.S. Common Rule.

Dietary assessment

A self-administered FFQ was used to assess participants' diet in the past three months. The FFQ was designed to capture the multi-ethnic and regional eating patterns in the US [21]. The main section of FFQ contained 122 foods or food groups with questions on the usual frequency of intake (from "never or less than once per month" to "2+ per day" for foods and to "6+ per day" for beverages) and portion size (small, medium or large compared to the stated medium portion size) [22]. In addition, nineteen adjustment questions permitted more refined calculation of fat intake by asking questions related to food preparation practices, and types of fat added [22]. Nutrient intakes were calculated by linking FFQ responses to the Nutrition Data Systems for Research (NDS-R, version 2005, University of Minnesota, Minneapolis, MN) [23]. In a study with 113 women selected from the WHI, the energy-adjusted correlation coefficients calculated by comparing the intake of 30 nutrients estimated from the FFQ with means from four 24 h dietary recalls and a 4-day food record ranged from 0.18 for vitamin B12 to 0.68 for magnesium with a mean of 0.49 [22].

All WHI-DM participants completed the FFQ at baseline and year 1 of follow-up, and thereafter one third of participants completed the FFQ on a rotating basis each year from year 2 to year 9. In the WHI-OS, participants completed an FFQ at baseline and at year 3 of follow-up. We analysed participants' dietary data from their first occurring FFQs after primary cancer diagnoses, which occurred on average 1.5 years after cancer diagnoses. Dietary supplement use information was assessed at baseline and annual visits for WHI-DM and at year 3 follow-up visits for WHI-OS when participants brought in their dietary supplements in their original pill bottles. Similar to the identification of post-cancer diagnosis FFQ, we used dietary supplement information reported most recently after participants' first primary cancers.

Calculation of energy-adjusted DII score

The majority of participants (95%) in the present study took supplements after a primary cancer diagnosis, and most nutrients contained in dietary supplements have somewhat anti-inflammatory properties [11]. Therefore, we calculated both energy-adjusted DII (E-DII) score from diet plus supplements and from diet only to represent overall post-cancer dietary inflammatory potential with and without supplements.

E-DII score for each individual was calculated by linking dietary intake derived from the post-cancer diagnosis FFQ with the literature-derived inflammatory effect scores for food parameters included in the DII [11]. A detailed description of the development of DII has been published previously [11]. Briefly, inflammatory effect scores for forty-five food parameters (i.e. components of DII), which included macronutrients and micronutrients as well as some bioactive components such as flavonones were derived based on findings of 1943 qualifying research articles published until 2010 on the effect of dietary factors on six well-established inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein (CRP)) [11]. The WHI FFQ-derived food and nutrient consumption was first adjusted for total energy using a nutrient-density approach [24]. To avoid the arbitrariness as a result of simply using raw intake amounts, the energy-adjusted dietary intake was subsequently standardised to a worldwide dietary database representing energy-adjusted dietary intake from 11 populations living in different countries across the world. To minimise the effect of right skewing, the standardised scores were converted to a proportion (value from −1 to 1), then these proportions were centred (on zero) by doubling each value and subtracting 1. The centred proportion score was then multiplied by the literature-derived inflammatory effect score for each DII component and summed across all components to obtain the overall E-DII score [11]. Higher E-DII scores represent more pro-inflammatory diets, whereas lower (i.e. more negative) E-DII scores indicate more anti-inflammatory diets. In our study, we used 32 components available in the WHI FFQ to calculate the E-DII score, which included alcohol, vitamin B12, vitamin B6, β-carotene, caffeine, carbohydrate, cholesterol, energy, total fat, fibre, folic acid, iron, magnesium, monounsaturated fatty acids, niacin, n-3 fatty acids, n-6 fatty acids, onion, protein, polyunsaturated fatty acids, riboflavin, saturated fat, selenium, thiamin, trans fat, vitamin A, vitamin C, vitamin D, vitamin E, zinc, green/black tea, isoflavones, as thirteen DII components, including ginger, turmeric, garlic, oregano, pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones and anthocyanidins, were not available. The DII score has been construct-validated against inflammatory biomarkers in over 40 populations, including in the WHI where it was observed that the DII score calculated from diet plus supplement intake of 32 components we included in this study was found to be significantly associated with concentrations of the inflammatory biomarkers IL-6 and TNF-α receptor 2 [16].

Assessments of other covariates

Demographic and socioeconomic information on age at study entry, race/ethnicity, educational level and family income level was self-reported at baseline. Smoking status and recreational physical activity, which included walking, mild, moderate and strenuous physical activity in MET-hours/week, were assessed at baseline using the self-administered questionnaires for all WHI-DM and WHI-OS participants and updated for the WHI-DM only at years 1, 3, 6 and 9. Data on smoking status and physical activity assessed at baseline were used in the analyses to ensure consistency in the assessment timing in the entire study population [25]. Physical activity was categorised into four levels (0, 0.1–3,3.1–8.9, 9 or more MET-hours/week) to be consistent with previous publications in this population [2, 25]. Baseline, instead of post-cancer diagnosis, weight and height, which were measured using standard methods during clinic visits, were used to calculate BMI as weight (kg)/height $(m)^2$ due to considerable missing data on post-cancer diagnosis information for WHI-OS [2]. BMI was further categorised based on World Health Organization criteria [26].

Incident cancer adjudication and ascertainment methods have been described in detail elsewhere [20]. Briefly, local physician adjudicators first reviewed the medical records of participants who self-reported outcomes to assign a diagnosis, followed by centralised review and coding based on diagnostic documents at the CCC. Detailed cancer characteristics, such as stage, anatomic subsite, diagnosis date, the extent of disease (stage, tumour size, laterality), tumour morphology (behaviour, grade, histology) were recorded using the Surveillance, Epidemiology and End Results coding guidelines [27].

Ascertainment of death

Four mortality outcomes were included in our analyses: death from any cause, death from total cancer, death from CVD and death from other causes than cancers and CVD. Based on ICD-9 codes 390–459 or ICD-10 codes I00–I99, CVD deaths included deaths from definite coronary heart disease (CHD), cerebrovascular diseases, pulmonary embolism, possible CHD (defined as no known non-atherosclerotic cause and death certificate consistent with CHD as an underlying cause), other CVD and unknown CVD. Causes of death other than cancers and CVDs in the WHI included homicide, accident, suicide, other injuries, Alzheimer's, pneumonia, chronic obstructive pulmonary disease, pulmonary fibrosis, renal failure, sepsis, amyotrophic lateral sclerosis, dementia, pancreatic diseases, Parkinson's disease, hepatic cirrhosis, known other causes and unknown causes. The case number and percentage of each death caused among the total deaths in the study were described in Supplemental Table 2. Participants' vital statuses were continuously tracked via mailings for the WHI-OS or by contacts at annual clinic visits for WHI-CT [18]. Autopsy and hospitalisation records were the most important source to determine the underlying cause of death; otherwise, death certificates, medical records or other records were used. Data linkage with the National Death Index was performed periodically as a supplemental method to identify otherwise unreported deaths and to confirm causes of death [20].

Statistical analysis

Sociodemographic, clinical and lifestyle characteristics of the study population were described with means and standard errors for continuous variables and number and frequencies for categorical variables by quartiles of E-DII scores from diet plus supplements.

For each of the studied mortality outcomes, participants were followed up from their first primary cancer diagnoses until death or censored at a loss to follow-up, the last National Death Index search date for the participant, or the end of data collection in the WHI Extension II Study by September 2014. Cox proportional hazards models, with person-years as the underlying time metric, were applied to estimate age- and energy-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) with women in the highest E-DII quartile as the referent. WHI study arms, family income levels, age at cancer diagnosis, race/ethnicity, educational level, baseline recreational physical activity level, baseline smoking status, baseline BMI status, cancer stage, cancer grade, years from cancer diagnosis to FFQ and daily total energy intake were adjusted for in the multivariable-adjusted model to be consistent with prior studies on post-cancer dietary quality and mortality risk in this population [2, 17, 25]. Cancer stage and cancer grade were used as proxies for cancer treatment data which is only available on a subset of women enroled in the WHI Life and Longevity After Cancer (LILAC) study [28, 29]. We first conducted separate multivariable-adjusted analyses with and without BMI in the model, considering BMI may play a role as a mediator in the diet and mortality association [30]. However, since the two models generated similar effect estimates, we reported the final multivariable model, including BMI. We conducted the same analysis for E-DII score from diet only and from diet plus supplements with the exception that we additionally adjusted for DII from supplement use in the diet-only models, which was calculated by subtracting DII from diet only from DII from diet plus supplements. The proportional hazard (PH) assumption was examined using the Schoenfeld residual test, and there was no evidence that E-DII or any covariates violated the PH assumption [31]. To account for the immortal time bias that no subjects were at risk of death in the time period from cancer diagnosis to FFQ completion, we added a binary time-dependent covariate in the model to stratify participants' vital status before and after the post-diagnosis FFQ. To test the linear trend of mortality across E-DII quartiles, a continuous E-DII variable was used after confirming the linear assumption was sufficient based on the restricted cubic spline test [32].

Diet may affect survival outcomes of cancer patients differentially according to cancer stage and cancer grade, which are important predictors for prognosis [9, 33]. Therefore, stratified analyses on the associations of post-cancer diagnosis E-DII with all-cause mortality and with total cancer mortality were performed by cancer stage and cancer grade separately. Stratified analyses were not performed for the other two mortality outcomes due to the limited number of death cases. We also performed stratified analyses by smoking status and BMI status on E-DII from diet and supplements with all-cause mortality, as evidence suggested anti-inflammatory diets, including supplements may reduce oxidative stress from smoking and improve metabolic function in obesity [34, 35]. The likelihood ratio tests with cross-products of E-DII quartiles and each above-mentioned effect modifier added separately into the multivariable-adjusted Cox model were used to assess the statistical significance of the effect modifications.

In sensitivity analyses, we excluded participants from the DM-intervention arm who were known to be actively attempting to change diet and reran analyses for all four mortality outcomes. Secondly, we added baseline CVD status (yes/no) into the multivariable-adjusted Cox model because prevalent CVD cases at baseline were likely to change their diet habits even before a cancer diagnosis, and they were also at a higher risk of mortality in the follow-up compared to CVD disease-free participants which could attenuate the results. Thirdly, we excluded subjects with an FFQ completed within (1) 6 months and (2) 1.5 years (median interval from cancer diagnosis to FFQ completion) after a cancer diagnosis to minimise reverse causality as a cancer treatment may have affected diet in this period due to side effects. We also added baseline E-DII as a covariate in the multivariable-adjusted model to account for the baseline dietary effect. To evaluate potential selection bias as a result of removing women who died before they could complete a FFQ after cancer diagnoses, we compared the distributions of important demographic, lifestyle factors and tumour characteristics between our study sample and all the cancer survivors ($n = 21{,}964$) from which our study population was drawn.

All statistical analyses were conducted using SAS (version 9.4, Cary, NC). All tests were two-sided with P-value < 0.05 considered as statistical significance if not otherwise noted.

Reporting summary

Further information on experimental design is available in the Nature Research Reporting Summary linked to this paper.

RESULTS

Among the overall cancer survivors in this study, the top three diagnosed primary cancers were breast cancer (52.7%), colorectal cancer (11.1%) and endometrial cancer (9.2%) (Supplemental Table 1). After a median follow-up of 13.0 years, 1156 deaths occurred; among them, 60.1% were from cancer and 14.4% were from CVD (Supplemental Table 2). E-DII scores from diet plus supplements ranged from −7.0 to +3.8, and E-DII scores from diet only ranged from −5.96 to 4.13. As shown in Table 1, compared to post-menopausal women with the most pro-inflammatory diet plus supplements (i.e. E-DII quartile 4), women consuming diet plus supplements with more anti-inflammatory potential reported more recreational physical activity at baseline, and were more likely to be non-Hispanic White, have lower BMI, higher educational level, higher family income level and were less likely to be current smokers.

HRs for four mortality outcomes across E-DII quintiles from diet plus supplements are presented in Table 2. Compared to women with most pro-inflammatory diets plus supplements, women whose diet plus supplements intake were most anti-inflammatory had 42% lower risk of death from any cause ($HR_{Q1vs.Q4} = 0.58$, 95% CI = 0.49–0.70, P-trend < 0.001), 42% lower risk of death from cancer ($HR_{Q1vs.Q4} = 0.58$, 95% CI = 0.46–0.73, P-trend < 0.001), 53% lower risk of death from CVD ($HR_{Q1vs.Q4} = 0.47$, 95% CI = 0.28–0.78, P-trend = 0.04) and 32% lower risk of death from other causes ($HR_{Q1vs.Q4} = 0.68$, 95% CI = 0.48–0.96, P-trend = 0.03) (Table 2). The associations with all four mortality outcomes for E-DII from diet only were weaker than E-DII from diet plus supplements, but remained statistically significant for all-cause

Table 1. Characteristics of 3434 post-menopausal women diagnosed with invasive cancers in the WHI-DM and OS by quartiles of E-DII score from diet plus supplements.

	Most anti-inflammatory			**Most pro-inflammatory**
	E-DII Quartile 1 (−7.001, −4.434)	**E-DII Quartile 2 (−4.433, −3.420)**	**E-DII Quartile 3 (−3.419, −1.897)**	**E-DII Quartile 4 (−1.896, 3.790)**
No. of subjects	859	858	858	859
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Age at cancer diagnosis (years)	65.78 (0.24)	66.85 (0.23)	66.76 (0.23)	66.75 (0.24)
Years from cancer diagnosis to FFQ	1.48 (0.03)	1.46 (0.03)	1.41 (0.04)	1.40 (0.04)
Total energy intake after cancer diagnosis (kcal/day)	1371.13 (14.99)	1488.08 (17.25)	1604.16 (19.60)	1676.72 (23.14)
Physical activity at enrolment (MET-hours/week)	15.37 (0.49)	12.74 (0.44)	10.85 (0.42)	9.48 (0.42)
	N (%)[a]	N (%)[a]	N (%)[a]	N (%)[a]
WHI components				
WHI OS	460 (53.55)	411 (47.90)	375 (43.71)	330 (38.42)
WHI DM-intervention	210 (24.45)	212 (24.71)	159 (18.53)	131 (15.25)
WHI DM-control	189 (22.00)	235 (27.39)	324 (37.76)	398 (46.33)
Race/Ethnicity				
White non-Hispanic	774 (90.10)	781 (91.03)	757 (88.23)	727 (84.63)
Hispanic/Latino	14 (1.63)	17 (1.98)	17 (1.98)	24 (2.79)
Black/African American	35 (4.07)	36 (4.20)	52 (6.06)	80 (9.31)
Other	36 (4.19)	24 (2.80)	32 (3.73)	28 (3.26)
Educational level				
High school or below	174 (20.26)	223 (25.99)	227 (26.46)	306 (35.62)
Some college	243 (28.29)	222 (25.87)	257 (29.95)	259 (30.15)
College	113 (13.15)	111 (12.94)	114 (13.29)	90 (10.48)
Postgraduate	329 (38.30)	302 (35.20)	260 (30.30)	204 (23.75)
Family income level				
<20,000	91 (10.59)	98 (11.42)	133 (15.50)	153 (17.81)
20,000–49,999	343 (39.93)	407 (47.44)	387 (45.10)	421 (49.01)
≥50,000	425 (49.48)	353 (41.14)	338 (39.39)	285 (33.18)
Cancer stage				
Localised	618 (71.94)	593 (69.11)	562 (65.50)	547 (63.68)
Regional	174 (20.26)	187 (21.79)	221 (25.76)	210 (24.45)
Distant	67 (7.80)	78 (9.09)	75 (8.74)	102 (11.87)
Cancer grade				
Well differentiated	162 (18.86)	184 (21.45)	151 (17.60)	130 (15.13)
Moderately differentiated	315 (36.67)	272 (31.70)	317 (36.95)	301 (35.04)
Poorly differentiated	161 (18.74)	175 (20.40)	148 (17.25)	184 (21.42)
Anaplastic	34 (3.96)	27 (3.15)	39 (4.55)	28 (3.26)
T cell or B cell	23 (2.68)	22 (2.56)	29 (3.38)	33 (3.84)
Unknown/not done	164 (19.09)	178 (20.75)	174 (20.28)	183 (21.30)
Smoking status at enrolment				
Never smoked	392 (45.63)	439 (51.17)	399 (46.50)	410 (47.73)
Past smoker	419 (48.78)	379 (44.17)	413 (48.14)	376 (43.77)
Current smoker	48 (5.59)	40 (4.66)	46 (5.36)	73 (8.50)
BMI status at enrolment (kg/m^2)				
Underweight (BMI < 18.5)	8 (0.93)	3 (0.35)	7 (0.82)	3 (0.35)
Normal weight (18.5≤BMI < 25)	355 (41.33)	309 (36.01)	246 (28.67)	200 (23.28)
Overweight (25 ≤ BMI < 30)	293 (34.11)	291 (33.92)	300 (34.97)	284 (33.06)
Obese (BMI ≥ 30)	203 (23.63)	255 (29.72)	305 (35.55)	372 (43.31)

BMI body mass index, *DM* dietary modification, *E-DII* energy-adjusted dietary inflammatory index, *FFQ* food frequency questionnaire, *OS* observational study, *SE* standard error, *WHI* Women's Health Initiative.

[a]The sum of percentages in certain E-DII quartile for some categorical variables may not add up to 100% because of rounding.

mortality, cancer mortality and CVD mortality (all P-trends < 0.05) (Supplemental Table 3).

In the stratified analyses, the associations between anti-inflammatory diet plus supplements intake and all-cause mortality appeared stronger among those with late-stage cancer, with HRs of 0.70 (95% CI = 0.55–0.90) for localised stage, 0.63 (95% CI = 0.44–0.90) for regional stage and 0.36 (95% CI = 0.24–0.55) for distant stage, although no significant effect modification was detected ($P_{interaction} = 0.34$) (Table 3). Similarly, for cancer mortality, there was a suggestion of stronger associations of post-diagnosis anti-inflammatory diet plus supplements intake among women with cancers diagnosed at a later stage (for distant cancers: $HR_{Q1vs.Q4} = 0.38$, 95% CI = 0.24–0.60, P-trend < 0.001). There was no significant interaction between cancer grade and E-DII for either all-cause mortality ($P_{interaction} = 0.19$) or cancer mortality ($P_{interaction} = 0.29$). Only women diagnosed with moderately differentiated cancers had lower all-cause mortality risk associated with a more anti-inflammatory diet plus supplements ($HR_{Q1vs.Q4} = 0.65$, 95% CI = 0.48–0.89, P-trend = 0.02). Associations with cancer mortality were attenuated and no longer statistically significant when stratified by cancer grade, likely due to reduced sample size (Table 3). E-DII from diet only had similar patterns of associations with all-cause mortality when stratified by cancer stage and cancer grade, but associations were generally weaker compared to results for E-DII from diet plus supplements. The association between cancer mortality and inflammatory potential from diet only was statistically significant only among women diagnosed at distant stages (Supplemental Table 4). Effect modification on the association between E-DII score from diet plus supplements and all-cause mortality was not statistically significant by smoking status (P-interaction = 0.67) or BMI status (P-interaction = 0.21) (data not shown).

In the sensitivity analyses excluding women in the DM-intervention arm ($n = 712$) or excluding those with FFQs completed within 6 months ($n = 716$) or 1.5 years ($n = 1986$) after their cancer diagnoses, post-diagnosis mortality associations with E-DII from diet plus supplements were not materially changed for any outcome, though a significant trend was found only for all-cause mortality and total cancer mortality but not CVD-specific mortality or mortality from other causes (Table 4). Adding CVD status at baseline did not change the mortality associations with E-DII from diet plus supplements (Table 4). The sensitivity analyses for E-DII from diet only also generated similar estimates of association with mortality risk as compared to those from primary analyses (Supplemental Table 5). Adding baseline E-DII in the multivariable-adjusted model did not substantially change mortality associations for both E-DII from diet only and from diet plus supplements (data not shown). Compared to all the women diagnosed with cancer during follow-up of the WHI, our study sample was younger at cancer diagnosis, had shorter interval from enrolment to diagnosis of first invasive cancer, was more likely to be obese, be in the WHI-DM arm, have higher education level and family income level and more likely to be diagnosed at earlier cancer stages and with well or moderately differentiated cancer grades, but were less likely to be current smokers at baseline (Supplemental Table 6).

DISCUSSION

In this large prospective cohort study of post-menopausal women diagnosed with invasive cancers, consuming a more anti-inflammatory diet plus supplements after cancer diagnosis was associated with lower all-cause mortality, cancer mortality, CVD mortality and mortality from other causes compared to women with more pro-inflammatory diet plus supplements intake. Associations with all-cause and cancer mortality appeared to be stronger among women diagnosed with cancers at the more distant stages or more poorly differentiated grades. Similar patterns of mortality associations but with slightly weaker strength were observed for E-DII from diet only as compared to E-DII from diet plus supplements.

The results of this study corroborated previous findings related to post-diagnosis DII and mortality risk among breast cancer survivors and colorectal cancer survivors [2, 17, 36–39]. In our previously published WHI study of 2150 post-menopausal women who were diagnosed with invasive breast cancer, more anti-inflammatory diet plus supplements intake post-diagnosis was associated with a 56% lower risk of CVD death ($HR_{Q1VSQ4} = 0.44$, 95% CI = 0.24–0.82, P-trend = 0.005) and an 18% non-statistically significant lower all-cause mortality ($HR_{Q1VSQ4} = 0.82$, 95% CI = 0.63–1.05, P-trend = 0.17) [2]. In another WHI study, among 463 WHI post-menopausal women who developed colorectal cancer during follow-up, the most anti-inflammatory tertile of E-DII scores from diet plus supplements was related to significantly lower all-cause mortality ($HR_{T1vsT3} = 0.49$, 95% CI = 0.31–0.79) compared to the most pro-inflammatory E-DII tertile, but no association was found for total cancer mortality likely as a result of a limited number of cancer deaths in that smaller subsample of the WHI [17]. Due to the additional exclusion of participants with missing data on covariates in the current study, approximately 16% of breast cancer and 18% of colorectal cancer survivors in the previous studies were excluded in this study. Given that the association of E-DII from diet and supplements with all-cause mortality became stronger in women diagnosed with invasive cancers other than breast cancer or colorectal cancers ($HR_{Q1VSQ4} = 0.48$, 95% CI = 0.37–0.63) than that among the total cancer survivors ($HR_{Q1VSQ4} = 0.58$, 95% CI = 0.49–0.70), we could speculate the association we observed for total mortality in the present study was not mainly driven by these two largest cancer survivor groups in this study. In the previous study, the significant association of the most anti-inflammatory diets and supplements on all-cause mortality was present only among colorectal cancer survivors with regional/distant cancer stage or well/moderately differentiated cancer grades, which was comparable to our stratified associations among all cancer survivors where a stronger association appeared among women with more advanced cancer stages and moderately differentiated grade [17]. These findings of an effect in individuals with more advanced cancer stages were confirmed in another European cohort with 1404 long-term colorectal cancer survivors in which a significant positive association between DII and all-cause mortality was only present among patients with metastatic disease [38], and in an Italian retrospective cohort study with 726 prostate cancer patients where a strong relationship between elevated DII and increased risk of death from all-causes was only observed in patients with more aggressive prostate cancer who had Gleason score of 7–10 ($HR_{T3\ vs\ T1} = 2.78$, 95% CI = 1.41–5.48) but not among men with Gleason score of 2–6 [40]. Other than WHI, two other cohorts (one in Korea and the other in the US) investigated post-cancer diagnostic DII in relation to overall mortality among 511 and 1064 breast cancer survivors with an average age of 51.9 and 65.3, respectively, and both concluded that improved survival was observed with a more anti-inflammatory diet and anti-inflammatory diet plus supplements, which were consistent with our findings [36, 37]. However, no association was identified between DII following diagnosis of ovarian cancer and overall survival among 1375 ovarian cancer survivors in the Australian Ovarian Cancer Study [41].

Other a priori post-cancer diagnostic dietary indices have been investigated in a limited number of studies for their associations with overall mortality and cause-specific mortality, with the majority focusing on breast cancer and colorectal cancer survivors [39]. Consistent with our study findings for DII from diet only, these previous studies, which included total sample sizes of cancer survivors varying considerably from 230 to 8482 and total death cases from 121 to 2600 reported that better overall dietary quality, such as with the Healthy Eating Index (HEI) [6, 25, 42] or insulin-related scores [7, 43, 44] which were characterised by greater intake of foods that generally have anti-inflammatory potential

Table 2. Age-adjusted and multivariable-adjusted hazard ratios for post-diagnosis E-DII from diet plus supplements in relation to mortality outcomes among 3434 women diagnosed with invasive cancers in the WHI-DM and OS.

	Most anti-inflammatory E-DII Quartile 1	E-DII Quartile 2	E-DII Quartile 3	Most pro-inflammatory E-DII Quartile 4	*P*-trend[a]
All-cause mortality					
No. of total deaths	226	284	302	344	
Age and energy-adjusted HR (95% CI)[b]	0.54 (0.45–0.64)	0.70 (0.59–0.82)	0.79 (0.68–0.92)	1.00 (ref)	<0.001
MV-adjusted HR (95% CI)[b,c]	0.58 (0.49–0.70)	0.78 (0.66–0.92)	0.85 (0.72–0.99)	1.00 (ref)	<0.001
Total cancer mortality					
No. of cancer deaths	137	167	184	207	
Age and energy-adjusted HR (95% CI)[b]	0.55 (0.44–0.69)	0.71 (0.58–0.87)	0.82 (0.67–1.00)	1.00 (ref)	<0.001
MV-adjusted HR (95% CI)[b,c]	0.58 (0.46–0.73)	0.77 (0.62–0.95)	0.87 (0.71–1.06)	1.00 (ref)	<0.001
CVD mortality					
No. of CVD deaths	26	45	45	50	
Age and energy-adjusted HR (95% CI)[b]	0.44 (0.27–0.72)	0.74 (0.49–1.11)	0.79 (0.53–1.19)	1.00 (ref)	0.01
MV-adjusted HR (95% CI)[b,c]	0.47 (0.28–0.78)	0.83 (0.54–1.28)	0.84 (0.56–1.27)	1.00 (ref)	0.04
Mortality from other causes[d]					
No. of deaths from other causes[d]	63	72	73	87	
Age and energy-adjusted HR (95% CI)[b]	0.55 (0.39–0.76)	0.64 (0.46–0.87)	0.73 (0.53–0.99)	1.00 (ref)	<0.001
MV-adjusted HR (95% CI)[b,c]	0.68 (0.48–0.96)	0.78 (0.56–1.08)	0.82 (0.60–1.12)	1.00 (ref)	0.03

[a]Linear trend test represents the *P*-value for the continuous E-DII from diet plus supplements variable.
[b]In addition to age at cancer diagnosis and total energy intake, to account for the immortal time bias from the cancer diagnosis to the FFQ completion, a time-dependent covariate was added in the Cox model to stratify participants' status before and after the post-diagnosis FFQ. The most pro-inflammatory E-DII quartile was treated as the referent.
[c]The multivariable-adjusted (MV) model included the model in [b] and was additionally adjusted for family income level (<20,000, 20,000–49,999, ≥50,000), WHI study arm (OS, DM-intervention, DM-control), race/ethnicity (White non-Hispanic, Hispanic/Latino, Black/African American, other), education (high school or below, some college, college, postgraduate), cancer stage (localised, regional, distant), cancer grade (well differentiated, moderately differentiated, poorly differentiated, anaplastic, B cell or T cell, Unknown/not done), years from cancer diagnosis to FFQ (continuous), baseline physical activity in MET-h/week (0, 0–3,3–9,9 +), smoking status at baseline (never smoked, past smoker, current smoker), body mass index at baseline (underweight, normal, overweight, obese).
[d]Other causes referred to death causes other than cancer and CVD in this study, which included homicide, accident, suicide, other injury, Alzheimer's, pneumonia, chronic obstructive pulmonary disease, pulmonary fibrosis, renal failure, sepsis, amyotrophic lateral sclerosis, dementia, pancreatic diseases, Parkinson's disease, hepatic cirrhosis, known other causes and unknown causes.

Table 3. Multivariable-adjusted associations between E-DII from diet plus supplements and mortality outcomes (all-cause and cancer mortality) stratified by cancer stage and cancer grade in the WHI-DM and OS.

Subgroups	E-DII Quartile 1	E-DII Quartile 2	E-DII Quartile 3	E-DII Quartile 4	P-trend[a]	P-interaction[b]
All-cause mortality						
Cancer stage						0.34
Localised stage, *n* (%)[c]	128 (20.7)	150 (25.3)	149 (26.5)	165 (30.2)		
MV-adjusted HR (95% CI)[d]	0.70 (0.55–0.90)	0.84 (0.66–1.06)	0.87 (0.70–1.09)	1.00 (ref)	0.004	
Regional stage, *n* (%)[c]	57 (32.8)	80 (42.8)	98 (44.3)	93 (44.3)		
MV-adjusted HR (95% CI)[d]	0.63 (0.44–0.90)	0.88 (0.64–1.22)	0.91 (0.68–1.23)	1.00 (ref)	0.02	
Distant stage, *n* (%)[c]	41 (61.2)	54 (69.2)	55 (73.3)	86 (84.3)		
MV-adjusted HR (95% CI)[d]	0.36 (0.24–0.55)	0.59 (0.41–0.86)	0.72 (0.50–1.03)	1.00 (ref)	<0.001	
Cancer grade[e]						0.19
Well differentiated, n (%)[c]	30 (18.5)	33 (17.9)	38 (25.2)	33 (25.4)		
MV-adjusted HR (95% CI)[d]	0.88 (0.51–1.52)	0.65 (0.39–1.10)	1.02 (0.63–1.66)	1.00 (ref)	0.33	
Moderately differentiated, *n* (%)[c]	79 (25.1)	82 (30.1)	106 (33.4)	114 (37.9)		
MV-adjusted HR (95% CI)[d]	0.65 (0.48–0.89)	0.87 (0.64–1.17)	0.98 (0.74–1.29)	1.00 (ref)	0.02	
Poorly differentiated, *n* (%)[c]	47 (29.2)	70 (40.0)	63 (42.6)	75 (40.8)		
MV-adjusted HR (95% CI)[d]	0.67 (0.44–1.01)	0.99 (0.70–1.41)	1.10 (0.78–1.56)	1.00 (ref)	0.21	
Total cancer mortality						
Cancer stage						0.48
Localised stage, *n* (%)[c]	57 (9.2)	65 (11.0)	68 (12.1)	67 (12.3)		
MV-adjusted HR (95% CI)[d]	0.71 (0.49–1.04)	0.88 (0.61–1.25)	0.97 (0.69–1.37)	1.00 (ref)	0.04	
Regional stage, *n* (%)[c]	44 (25.3)	58 (31.0)	69 (31.2)	66 (31.4)		
MV-adjusted HR (95% CI)[d]	0.69 (0.46–1.05)	0.89 (0.61–1.30)	0.91 (0.64–1.30)	1.00 (ref)	0.09	
Distant stage, *n* (%)[c]	36 (53.7)	44 (56.4)	47 (62.7)	74 (72.6)		
MV-adjusted HR (95% CI)[d]	0.38 (0.24–0.60)	0.57 (0.38–0.86)	0.75 (0.51–1.11)	1.00 (ref)	<0.001	
Cancer grade[e]	0.29					
Well differentiated, *n* (%)[c]	15 (9.3)	12 (6.5)	15 (9.9)	14 (10.8)		
MV-adjusted HR (95% CI)[d]	1.12 (0.49–2.56)	0.58 (0.25–1.37)	0.88 (0.40–1.91)	1.00 (ref)	0.76	
Moderately differentiated, *n* (%)[c]	45 (14.3)	45 (16.5)	55 (17.4)	62 (20.6)		
MV-adjusted HR (95% CI)[d]	0.68 (0.44–1.03)	0.86 (0.57–1.30)	0.94 (0.64–1.37)	1.00 (ref)	0.12	
Poorly differentiated, *n* (%)[c]	30 (18.6)	48 (27.4)	47 (31.8)	45 (24.5)		
MV-adjusted HR (95% CI)[d]	0.64 (0.39–1.07)	1.07 (0.69–1.67)	1.26 (0.82–1.93)	1.00 (ref)	0.25	

[a]Linear trend test represented the *P*-value for the continuous E-DII variable.
[b]Interaction test was performed by adding the cross-product of E-DII quartile and cancer stage or grade in the multivariable-adjusted model (MV model).
[c]Number of deaths from the specific cause and proportion of deaths from the cause among the total number of cancer cases within each quartile.
[d]The MV model was adjusted for age at cancer diagnosis, income levels, WHI study arm, race/ethnicity, education levels, years from cancer diagnosis to FFQ, baseline physical activity in MET-h/week, smoking status at baseline, total energy intake per day, BMI, cancer stage and cancer grade with the time-dependent covariate in the model to stratify participants' status before and after the post-diagnosis FFQ.
[e]Three categories of cancer grade were included while other types including "unknown/not done," B cell or T cell and Anaplastic were not included because of unknown grade status for interpretation or few case numbers that resulted in unstable estimates.

(e.g. fruits and vegetables, legumes, whole grains), significantly improve overall survival among breast cancer survivors and colorectal cancer survivors [39]. However, associations with cancer-specific mortality or CVD mortality were not consistent across previous findings, mainly owing to different case sample sizes and populations as well as the different dietary patterns examined in each study [9, 39].

Few studies have explored post-diagnosis dietary quality and mortality among multiple cancer types combined, which has the benefit of increased sample size and power as well as a better representation of cancer survivors [45]. In the Iowa Women's Health Study, including 2017 older cancer survivors primarily composed of breast cancer, colorectal cancer and gynaecological cancer survivors with an average age of 70.3 at cancer diagnosis, there were 461 total deaths and 184 cancer-specific deaths during a mean follow-up time of 5.4 years [45]. Those with better alignment with the 2007 World Cancer Research Fund/American Institute for Cancer Research dietary recommendations had lower all-cause mortality ($HR_{>4\ vs.<4} = 0.80$, 95% CI = 0.64–1.00, *P*-trend = 0.05) and non-statistically significant reduced total cancer mortality ($HR_{>4\ vs.<4} = 0.76$, 95% CI = 0.53–1.09) [45]. Based on data from 230 women who had a previous breast or gynaecological (i.e. ovarian, cervical or uterine) cancer diagnosis at a mean age of 44 years old among whom 121 death cases occurred in the third National Health and Nutrition Examination Survey (NHANES III) in the US, higher HEI score was associated with 57% lower all-cause mortality, the only outcome assessed in this study ($HR_{\geq 70 vs.<70} = 0.43$, 95% CI = 0.29–0.64) [42]. In our study, we observed similar risk reduction for all-cause mortality and total cancer mortality, likely as a result of the large proportion of cancer deaths in this sample (60%), which supports an

Table 4. Sensitivity analyses of multivariable-adjusted hazard ratios of E-DII from diet plus supplements in relation to mortality outcomes in the WHI-DM and OS.

	Most anti-inflammatory E-DII Quartile 1	E-DII Quartile 2	E-DII Quartile 3	Most pro-inflammatory E-DII Quartile 4	*P*-trend[a]
Excluding DM-intervention arm (*N* = 2722)					
N[b]	649	646	699	728	
All-cause mortality					
No. of deaths	180	221	249	291	
MV-adjusted HR (95% CI)[c]	0.59 (0.48–0.72)	0.77 (0.64–0.93)	0.84 (0.70–1.00)	1.00 (ref)	<0.001
Total cancer mortality					
No. of deaths	109	128	148	180	
MV-adjusted HR (95% CI)[c]	0.56 (0.43–0.72)	0.73 (0.58–0.92)	0.81 (0.65–1.01)	1.00 (ref)	<0.001
CVD mortality					
No. of deaths	21	38	42	40	
MV-adjusted HR (95% CI)[c]	0.49 (0.28–0.87)	0.92 (0.58–1.47)	0.99 (0.63–1.54)	1.00 (ref)	0.13
Mortality from other causes[d]					
No. of deaths	50	55	59	71	
MV-adjusted HR (95% CI)[c]	0.76 (0.51–1.13)	0.82 (0.57–1.18)	0.86 (0.60–1.22)	1.00 (ref)	0.15
Additionally adding CVD status at baseline in the MV-adjusted model (*N* = 3386)[e]					
N[b]	852	849	842	843	
All-cause mortality					
No. of deaths	224	280	296	336	
MV-adjusted HR (95% CI)[c]	0.59 (0.49–0.71)	0.78 (0.66–0.92)	0.85 (0.72–0.99)	1.00 (ref)	<0.001
Total cancer mortality					
No. of deaths	135	164	181	203	
MV-adjusted HR (95% CI)[c]	0.58 (0.46–0.74)	0.76 (0.62–0.95)	0.88 (0.72–1.08)	1.00 (ref)	<0.001
CVD mortality					
No. of deaths	26	45	44	48	
MV-adjusted HR (95% CI)[c]	0.46 (0.28–0.77)	0.86 (0.57–1.32)	0.82 (0.54–1.25)	1.00 (ref)	0.04
Mortality from other causes[d]					
No. of deaths	63	71	71	85	
MV-adjusted HR (95% CI)[c]	0.69 (0.48–0.98)	0.78 (0.56–1.09)	0.80 (0.58–1.11)	1.00 (ref)	0.03
Excluding participants with FFQs completed within 6 months of cancer diagnosis (*N* = 2718)					
N[b]	708	694	656	660	
All-cause mortality					
No. of deaths	186	235	222	256	
MV-adjusted HR (95% CI)[c]	0.58 (0.47–0.71)	0.81 (0.67–0.97)	0.81 (0.67–0.97)	1.00 (ref)	<0.001
Total cancer mortality					
No. of deaths	114	135	127	150	
MV-adjusted HR (95% CI)[c]	0.57 (0.44–0.74)	0.76 (0.59–0.97)	0.79 (0.62–1.00)	1.00 (ref)	<0.001
CVD mortality					
No. of deaths	23	37	34	41	
MV-adjusted HR (95% CI)[c]	0.46 (0.26–0.80)	0.85 (0.53–1.36)	0.77 (0.48–1.23)	1.00 (ref)	0.08

Table 4. continued

	Most anti-inflammatory E-DII Quartile 1	E-DII Quartile 2	E-DII Quartile 3	Most pro-inflammatory E-DII Quartile 4	*P*-trend[a]
Mortality from other causes[d]					
No. of deaths	49	63	61	65	
MV-adjusted HR (95% CI)[c]	0.69 (0.46–1.03)	0.93 (0.65–1.35)	0.92 (0.64–1.31)	1.00 (ref)	0.14
Excluding participants with FFQs completed within 1.5 years of cancer diagnosis (*N* = 1448)					
N[b]	388	370	351	339	
All-cause mortality					
No. of deaths	96	116	124	130	
MV-adjusted HR (95% CI)[c]	0.54 (0.40–0.71)	0.74 (0.56–0.96)	0.86 (0.67–1.11)	1.00 (ref)	<0.001
Total cancer mortality					
No. of deaths	54	64	69	74	
MV-adjusted HR (95% CI)[c]	0.51 (0.35–0.74)	0.67 (0.47–0.95)	0.82 (0.58–1.15)	1.00 (ref)	0.001
CVD mortality					
No. of deaths	10	25	20	19	
MV-adjusted HR (95% CI)[c]	0.35 (0.15–0.79)	1.15 (0.60–2.19)	0.98 (0.50–1.88)	1.00 (ref)	0.14
Mortality from other causes[d]					
No. of deaths	32	27	35	37	
MV-adjusted HR (95% CI)[c]	0.67 (0.40–1.14)	0.67 (0.40–1.15)	0.97 (0.60–1.57)	1.00 (ref)	0.11

[a]Linear trend test represented the *P*-value for the continuous E-DII variable.
[b]The cut-off points for the E-DII quartiles in the two sensitivity analyses in this table were chosen as same as those used in the main association analysis in the original sample of 3434 subjects to be consistent.
[c]The multivariable-adjusted (MV) model was adjusted for age at cancer diagnosis, income levels, WHI study arm, race/ethnicity, education levels, years from cancer diagnosis to FFQ, baseline physical activity in MET-h/week, smoking status at baseline, total energy intake per day, BMI, cancer stage and cancer grade with the time-dependent covariate in the model to stratify participants' status before and after the post-diagnosis FFQ, with exception in the second sensitivity where CVD status was additionally adjusted in the MV model.
[d]Other causes referred to death causes other than cancer and CVD in this study, which included homicide, accident, suicide, other injury, Alzheimer's, pneumonia, chronic obstructive pulmonary disease, pulmonary fibrosis, renal failure, sepsis, amyotrophic lateral sclerosis, dementia, pancreatic diseases, Parkinson's disease, hepatic cirrhosis, known other causes and unknown causes.
[e]There was missing CVD status data on 48 subjects, who were excluded from this analysis.

overall improved profile of cancer prognosis among post-menopausal women with higher diet quality with regards to inflammatory potential. Of note, the majority of the above-mentioned studies had smaller overall sample sizes and smaller numbers of total and cause-specific death cases, as well as younger average ages at cancer diagnosis than our study [39].

There have been three large randomised controlled trials with nutritional intervention among breast cancer survivors to evaluate post-cancer diagnostic dietary effects on cancer prognosis. In the Women's Healthy Eating and Living Study, 3088 women previously treated for early-stage breast cancer who were 18 to 70 years old at diagnosis were randomised to a diet that was low in fat and high in vegetables, fruit and fibre or a usual diet. After a mean 7.3-year follow-up, there was no effect of the intervention on breast cancer recurrence or overall survival [46]. In the Women's Intervention in Nutrition Study, a dietary intervention aimed at reducing fat did not increase overall survival among 2437 women with resected early-stage breast cancer who received conventional cancer treatment [47]. The DII includes anti-inflammatory scores for omega-3 fatty acids and pro-inflammatory scores for carbohydrates. Thus, consuming a low-fat diet with a concomitant substantial increase in carbohydrates could conceivably result in the less anti-inflammatory potential of the diet, which may partially explain the difference in results observed in the two clinical trials as compared to our study, in addition to different cancer populations and study designs. In contrast, results from a secondary analysis of the WHI-DM trial supported our finding that the intervention arm that consumed dietary patterns of low fat but increased vegetable, fruit and grain experienced a significant reduction in deaths after breast cancer diagnosis in a median 19.6-year follow-up compared to the control group (HR = 0.85, 95% CI = 0.74–0.96) [48].

Cancer patients are at increased risk of cancer, CVD and other comorbidities after diagnosis. In our study sample, the top causes of death and percent of total deaths included the following: breast cancer (16.3%), lung cancer (8.9%), ovarian cancer (6.1%), colon cancer (5.8%) and possible CHD (3.9%). Inflammation has been implicated in the development and progression of cancer and is related to response to treatment [12, 49]. After cancer develops, the increased expression of vital pro-inflammatory transcription factors within tumour cells mediates the expression of key cytokines and chemokines such as TNF-α and IL-6, as well as several inflammatory enzymes, forming a complex inflammatory tumour microenvironment. These inflammatory mediators have direct effects on tumour-cell and myeloid-cell function and contribute to the stimulation of the epithelial-to-mesenchymal transition and augmentation of metastasis, which increases the risk of other cancers and inflammatory diseases such as CVD, diabetes and associated complications [10, 12]. Diet-associated microbial dysbiosis could induce neuroinflammation, promoting brain and mental disorders that adversely influence survival [50]. Cachexia, which has a substantial impact on survival in cancer

patients, is also strongly associated with inflammation [51]. Thus, the role of diet in modifying chronic inflammation may impact susceptibility to and overall risk of succumbing to post-cancer diseases, providing a strong biologic explanation for the associations that we observed [52]. Later-stage or moderately/poorly differentiated cancers usually have a more inflammatory physiological state than early-stage cancers as a result of more disrupted metabolism, more weakened immune system and the biological changes related to metastasis [53]. Under this condition, where several antioxidants or bioactive compounds with functions to support important signalling pathways were likely in shortage, an anti-inflammatory diet providing these nutrients could exert a more protective effect on mortality, compared to the effect among early-stage cancer survivors [54]. This observation also could be partially explained by the fact that women diagnosed with more distant-stage cancers may undergo more and harsher treatments that put them at increased risk for comorbidities as a result of weakened immunity that could be modulated by diet; thus, diet appears to have a stronger impact among them than among early-stage cancer patients.

Strengths of the study include a relatively large sample size from a well-characterised prospective cohort of post-menopausal women in the US with long follow-up duration to accrue adequate events for each mortality outcome, rich data of important confounders for adjustment, and the application of E-DII, which is specifically designed to assess inflammatory potential of the whole diet while accounting for adjustment of total energy in the score. E-DII scores were in a similar range to E-DII scores in previous studies [55]. Detailed classification of causes of death minimised misclassification of outcomes. Careful sensitivity analyses were conducted to rule out potential biases, which produced robust results to support our findings. Limitations include the one-time assessment of diet and supplement use after the cancer diagnosis, although they may be prone to change in the long follow-up; however, the longitudinal stability of DII scores in the WHI-OS and WHI-DM participants was observed previously [56]. Data for some of the covariates (e.g. physical activity and BMI) were collected at baseline and had varying duration prior to each individual's diagnosis date with a median of 2.2 years (interquartile range, 1.2–3.6 years) between baseline and cancer diagnosis, and dietary supplement use information was not collected concurrently in the FFQ and was assessed with different means, which could all have resulted in non-differential misclassification. Because our analysis required a post-diagnosis FFQ, and women who were excluded were older and had worse prognostic factors than the included participants, it is conceivable that women consuming highly pro-inflammatory diets may have died before they could complete a post-diagnosis FFQ, which may bias findings towards null. Thirteen food parameters were not available in the E-DII calculation, and all of these components were anti-inflammatory, which could have led to a more positive E-DII score in our sample and non-differential misclassification, resulting in a potential underestimation of the associations between E-DII and mortality. However, as previously noted, the range of DII scores may rely more on the intake amount rather than on the number of DII components included [57]. Since we lacked information on some important variables such as primary cancer treatment, residual or unmeasured confounding may have existed in this study, but we adjusted cancer stage and cancer grade as a proxy for cancer treatment in the present analysis. The small number of deaths when stratifying by cancer grade resulted in reduced power for some analyses. The WHI study population had limited racial/ethnic diversity to allow for considerations of cultural context. Our study findings can only be generalised to women who were post-menopausal, and the majority of participants were non-Hispanic White (~88%) with relatively high socioeconomic status, therefore, a future investigation among other diverse cancer populations is needed.

In summary, among post-menopausal women after the cancer diagnosis, consuming a diet or diet plus supplements with more anti-inflammatory potential, as defined by lower E-DII scores, was associated with a lower risk of death from all-causes, cancer and CVD. Stronger associations were observed among women diagnosed with cancers at a later stage or moderately/poorly differentiated grade. Future large prospective cohort studies or clinical trials are warranted to confirm our study findings among diverse populations with different cancer types and explore whether dietary inflammatory potential after cancer diagnosis might affect survival by other important clinical characteristics of cancer.

DATA AVAILABILITY

WHI data are available upon submission of a written proposal and approval by the WHI Publications and Presentations Committee.

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AUTHOR CONTRIBUTIONS

Conception and design: J Zheng, FKT, JRH, SES. Development of methodology: J Zheng, J Zhang, JRH, NS, SES. Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): BC, CHK. Analysis and interpretation of

data (e.g. statistical analysis, biostatistics, computational analysis): J Zheng, J Zhang, SES. Writing, review and/or revision of the manuscript: J Zheng, FKT, J Zhang, BC, JRH, CHK, JKO, NS, SES. Study supervision: SES.

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COMPETING INTERESTS

JRH owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII^{TM}) from the University of South Carolina to develop computer and smart phone applications for patient counselling and dietary intervention in clinical settings. NS is an employee of CHI. The remaining authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The WHI protocol was approved by the Institutional Review Boards at the Clinical Coordinating Center (CCC) at the Fred Hutchinson Cancer Research Center (Seattle, WA) and at each of the participating Clinical Centers and conformed to the Declaration of Helsinki. All participants provided written informed consent in accordance with the U.S. Common Rule.

ADDITIONAL INFORMATION

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