Published OnlineFirst March 12, 2014; DOI: 10.1158/1055-9965.EPI-13-1303

Cancer Epidemiology, Biomarkers & Prevention

Research Article

The Association between Postdiagnosis Dietary Supplement Use and Total Mortality Differs by Diet Quality among Older Female Cancer Survivors

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Abstract

Background: Dietary supplements are widely used by cancer survivors. However, health effects among older cancer survivors are unclear.

Methods: We used the Iowa Women's Health Study, a prospective cohort study with 2,118 postmenopausal women with a confirmed cancer diagnosis (1986–2002), to evaluate the association between postdiagnosis dietary supplement use assessed in 2004 and subsequent all-cause mortality. Risk of death was evaluated using multivariable-adjusted Cox proportional hazards regression. We performed stratified analyses by diet quality score, dietary micronutrient intake, and perceived general health.

Results: Through 2010, 608 deaths were identified. Approximately 85% of the cancer survivors used dietary supplements. Overall supplement use and multivitamin use were not associated with mortality. Iron supplement use was associated with 39% higher risk of death [95% confidence interval (CI), 1.09–1.77]. This association was stronger among survivors with deteriorating general health. Folic acid supplement use was associated with higher risk of death, only among survivors reporting low-quality diets (HR, 2.33; 95% CI, 1.33–4.08; $P_{\text{interaction}} = 0.006$). Multivitamin use and using a greater number of supplements was associated with a trend towards higher mortality only among those with poor diet quality. Using vitamin E supplements in combination with multivitamin was associated with lower risk of death only among survivors with higher dietary vitamin E intake (HR, 0.61; 95% CI, 0.39–0.94; $P_{\text{interaction}} = 0.02$).

Conclusions: Postdiagnosis supplement use was associated with higher mortality among older female cancer survivors with poor general health and/or poor dietary intake.

Impact: The association between postdiagnosis dietary supplement use and mortality may differ by diet quality and health status among older female cancer survivors. *Cancer Epidemiol Biomarkers Prev; 23(5); 865–75. ©2014 AACR.*

Introduction

Approximately 50% of adults in the United States use dietary supplements (1, 2), and higher rates of dietary supplement use have been reported in women and older adults (1, 3, 4). The National Health and Nutrition Examination Survey (NHANES III) reported that 70% of U.S. adults above 70 years of age used dietary supplements (1). Prevalence of dietary supplement use is also higher among cancer survivors, with reports ranging from 55% to 85% (5–8). Given that both age and a cancer diagnosis are independently associated with a higher likelihood of supplement use, a higher rate of dietary supplement use is expected among older cancer survivors (5–7).

Older cancer survivors use dietary supplements for a variety of reasons, including decreasing the risk of recurrent or subsequent primary cancers (9), preventing other age-related chronic diseases and treatment-related side-effects such as cardiovascular disease, diabetes, and osteoporosis (10–14), feeling generally better, and/or as an "insurance" for obtaining adequate amounts of nutrients (15, 16). Despite the widespread use of dietary supplements, potential benefits and risks of dietary supplement use after cancer diagnosis have not been well studied, and thus short-term and long-term health effects of postdiagnosis supplementation are unknown.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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doi: 10.1158/1055-9965.EPI-13-1303

Published OnlineFirst March 12, 2014; DOI: 10.1158/1055-9965.EPI-13-1303

Several recent studies have evaluated the effects of postdiagnosis dietary supplement use on cancer recurrence or survival (17–21). Overall, current evidence indicates that dietary supplement use after cancer diagnosis is unlikely to improve prognosis or overall survival (17–22). A few studies have reported decreased risk of death related to the postdiagnosis use of antioxidants such as multivitamins and vitamins C and E (23–25) and increased risk of death related to carotenoid supplement use (24). However, evidence on long-term health effects of postdiagnosis dietary supplement use among cancer survivors is still limited due to the lack of long term follow-up in observational studies and the relatively short follow-up time in most randomized, controlled trials (22), or observational studies of one or a few types of dietary supplements among survivors of a specific cancer type, mostly breast cancer (17–19, 23–25). Because of insufficient evidence of benefits and occasional evidence of harms, current evidence-based nutrition guidelines, such as the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) guidelines for cancer prevention (26) and the American Cancer Society (ACS) guidelines for cancer survivors (27), recommend that cancer survivors meet nutritional needs through diet and avoid dietary supplements.

Here, we use data from the Iowa Women's Health Study (IWHS) to evaluate whether post-diagnosis use of multivitamin and other dietary supplements were associated with subsequent risk of death among older female cancer survivors. Furthermore, we evaluated whether the association between postdiagnosis dietary supplement use and mortality differed by survivors' diet quality. The prospective study design and large sample size allowed us to identify more than 2,100 older women who were diagnosed with incident cancer and to assess their dietary supplement use as well as dietary intake after cancer diagnosis.

Materials and Methods

Study population

In 1986, a self-administered questionnaire was mailed to women at the age of 55 to 69 randomly selected from the Iowa Department of Transportation driver's license list, and 41,836 women responded (42% response rate; ref. 28). The questionnaire included questions on demographics, anthropometrics, familial history of cancer, medical history, lifestyle, and usual dietary intake. Five follow-up questionnaires were administered to the remaining cohort participants by mail in 1987, 1989, 1992, 1997, and 2004. The IWHS was approved for human subject research by the Institutional Review Boards of the University of Minnesota and the University of Iowa. Return of the completed questionnaires was considered as a subject's consent to study participation.

The current analysis included cancer survivors selected from the IWHS participants with no history of cancer (except nonmelanoma skin cancer) at cohort baseline, but were diagnosed with cancer between 1986 and 2002, and were alive and completed the 2004 follow-up questionnaire. Incident cancers were identified via linkage with the State Health Registry of Iowa, a member of the National Cancer Institute's, Surveillance, Epidemiology and End Results (SEER) program. For each incident cancer, information on diagnosis date, age at diagnosis, type, stage, and morphology of cancer, first course of therapy, and subsequent cancer was collected. We did not include women who were diagnosed with cancer within two years before the 2004 follow-up questionnaire, because these short-term cancer survivors were likely to be actively receiving cancer treatment and thus may have had different dietary supplement use patterns and other lifestyle habits from long-term cancer survivors. We also excluded women who were diagnosed with nonmelanoma skin cancer ($n = 39$) and cancer *in situ* ($n = 556$) and those whose 2004 follow-up questionnaire was completed by proxy ($n = 49$).

Data collection at the 2004 follow-up survey

The most recent follow-up questionnaire in 2004 reevaluated the remaining cohort participants' demographics, anthropometrics, medical history, lifestyle, and usual dietary intake. Dietary intake was assessed using the Harvard food frequency questionnaire (FFQ) (29, 30), similar to the questionnaire used at the 1986 baseline survey. The validity and reproducibility of the Harvard FFQ have been shown in the IWHS population (31). Study participants were asked to report their usual intake of 127 food items for the past 12 months. Dietary supplement use, including multivitamin and 18 non-multivitamin supplements (vitamin A, B_6, C, D, and E, calcium, iron, selenium, zinc, folic acid, omega-3 fatty acids, beta-carotene, iodine, magnesium, vitamin B-complex, copper, cod liver oil, and Brewer's yeast), was also assessed in the FFQ. Dose and brand name of multivitamin and duration of use and daily dose of eight non-multivitamin supplements were also asked; however, this information was not included in the current study because of uncertain accuracy. Daily nutrient intake was computed by multiplying intake frequency of the specified unit of each food item by the nutrient content of that unit of food. Weekly intake of food groups (e.g., total fruits and vegetables) were calculated on the basis of reported serving numbers per week and serving sizes for each item. For accuracy of dietary intake data, we excluded cancer survivors who left more than 30 items blank or reported implausible energy intake (<600 or >5,000 kcal/day) on the FFQ. Body mass index (BMI) was computed based on self-reported height and weight. Physical activity level was categorized as three levels; "high" if they reported $\geq$2 times/week vigorous (e.g., jogging, racket sports, swimming, aerobics, strenuous sports) or $\geq$5 times/week moderate activities (e.g., bowling, golf, light sports, or physical exercise, gardening, taking long walks), "moderate" if they reported 2–4 times/week moderate or once/week vigorous and moderate activities, or otherwise "low" (32). The 2004 questionnaire

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also asked if a study participant was currently undergoing cancer treatment.

Endpoint ascertainment

Vital status of the cohort participants has been identified through the annual linkage with the State Health Registry of Iowa, supplemented with the National Death Index. For each death, the date and the cause of death were obtained. Follow-up person-years were assigned for each cancer survivor from January 1, 2004 through the date of death, the date of emigration from Iowa, or December 31, 2010, whichever occurred first.

Statistical analysis

After exclusions, the analytic cohort comprised 2,118 cancer survivors. We computed a diet quality score indicating the level of adherence to the six dietary recommendations for sugary drinks, fruits and vegetables, fiber, red and processed meat, alcohol, and sodium included in the WCRF/AICR guidelines for cancer prevention (26). Cancer survivors received 0 points for each indicator if they did not meet the recommendation, 0.5 for partial recommendation adherence, or one point for complete recommendation adherence (Supplementary Table S1; ref. 33). Scores for the six dietary recommendations (increasing total fruit and vegetable and dietary fiber intake, and limiting red meat and processed meat product, alcohol, and sodium intake) were summed as a dietary quality score (maximum score = 6). Characteristics of cancer survivors, their cancers, and their usual dietary intake were compared by the use of at least one dietary supplement, and by low (<median = 4.5) and high (≥median) diet quality scores using χ^2test and student *t* test for categorical and continuous variables, respectively. Multivariable-adjusted HRs and their 95% confidence intervals (CI) for the risk of death were computed for dietary supplement users versus nonusers in three Cox proportional hazards regression models. Model 1 included age and total energy intake (kcal/day) as covariates because cancer survivors may have used dietary supplements due to insufficient dietary intake. In Model 2, we added factors that were associated with the risk of death ($P < 0.05$), including BMI, education (<high school, high school, >high school), physical activity level (low, medium, high), current smoking (yes/no), total comorbidity count, perceived general health (excellent/very good, good, fair/poor), history of diabetes (yes/no), history of hypertension (yes/no), type (breast, colorectal, gynecologic, other) and stage of cancer (localized, regional, distant), surgery and chemotherapy as a first course of therapy (yes/no), number of cancers, current cancer treatment (yes/no), and years since cancer diagnosis. The total comorbidity count (range: 0–11) included self-reported presence or absence of comorbid conditions that could affect mortality in the baseline and any follow-up surveys, including Parkinson's disease, rheumatoid arthritis, diabetes, hip fractures, hypertension, heart attack, heart disease, and stroke. Model 3 additionally adjusted for diet quality scores. To evaluate whether the association varied by cancer type, we stratified the analyses by major types of cancer (breast, colorectal, gynecologic, including cervical, endometrial, ovarian, and other female genital organ, and other cancers).

We performed stratified analyses by low and high diet quality scores, because we were unable to ascertain whether dietary supplement use was for nutrition repletion or general health promotion. We also compared the risk of death by number (0, 1, 2–4, and ≥5) and type of supplements (none, multivitamin only, multivitamin and other supplements, and non-multivitamin supplements only) among all cancer survivors and by diet quality scores. To further evaluate whether excess intake of nutrients from dietary supplements and diet was associated with the risk of death, we stratified the association between the use of individual non-multivitamin supplements alone or in combination with multivitamin and the risk of death by dietary micronutrient intake levels. Depending on the distribution of each dietary micronutrient intake, the recommended daily allowance (RDA) for postmenopausal women or half the RDA was used as a cut point for low and high intake. We also performed exploratory analyses stratifying by perceived general health (fair/poor, good, and excellent/very good). Interactions were tested by including cross-products in regression models. Statistical significance level was defined as $P < 0.05$.

Results

During the mean follow-up of 6.1 years, we identified 608 deaths, including 245 from cancer and 197 from cardiovascular disease. The average age at the 2004 survey was 78.9 years (range: 73–88 years). The mean age at cancer diagnosis was 70.3 years (range: 54–86 years). The average time since cancer diagnosis was 6.1 years at the 2004 survey, with 39% of the women surviving 10 years or longer. The most common cancer types were breast (n = 969), colorectal (n = 398), and gynecologic (n = 285). About 70% of the women survived localized cancer, and 93% underwent a surgery as a first course of therapy. Eleven percent of the survivors were receiving cancer treatment at the time of the 2004 survey. Compared with nonusers, dietary supplement users were slightly younger, had lower BMI, higher education, fewer comorbid conditions, and were less likely to smoke or be diabetic, and were physically active (Table 1). Dietary supplement users and nonusers did not differ in characteristics of their cancers. Cancer survivors with low diet quality scores were more likely to be current smokers, physically inactive, diabetic, perceiving poorer general health, having survived their cancers for shorter periods, and undergoing cancer therapy compared with those with high diet quality scores.

The mean diet quality score was 4.5 (range: 2.0–6.0) and was not different between cancer survivors who used dietary supplements and those who did not (Table 2).

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Table 1. Characteristics of cancer survivors and their cancers by dietary supplement use and diet quality

	All	Dietary supplement use			Diet quality score[a]		
	All (n = 2,118)	Users (n = 1,792)	Nonusers (n = 326)	P[b]	<4.5 (n = 670)	≥4.5 (n = 1,448)	P[b]
Age[c], y	78.9 ± 3.9	78.9 ± 3.9	79.2 ± 3.9	<0.0001	78.8 ± 3.9	79.0 ± 3.9	0.42
BMI[c], kg/m^2	26.9 ± 5.3	26.8 ± 5.2	28.0 ± 5.9	0.0002	26.8 ± 5.6	27.0 ± 5.2	0.54
≥High school education (%)[d]	86.4	87.7	79.1	<0.0001	85.5	86.8	0.42
Current smoking (%)	3.5	2.7	8.0	<0.0001	5.9	2.4	<0.0001
Low physical activity (%)	52.1	50.0	63.8	<0.0001	59.3	48.7	<0.0001
Total comorbidity count[c]	2.1 ± 1.6	2.0 ± 1.6	2.2 ± 1.6	0.09	2.1 ± 1.5	2.1 ± 1.6	0.91
Diabetes (%)[e]	16.6	15.7	21.2	0.02	14.3	17.6	0.06
High blood pressure (%)[e]	64.5	63.8	68.4	0.11	65.5	64.1	0.52
Perceived general health (%)							
Excellent or very good	27.6	28.3	23.9	0.07	23.1	29.7	0.006
Good	49.6	49.8	48.8		51.8	48.6	
Fair or poor	22.8	21.9	27.3		25.1	21.7	
Age at cancer diagnosis[c], y	70.3 ± 6.1	70.3 ± 6.1	70.2 ± 6.2	0.78	70.4 ± 6.0	70.2 ± 6.1	0.41
Cancer type (%)							
Breast	45.7	45.9	45.1	0.81	46.1	45.6	0.97
Colorectal	18.8	18.5	20.3		18.2	19.0	
Gynecologic	13.5	13.3	14.1		13.4	13.5	
Other cancer	22.0	22.3	20.5		22.3	21.9	
Cancer stage (%)							
Localized	70.7	70.7	70.9	0.95	68.5	71.8	0.29
Regional	21.1	21.1	21.2		22.1	20.6	
Distant	5.9	5.9	6.1		6.4	5.7	
Unknown	2.3	2.3	1.8		3.0	1.9	
First course of cancer therapy							
Surgery (%)	93.3	93.0	94.7	0.26	93.0	93.4	0.75
Chemotherapy (%)	16.8	17.0	15.5	0.51	15.4	17.4	0.25
Radiation (%)	22.2	22.4	20.9	0.54	22.7	21.9	0.70
Hormone therapy (%)	22.5	23.0	19.3	0.14	22.9	22.3	0.74
Immunotherapy (%)	2.3	2.3	2.2	0.88	2.6	2.2	0.55
Time since cancer diagnosis (%)							
2–<5 y	29.4	29.9	26.7	0.47	31.3	28.5	0.09
5–<10 y	31.6	31.5	31.9		33.0	30.9	
≥10 y	39.0	38.6	41.4		35.7	40.6	
Subsequent cancer (%)	12.7	12.4	13.8	0.50	13.6	12.2	0.38
Current cancer treatment (%)	11.0	11.1	10.7	0.83	13.3	10.0	0.03

[a]A score for adherence to the dietary recommendations in the 2007 WCRF/AICR guidelines for cancer prevention (range: 0–6).
[b]Student t test for continuous variables and x^2 test for categorical variables.
[c]Mean ± SD.
[d]Data from cohort baseline (1986).
[e]Self-reported in the baseline or any follow-up surveys.

Compared with nonusers, dietary supplement users had slightly higher intake of protein, fruits and vegetables, and whole grains. Dietary intake of micronutrients, including vitamins A, D, and iron, were higher among dietary supplement users than nonusers; however, differences appeared minimal. Total intake (dietary and supplemental) of all micronutrients was higher among supplement users than nonusers. The mean (SD) diet quality scores were 3.8 (0.4) and 4.8 (0.4) in low (<4.5) and high (≥4.5) diet quality score groups (P < 0.0001). Cancer survivors with low diet quality scores had lower intake of total energy, protein, carbohydrate, fruits and vegetables, total meat, and whole grains, but higher alcohol intake compared with those with high diet quality scores ($P < 0.05$ for all). Fat intake (total and saturated) was not different between low and high diet quality score groups. Both dietary and total intakes of all micronutrients, except for total vitamin E, were

Published OnlineFirst March 12, 2014; DOI: 10.1158/1055-9965.EPI-13-1303

Table 2. Dietary factors[a] in relation to overall dietary supplement use and diet quality

		Dietary supplement use			Diet quality score[b]		
	All (n = 2,118)	Users (n = 1,792)	Nonusers (n = 326)	P	<4.5 (n = 670)	≥4.5 (n = 1,448)	P
Diet quality score[b]	4.5 ± 0.6	4.5 ± 0.6	4.4 ± 0.6	0.002	3.8 ± 0.4	4.8 ± 0.4	<0.0001
Total energy, kcal/d	1934 ± 696	1939 ± 695	1911 ± 704	0.51	1856 ± 742	1970 ± 670	0.0004
Protein, gm/d	86.0 ± 34.9	86.7 ± 35.1	82.3 ± 33.1	0.04	80.1 ± 35.3	88.8 ± 34.2	<0.0001
Carbohydrate, gm/d	239.8 ± 96.6	240.4 ± 96.5	236.6 ± 97.6	0.51	220.5 ± 101.2	248.8 ± 93.2	<0.0001
Total fat, gm/d	73.6 ± 30.3	73.5 ± 30.2	74.4 ± 30.9	0.61	73.7 ± 31.4	73.6 ± 29.8	0.92
Saturated fat, gm/d	25.4 ± 11.2	25.4 ± 11.2	25.7 ± 11.4	0.66	25.7 ± 11.7	25.3 ± 10.9	0.46
Fruits and vegetables, servings/wk	45.3 ± 25.2	45.9 ± 25.2	42.3 ± 25.1	0.02	32.6 ± 22.8	51.2 ± 24.1	<0.0001
Total meat, servings/wk	12.7 ± 7.1	12.8 ± 7.1	12.5 ± 7.1	0.55	12.3 ± 7.5	12.9 ± 6.9	0.04
Whole grains, gm/d	32.1 ± 23.7	32.7 ± 24.1	29.1 ± 20.8	0.01	26.6 ± 19.3	34.7 ± 25.0	<0.0001
Alcohol, gm/d	2.2 ± 6.4	2.3 ± 6.4	1.9 ± 6.4	0.31	4.3 ± 9.4	1.3 ± 4.0	<0.0001
Dietary intake							
Vitamin A, IU/d	10798 ± 7951	10948 ± 8143	9971 ± 6746	0.04	8214 ± 7487	11993 ± 7877	<0.0001
Folate, μg/d	388.3 ± 177.6	391.0 ± 179.6	373.5 ± 165.9	0.10	332.3 ± 167.7	414.2 ± 176.2	<0.0001
Vitamin D, IU/d	237.4 ± 158.8	240.2 ± 160.0	221.9 ± 151.6	0.06	219.3 ± 156.8	245.8 ± 159.1	0.0004
Vitamin E, IU/d	11.4 ± 6.0	11.4 ± 6.0	11.0 ± 5.6	0.27	10.1 ± 5.2	12.0 ± 6.2	<0.0001
Iron, gm/d	15.3 ± 7.8	15.5 ± 8.1	14.6 ± 6.4	0.07	13.8 ± 7.0	16.0 ± 8.1	<0.0001
Calcium, mg/d	846.6 ± 439.1	852.8 ± 433.0	812.5 ± 470.2	0.13	790.1 ± 460.1	872.8 ± 426.7	<0.0001
Total intake[c]							
Vitamin A, IU/d	14255 ± 313	15029 ± 9,485	9999 ± 6754	<0.0001	11529 ± 9046	15517 ± 9141	<0.0001
Folate, μg/d	651.5 ± 313.1	701.9 ± 307.1	374.7 ± 167.4	<0.0001	580.2 ± 317.2	684.6 ± 305.8	<0.0001
Vitamin D, IU/d	529.0 ± 321.2	584.5 ± 312.4	224.3 ± 155.6	<0.0001	507.6 ± 329.0	538.9 ± 317.1	0.04
Vitamin E, IU/d	114.0 ± 145.8	132.7 ± 151.2	11.1 ± 5.8	<0.0001	105.5 ± 139.2	117.9 ± 148.7	0.07
Iron, gm/d	24.1 ± 19.2	25.8 ± 20.2	14.7 ± 6.5	<0.0001	22.2 ± 18.9	25.0 ± 19.3	0.002
Calcium, mg/d	1318.8± 645.5	1410.9 ± 630.2	813.0 ± 471.0	<0.0001	1219.0 ± 662.0	1365.1 ± 632.6	<0.0001

[a]Mean ± SD.
[b]A score for adherence to the dietary recommendations in the 2007 WCRF/AICR guidelines for cancer prevention (range: 0–6).
[c]Sums of the nutrient intake from natural and fortified foods and dietary supplements.

higher among survivors with high versus low diet quality scores ($P < 0.05$ for all).

Approximately 85% of cancer survivors used dietary supplements. Multivitamin was the most commonly used dietary supplement (64%), followed by calcium, vitamins E, C, D, and iron. Multivitamin use was not associated with the risk of death (Table 3). Compared with nonusers, folic acid and iron supplement users were at 51% (95% CI, 1.13–2.00) and 68% (95% CI, 1.34–2.11) higher risk of death, respectively, after adjusting for age and total energy intake (Model 1). After additional adjustment for other covariates and diet quality scores, the risk of death among iron supplement users versus nonusers remained higher (HR, 1.39; 95% CI, 1.09–1.77; Model 3). The association with folic acid supplement use was no longer observed after additional adjustment for other covariates. None of the other non-multivitamin supplements were associated with the risk of death. These results did not differ by cancer type (breast, colorectal, gynecologic, and other cancers; Supplemental Table S2).

When stratified by diet quality scores, the risk of death was 2.3 times higher for folic acid supplement users versus nonusers only among survivors with low diet quality scores (95% CI, 1.33–4.08; $P_{\text{interaction}} = 0.006$; Table 4). Although the associations were not statistically significant, the risk of death was 28% higher among multivitamin users versus nonusers among those with low diet quality scores (95% CI, 0.93–1.76), whereas the risk was 10% lower in multivitamin users versus nonusers among survivors with high diet quality scores (95% CI, 0.72–1.12, $P_{\text{interaction}} = 0.02$). There was no effect modification by diet quality on the association between other dietary supplements and the risk of death. The number of dietary supplements and supplement type (none, multivitamin only, multivitamin and others, or others only) were not associated with the risk of death (Table 5). Despite not being statistically significant, a trend toward higher risk of death with an increasing number of supplements was observed among survivors eating low quality diets ($HR_{\geq 5 \text{ vs. } 0} = 1.34$, 95% CI, 0.78–2.29), whereas the opposite trend was observed for cancer survivors with high diet

Published OnlineFirst March 12, 2014; DOI: 10.1158/1055-9965.EPI-13-1303

Table 3. Dietary supplement use and all-cause mortality among cancer survivors

		Dietary supplement use		HR (95% CI)[a]		
	User%	Nonusers (deaths/N)	Users (deaths/N)	Model 1[b]	Model 2[c]	Model 3[d]
Any supplement	84.6	99/326	509/1792	0.93 (0.75–1.15)	0.99 (0.79–1.25)	1.00 (0.80–1.26)
Multivitamin	63.8	219/709	369/1352	0.89 (0.76–1.06)	1.02 (0.86–1.22)	1.02 (0.85–1.22)
Vitamin A	5.2	536/1899	34/111	1.12 (0.79–1.58)	1.16 (0.80–1.67)	1.19 (0.83–1.69)
Beta-carotene	2.3	593/2069	15/49	1.03 (0.62–1.72)	1.30 (0.76–2.23)	1.25 (0.74–2.10)
Vit. B complex	7.9	561/1950	47/168	0.94 (0.70–1.26)	0.97 (0.70–1.33)	0.98 (0.72–1.34)
Vitamin B_6	7.0	523/1848	44/149	1.03 (0.76–1.41)	0.97 (0.70–1.35)	0.99 (0.72–1.37)
Folic acid	6.4	556/1982	52/136	1.51 (1.13–2.00)	1.21 (0.88–1.65)	1.21 (0.89–1.64)
Vitamin C	27.0	402/1426	169/572	1.06 (0.89–1.27)	1.02 (0.84–1.24)	1.05 (0.87–1.27)
Vitamin D	12.0	538/1863	70/255	0.89 (0.69–1.14)	0.84 (0.64–1.11)	0.82 (0.63–1.08)
Vitamin E	31.0	402/1356	164/657	0.86 (0.71–1.03)	0.91 (0.75–1.10)	0.93 (0.77–1.12)
Calcium	59.3	243/791	336/1255	0.86 (0.73–1.02)	0.91 (0.77–1.09)	0.91 (0.76–1.08)
Copper	0.8	603/2102	5/16	1.11 (0.46–2.68)	1.25 (0.51–3.04)	1.26 (0.51–3.06)
Iron	10.0	481/1780	88/211	1.68 (1.34–2.11)	1.43 (1.12–1.83)	1.39 (1.09–1.77)
Magnesium	6.0	568/1991	40/127	1.11 (0.81–1.53)	1.12 (0.79–1.59)	1.17 (0.83–1.65)
Selenium	4.2	537/1880	23/88	0.86 (0.57–1.31)	1.02 (0.64–1.61)	1.04 (0.67–1.64)
Zinc	8.0	513/1805	48/169	0.96 (0.71–1.29)	0.99 (0.72–1.36)	0.98 (0.72–1.34)

[a]HRs and 95% CIs compared with nonusers of each dietary supplement in each stratum as a reference group.
[b]Adjusted for age and energy intake.
[c]Adjusted for age, energy intake, body mass index, physical activity level, current smoking, total comorbidity index, perceived general health, history of diabetes, history of high blood pressure, cancer type, cancer stage, surgery, chemotherapy, number of cancers, current cancer treatment, and years since cancer diagnosis.
[d]Adjusted for covariates included in Model 2 plus diet quality score.

quality scores, with the risk of death being lower as the number of dietary supplements increased ($HR_{\geq 5 \text{ vs. } 0}$, 0.86; 95% CI, 0.59–1.26; $P_{\text{interaction}} = 0.04$). Similarly, the risk of death appeared to be higher (HR, 1.40; 95% CI, 0.90–2.17) among survivors using both multivitamin and other supplements compared with those who did not use any dietary supplements only among cancer survivors with low diet quality scores ($P_{\text{interaction}} = 0.02$).

The use of vitamin E supplements in combination with multivitamin was associated with lower risk of death (HR, 0.61; 95% CI, 0.39–0.94) only among cancer survivors whose dietary vitamin E intake was at or above half the RDA ($P_{\text{interaction}} = 0.02$; Table 6). No interaction was observed for vitamin E supplement use without multivitamin. Iron supplement use, alone and in combination with multivitamin, was associated with higher mortality regardless of dietary iron intake.

When stratified by perceived general health, higher risk of death related to iron supplement use was observed among women with fair or poor (HR, 1.52; 95% CI, 1.05–2.18) and good (HR, 1.46; 95% CI, 1.01–2.10) general health, but not those with excellent or very good general health (HR, 1.08; 95% CI, 0.47–2.46; Supplementary Table S3). Higher risk of death was also observed related to the use of copper or selenium supplements only among women with poor or fair general health. However, these results, particularly interactions, should be interpreted with caution, because the numbers of users of these supplements were very small and a large number of associations were tested. None of the other dietary supplements were associated with the risk of death regardless of perceived general health.

Discussion

In this prospective study of older female cancer survivors, the use of iron supplements was associated with higher risk of death, especially among cancer survivors with deteriorating perceived general health. No other dietary supplements were associated with the risk of death. Folic acid supplement use was associated with higher risk of death only among cancer survivors eating poor quality diets. Using vitamin E supplements in combination with multivitamin was associated with lower risk of death only among cancer survivors with dietary vitamin E intake exceeding half the RDA.

Although using multivitamin to insure adequate nutrient intake was previously recommended for cancer survivors (27), recent evidence suggests that multivitamin use may not be helpful to decrease the risk of cancer recurrence or to improve overall survival after cancer diagnosis (17, 19, 20, 34). Studies have shown that cancer survivors are at higher risk for certain nutrient deficiencies (e.g., vitamin D) (35), and repletion via supplementation

Published OnlineFirst March 12, 2014; DOI: 10.1158/1055-9965.EPI-13-1303

Table 4. Dietary supplement use and all-cause mortality stratified by diet quality

	Diet quality score[a] < 4.5 (*n* = 670)			Diet quality score[a] ≥ 4.5 (*n* = 1,448)			
	Nonusers	Users		Nonusers	Users		
	Deaths/n	Deaths/n	HR (95% CI)[b]	Deaths/n	Deaths/n	HR (95% CI)[b]	$P_{interaction}$
Any supplements	34/119	178/551	1.28 (0.85–1.92)	65/207	331/1,241	0.89 (0.67–1.17)	0.09
Multivitamin	70/246	134/406	1.28 (0.93–1.76)	149/463	235/946	0.90 (0.72–1.12)	0.02
Vitamin A	187/606	13/29	1.71 (0.95–3.06)	349/1,293	21/82	0.95 (0.61–1.49)	0.12
Beta-carotene	207/655	5/15	0.99 (0.39–2.48)	386/1,414	10/34	1.37 (0.72–2.58)	0.72
Vitamin B complex	194/625	18/45	1.15 (0.68–1.95)	367/1,325	29/123	0.87 (0.58–1.29)	0.30
Vitamin B_6	182/597	16/41	1.46 (0.85–2.52)	341/1,251	28/108	0.84 (0.56–1.26)	0.15
Folic acid	192/635	20/35	2.33 (1.33–4.08)	364/1,347	31/101	0.96 (0.65–1.42)	0.006
Vitamin C	135/458	61/172	1.28 (0.92–1.78)	267/968	108/400	0.94 (0.74–1.19)	0.11
Vitamin D	188/585	24/85	0.83 (0.52–1.31)	350/1,278	46/170	0.81 (0.58–1.12)	0.84
Vitamin E	137/440	60/200	1.00 (0.73–1.38)	265/916	104/457	0.87 (0.68–1.10)	0.31
Calcium	87/282	114/370	1.07 (0.79–1.45)	156/509	222/885	0.82 (0.66–1.02)	0.11
Copper	209/664	3/6	1.60 (0.48–5.34)	394/1,438	2/10	0.77 (0.19–3.12)	0.38
Iron	171/570	27/68	1.36 (0.86–2.13)	310/1,210	61/143	1.46 (1.09–1.95)	0.98
Magnesium	200/634	12/36	0.85 (0.45–1.60)	368/1,357	28/91	1.26 (0.84–1.89)	0.42
Selenium	185/604	10/26	0.98 (0.47–2.03)	352/1,276	13/62	1.05 (0.59–1.89)	0.89
Zinc	180/580	17/53	1.09 (0.65–1.81)	333/1,225	31/116	0.87 (0.58–1.30)	0.49

[a]A score for adherence to the dietary recommendations in the 2007 WCRF/AICR guidelines for cancer prevention (range: 0–6).
[b]Hazard ratios (HR) and 95% confidence intervals (CI) compared with nonusers of each dietary supplement in each stratum as a reference group. Adjusted for age, energy intake, body mass index, physical activity level, current smoking, total comorbidity index, perceived general health, history of diabetes, history of high blood pressure, cancer type, cancer stage, surgery, chemotherapy, number of cancers, current cancer treatment, and years since cancer diagnosis.

may improve survival (36, 37). Thus, in the 2012 update of their nutrition and physical activity guidelines for cancer survivors, the ACS emphasized the need to first assess whether an individual is deficient in a specific nutrient before initiating supplements (38). In our study, however, dietary supplement users and nonusers had similar dietary intake, including diet quality scores and most macro- and micronutrients. Excess nutrient intake, from dietary

Table 5. Number and type of dietary supplements and all-cause mortality among cancer survivors

	All survivors		Diet quality score[a] <4.5 (*N* = 670)		Diet quality score[a] ≥4.5 (*N* = 1,448)		
	Deaths/N	HR (95% CI)[b]	Deaths/*N*	HR (95% CI)[b]	Deaths/*N*	HR (95% CI)[b]	$P_{interaction}$
Number of supplements used							
0	99/326	1.00	34/119	1.00	65/207	1.00	
1	137/441	1.07 (0.81–1.40)	48/153	1.19 (0.73–1.93)	89/288	1.01 (0.72–1.42)	
2–4	287/1,058	0.97 (0.76–1.24)	99/306	1.27 (0.82–1.97)	188/752	0.84 (0.62–1.13)	
≥5	85/293	1.02 (0.75–1.39)	31/92	1.34 (0.78–2.29)	54/201	0.86 (0.59–1.26)	
P_{trend}		0.78		0.25		0.18	0.04
Type of supplements							
No supplement	99/326	1.00	34/119	1.00	65/207	1.00	
Multivitamin only	74/261	0.96 (0.70–1.32)	27/93	0.93 (0.53–1.62)	47/168	0.98 (0.66–1.45)	0.86
Multivitamin + others	295/1,091	1.00 (0.78–1.28)	107/313	1.40 (0.90–2.17)	188/778	0.83 (0.62–1.12)	0.02
Others only	122/391	0.97 (0.73–1.28)	37/131	1.04 (0.62–1.74)	85/260	0.93 (0.66–1.30)	0.75

[a]A score for adherence to the dietary recommendations in the 2007 WCRF/AICR guidelines for cancer prevention (range: 0–6).
[b]Adjusted for age, energy intake, body mass index, physical activity level, current smoking, total comorbidity index, perceived general health, history of diabetes, history of high blood pressure, cancer type, cancer stage, surgery, chemotherapy, number of cancers, current cancer treatment, years since cancer diagnosis, and dietary quality score (for nonstratified analyses).

Published OnlineFirst March 12, 2014; DOI: 10.1158/1055-9965.EPI-13-1303

Table 6. Dietary supplement use (non-multivitamin supplements and multivitamins + individual supplements) and all-cause mortality stratified by dietary nutrient intake

	Each individual supplement				Multivitamins[d] + each individual supplement			
	Nonusers	Users			Nonusers	Users		
	Deaths/n	Deaths/n	HR (95% CI)[c]	$P_{interaction}$	Deaths/n	Deaths/n	HR (95% CI)[c]	$P_{interaction}$
Dietary vitamin A[a]								
<2,300 IU/d	14/24	0/1	N/A	N/A	8/13	0/1	N/A	N/A
≥2,300 IU/d	522/1,875	34/110	1.19 (0.84–1.69)		193/650	24/81	1.20 (0.78–1.85)	
Dietary folate[a]								
<400 μg/d	339/1,207	42/90	1.35 (0.94–1.94)	0.12	128/435	31/67	1.39 (0.90–2.16)	0.20
≥400 μg/d	217/775	10/46	0.76 (0.39–1.50)		81/251	9/38	0.82 (0.39–1.73)	
Dietary vitamin D[b]								
<400 IU/d	473/1,604	61/214	0.85 (0.64–1.13)	0.68	176/553	40/140	0.94 (0.65–1.36)	0.86
≥400 IU/d	65/259	9/41	0.70 (0.32–1.55)		22/78	7/27	0.76 (0.28–2.10)	
Dietary vitamin E[b]								
<11.25 IU/d	240/803	104/392	1.00 (0.79–1.27)	0.27	96/321	80/288	1.15 (0.84–1.57)	0.02
≥11.25 IU/d	162/553	60/265	0.80 (0.58–1.11)		75/216	40/204	0.61 (0.39–0.94)	
Dietary iron[a]								
<8 mg/d	54/179	11/28	1.40 (0.65–3.03)	0.88	28/76	7/17	1.48 (0.58–3.79)	0.79
≥8 mg/d	427/1,601	77/183	1.37 (1.06–1.77)		153/534	49/121	1.42 (1.01–2.01)	
Dietary calcium[a]								
<1,200 mg/d	195/631	285/1,016	0.93 (0.77–1.13)	0.48	103/317	202/742	0.93 (0.72–1.20)	0.92
≥1,200 mg/d	48/160	51/239	0.76 (0.48–1.20)		24/73	41/183	0.85 (0.47–1.53)	

[a]Cancer survivors were categorized into two groups depending on whether their nutrient intake from a diet was < or ≥ RDA.
[b]Cancer survivors were categorized into two groups depending on whether their nutrient intake from a diet was < or ≥ half the RDA.
[c]HRs and 95% CIs compared with nonusers of dietary supplement (overall or multivitamin) in each stratified category as a reference group. Adjusted for age, energy intake, body mass index, physical activity level, current smoking, total comorbidity index, perceived general health, history of diabetes, history of high blood pressure, cancer type, cancer stage, surgery, chemotherapy, number of cancers, current cancer treatment, years since cancer diagnosis, and diet quality score.
[d]Multivitamins for the elderly are purposely iron-free because individuals aged 50 and older require less iron and generally meet their iron needs through diet alone, and high iron stores have been suggested to have adverse health effects.

supplements and an adequate diet, may have adverse health effects. For example, recent studies indicate that high folate intake may accelerate the carcinogenic process in the presence of precancerous lesions, which is more likely the case for the elderly and cancer survivors compared with younger and healthier populations (39, 40). In our study, however, folic acid supplement use alone or in combination with multivitamin was not associated with the risk of death, even among women whose dietary folate intake exceeded half the RDA. Higher risk of death observed among folic acid supplement users with low diet quality scores may partly be because of residual confounding by their deteriorating health due to their cancer, cancer treatment, or other comorbid conditions.

Decreased risk of death related to postdiagnosis vitamin E supplement use was previously reported (23, 24). In our study, overall postdiagnosis vitamin E supplement use was not associated with mortality, but cancer survivors using vitamin E supplements and multivitamin in addition to at least half the RDA of dietary vitamin E intake were at decreased risk of death in our study.

Evidence supporting potential harmful effects of iron supplements on overall survival is limited. One prospective cohort study reported a nonsignificant increase in the risk of death among U.S. adults who took iron at a dosage above the RDA (18 mg/day for premenopausal women) compared with nonusers (41). Population-based case–control studies have shown 34% to 56% higher odds of iron supplement use among colorectal cancer cases than control subjects (42, 43). Recent systematic review and meta-analysis of epidemiologic studies have concluded that higher heme iron intake was associated with a trend towards higher risk of cancer (44). However, higher levels of biomarkers for iron stores (mostly serum ferritin) were associated with lower risk of cancer in the same meta-analysis. More than 90% of cancer survivors in our study met the RDA of iron intake from diet only. Among survivors whose dietary iron intake met the RDA, 10% used iron supplements. Excessive iron intake from regular iron supplement use coupled with adequate iron intake from a diet may be a concern for its harmful effects on general health. While iron deficiency is a common nutritional

Published OnlineFirst March 12, 2014; DOI: 10.1158/1055-9965.EPI-13-1303

deficiency in younger women, older women are more likely to have high iron stores due to a smaller lean body mass and a decreased loss of iron through menstruation (45). Therefore, multivitamins formulated specifically for the elderly are purposely iron-free; however, we were unable to determine whether the multivitamins used by our study participants contained iron.

Higher risk of death observed among cancer survivors who used iron supplements may possibly be a result of health conditions for which iron supplement use is indicated or suggested by health professionals. In fact, higher risk related to iron supplement use was stronger among cancer survivors with deteriorating general health. The prevalence of anemia, a condition that may be due to iron insufficiency, has been reported to increase directly with older age from 10% to 11% in over 65-year olds to 26% to 30% in over 75-years olds (46). This age-related increase in prevalence of anemia can be due to the higher rate of age-related comorbidities such as cardiovascular disease, renal insufficiency, chronic malabsorption, and inflammation. In the current study, significantly more iron supplement users (33%) reported fair or poor perceived general health compared with nonusers (23%; $P < 0.05$, data not shown). However, neither recent comorbid cardiovascular diseases reported in the 2004 survey nor comorbid cardiovascular diseases reported at baseline and/or any follow-ups differed between iron supplement users and nonusers (data not shown). It is possible that cancer survivors used iron supplements because of their comorbid conditions other than cardiovascular diseases, which resulted in worse survival. Consumer advertising suggests that iron supplements can improve energy levels because iron deficiency results in anemia-related fatigue. Thus, many women feeling fatigue may have used iron supplements in the absence of actual anemia or iron deficiency.

Higher risk of death was also observed among cancer survivors using a larger number of dietary supplements and eating lower quality diets. Users of multiple supplements have been reported to have normal blood nutrient status, better diet quality, normal levels of chronic disease-related biomarkers such as cholesterol and triglycerides, and other health behaviors (3–5, 7, 47). Indeed, more of the survivors using dietary supplements in our study reported somewhat higher protein, whole grain, and fruit and vegetable intake. However, cancer survivors who used a large number of dietary supplements may be different from those using only one or a few. For example, these survivors may have used multiple dietary supplements due to comorbid conditions or cancer- and/or treatment-related symptoms, or to make up their insufficient dietary intake resulting from these health conditions. In addition, most (92%) of iron supplement users in our study also used multiple dietary supplements. About 38% of iron supplement users reported using five or more dietary supplements, while the counterpart of iron supplement nonusers was only 11%.

Our study is one of the first large-scale population-based studies analyzing health outcomes of dietary supplement use specifically among older cancer survivors, a rapidly expanding and understudied population. The prospective study design and a large number of participants are major strengths of this study. We were able to identify more than 2,100 cancer survivors during the 17 years of follow-up for cancer incidence, with more than 600 deaths during the subsequent follow-up of the cancer survivors. Dietary supplement use and dietary intake were collected at least two years after a cancer diagnosis and before the subsequent follow-up.

One limitation is that dietary supplement use and perceived general health were assessed cross-sectionally at the 2004 follow-up. Therefore, dietary supplement use, especially iron supplement and multiple supplement use, might have merely been an indicator of deteriorating health condition, which may be a real cause of higher risk of subsequent death among older cancer survivors. Although we adjusted for perceived general health, total comorbidity count, and cancer characteristics, residual confounding by measured and/or unmeasured comorbid conditions and cancer characteristics cannot be ruled out. Residual confounding by other health behaviors that are related to dietary supplement use, mortality, as well as diet quality scores (e.g., smoking, physical activity level), may also be possible. Considering the large number of associations tested, concerns for potential chance findings exist, especially for interactions due to smaller numbers of deaths in subgroups. Another concern is the potential for survival bias because the current study included only women who had survived until the 2004 follow-up questionnaire and were able to complete the questionnaire. Our study participants reported somewhat better adherence to the dietary recommendations such as total fruit and vegetable intake compared with the U.S. general cancer survivor population (48). Therefore, our study findings may not apply to cancer survivors who have very poor health status and/or dietary intake. Finally, our study subjects were older women, and virtually all women (>99%) were white, which limits the generalizability of our findings to younger adults, men, or ethnic minority groups.

In conclusion, the use of most dietary supplements after cancer diagnosis was not associated with the risk of death in this study among older female cancer survivors. However, using folic acids, multivitamin, or a greater number of dietary supplements appeared to be associated with higher risk of death only among survivors eating lower quality diets. Iron supplement use among older female cancer survivors was associated with higher risk of death especially among those who had deteriorating health. Associations between postdiagnosis dietary supplement use and mortality may differ by health status and diet quality among older female cancer survivors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M. Inoue-Choi, H. Greenlee, K. Robien
Development of methodology: M. Inoue-Choi, K. Robien
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Robien
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Inoue-Choi, H. Greenlee, S.J. Oppeneer, K. Robien
Writing, review, and/or revision of the manuscript: M. Inoue-Choi, H. Greenlee, S.J. Oppeneer, K. Robien
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Inoue-Choi
Study supervision: K. Robien

Grant Support

This study was supported by National Cancer Institute R01 CA039742 (to M. Inoue-Choi and K. Robien), K23 CA141052 (to H. Greenlee), and T32 CA132670 (to S.J. Oppeneer).

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Received December 9, 2013; revised February 19, 2014; accepted February 27, 2014; published OnlineFirst March 12, 2014.

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