

Research Article

Adherence to the WCRF/AICR Guidelines for Cancer Prevention Is Associated with Lower Mortality among Older Female Cancer Survivors

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Abstract

Background: The 2007 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) guidelines encourage cancer survivors to follow its cancer prevention recommendations. We evaluated whether adherence to the WCRF/AICR guidelines for cancer prevention was associated with lower mortality among older female cancer survivors.

Methods: From 2004 to 2009, 2,017 participants in the Iowa Women's Health Study who had a confirmed cancer diagnosis (1986–2002) and completed the 2004 follow-up questionnaire were followed. Adherence scores for the WCRF/AICR guidelines for body weight, physical activity, and diet were computed assigning one, 0.5 or 0 points to each of eight recommendations depending on the degree of adherence. All-cause ($n = 461$), cancer-specific ($n = 184$), and cardiovascular disease (CVD)-specific mortality ($n = 145$) were compared by the total adherence score and by adherence scores for each of the three components of the recommendations.

Results: Women with the highest (6–8) versus lowest (0–4) adherence score had lower all-cause mortality [HR = 0.67; 95% confidence of interval (CI), 0.50–0.94]. Meeting the physical activity recommendation was associated with lower all-cause ($P_{\text{trend}} < 0.0001$), cancer-specific ($P_{\text{trend}} = 0.04$), and CVD-specific mortality ($P_{\text{trend}} = 0.03$). Adherence to dietary recommendations was associated with lower all-cause mortality ($P_{\text{trend}} < 0.05$), whereas adherence to the body weight recommendation was associated with higher all-cause mortality ($P_{\text{trend}} = 0.009$).

Conclusions: Adherence to the WCRF/AICR guidelines was associated with lower all-cause mortality among older female cancer survivors. Adherence to the physical activity recommendation had the strongest association with lower all-cause and disease-specific mortality.

Impact: Older cancer survivors may decrease their risk of death by leading a healthy lifestyle after a cancer diagnosis. *Cancer Epidemiol Biomarkers Prev*; 22(5); 792–802. ©2013 AACR.

Introduction

As a consequence of early detection, improvements in cancer treatment, and an aging population, the number of older cancer survivors is growing. Currently 68% of people diagnosed with cancer survive at least 5 years and 60% of the nearly 12 million cancer survivors are ages 65 years or older in the United States (1, 2). Aging and status as a cancer survivor may increase older cancer survivors' risk of recurrent and subsequent cancer (3) and other age-related chronic health conditions (4, 5), such as cardiovascular disease (CVD; refs. 6 and 7), diabetes (8), and

osteoporosis (9). Thus, cancer survivorship in older adults is a growing area of investigation.

Health behaviors, such as maintaining ideal body weight, staying physically active, and eating a healthy diet, have well-described associations with decreased risk for developing primary cancer (10–16). According to the American Cancer Society (ACS), approximately one-third of the cancer deaths in the United States are attributable to poor nutrition, physical inactivity, and excess body weight (2). Based on systematic reviews of the existing evidence, cancer prevention guidelines for weight control, physical activity, and diet have been published by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), the ACS, and others (16, 17). However, in 2007, the WCRF/AICR Expert Review Panels were unable to establish guidelines specific to cancer survivors because of lack of evidence, and simply encouraged cancer survivors to follow their cancer prevention recommendations. Recently, additional studies evaluating the health effects of these behaviors among cancer survivors have accumulated (18–22). In 2012, based on the new scientific evidence, the ACS updated their

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nutrition and physical activity guidelines for cancer survivors (23). However, most of the completed randomized control trials (RCT) evaluating health behaviors in cancer survivors have been restricted to short-term trials, targeted only a single health behavior, and were conducted with a relatively small number of survivors with a specific cancer. Whether multiple healthy lifestyle modifications, including maintaining an ideal body weight, staying physically active, and eating a healthy diet, also benefit cancer survivors' health outcomes remains to be answered.

Here, we evaluated whether adherence to the 2007 WCRF/AICR body weight, physical activity, and dietary guidelines, combined or individually, is associated with lower all-cause, cancer-specific, and CVD-specific mortality among older female cancer survivors in the Iowa Women's Health Study (IWHS). To our knowledge, the effect of multiple health behaviors on survival after cancer diagnosis has not been evaluated in a prospective cohort study. The IWHS is an ongoing large prospective cohort study that has followed postmenopausal women for more than 26 years. The prospective study design and large sample size allowed us to collect health behaviors both pre- and post-cancer diagnosis from more than 2,000 women who had survived incident cancer during the follow-up period.

Materials and Methods

The Iowa Women's Health Study

The IWHS is a prospective cohort study to investigate the association of dietary and other factors with risk of cancer and other chronic diseases (24). In 1986, a self-administered questionnaire was mailed to 99,826 women aged 55–69 who were identified from the Iowa Department of Transportation list of licensed drivers. Of these women, 41,836 women (42%) responded to the questionnaire collecting information on demographics, anthropometry, medical and family history, lifestyle factors, and usual dietary intake. Five follow-up questionnaires were administered to the remaining cohort participants by mail in 1987, 1989, 1992, 1997, and 2004. Incident cancers are identified by annual 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 primary cancer, detailed information including age at diagnosis, type and stage of cancer, first course of therapy, and subsequent cancer diagnosis is obtained. The annual migration rate from Iowa among the IWHS participants is <1%, resulting in a nearly complete follow-up of incident cancers (25). The IWHS was approved for human subject research by the Institutional Review Board of the University of Minnesota (Minneapolis, MN). The return of the questionnaires was considered as a subject's consent to participate in the study.

Study subjects

Cancer survivors were selected from cohort participants who were alive and completed the latest follow-up

questionnaire in 2004. The IWHS cancer survivors who completed the 2004 questionnaire were younger, more educated, less obese, less likely to be smokers, healthier as measured by a perception of overall health, more physically active, and reported fewer comorbid conditions at cohort baseline, compared to survivors who died before or did not respond to the 2004 follow-up (26). Women were excluded from this analysis if they reported a previous cancer diagnosis at cohort baseline ($n = 1,511$), reported a cancer on the 2004 questionnaire that was not identified via the annual linkage with the State Health Registry ($n = 82$), and/or their 2004 questionnaire was completed by proxy ($n = 3$). Women diagnosed with cancer within 2 years prior to the 2004 follow-up were also not eligible for this study because these short-term cancer survivors were more likely to be receiving cancer treatment that could have resulted in a modification to their lifestyle when they completed the questionnaire. In addition, cancer survivors who reported implausible dietary intake (left >30 items blank or reported energy intake estimates <600 or >5,000 kcal/day) in the 2004 food frequency questionnaire (FFQ; $n = 198$) or who did not report weight, height, or physical activity in the 2004 questionnaire ($n = 74$) were excluded. We also excluded 63 survivors whose body mass index (BMI) was in the underweight category (<18.5) on the grounds that being underweight can be a result of many health conditions, including advanced or recurrent cancers as well as other age-related chronic diseases among older cancer survivors. As a result, 2,017 cancer survivors who were diagnosed with incident invasive cancer (except non-melanoma skin cancers) between 1986 and 2002 were followed for mortality from the 2004 survey through the end of 2009.

Data collection with the 2004 follow-up survey

Demographics, medical history, anthropometry, and lifestyle factors including physical activity and dietary intake, were reassessed in the 2004 follow-up questionnaire. BMI was calculated (kilograms per square meter) using self-reported height and weight. Survivors were categorized into 3 physical activity levels; "high" if they reported ≥ 2 times/week vigorous (e.g., jogging, racket sports, swimming, aerobics, strenuous sports) or ≥ 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" (27). Usual intake frequency of 127 food items was assessed using the Harvard FFQ (28, 29), which has been validated in the IWHS population (30). Usual intake of food groups (e.g., total and red meat intakes) was computed based on a serving size for each food item. The 2004 questionnaire also included a single question asking whether a woman was currently undergoing cancer treatment. The total comorbidity count included self-reported presence of comorbid conditions that could affect mortality assessed in the baseline and any follow-up. These

comorbid conditions included Parkinson's disease, rheumatoid arthritis, diabetes, hip fractures, hypertension, heart attack, heart disease, and stroke.

The WCRF/AICR guidelines adherence score

A level of adherence to the 8 recommendations in the 2007 WCRF/AICR guidelines for cancer prevention was determined for each cancer survivor using the scoring pattern outlined in Table 1. Participants received 0 points for each indicator if they did not meet the recommendation, 0.5 points for partial recommendation adherence, or 1 point for complete recommendation adherence. The recommendation to limit nutrient dense foods was excluded as an indicator because data on calorie intake by food grams was not available. The recommendation against dietary supplement use for cancer prevention was also excluded, because we were unable to ascertain the reason for supplement use, such as nutrient repletion versus general health promotion. In addition, the breastfeeding recommendation was not applicable for this older study population and thus was excluded from our scoring. Scores for the 8 indicators (1 each for body weight and physical activity, and 6 for dietary recommendations) were summed as the WCRF/AICR recommendation adherence score (range 0–8). We further separated the adherence score into the 3 components of the WCRF/AICR guidelines—body weight (0–1), physical activity (0–1), and diet (0–6). A score for adherence to the WCRF/AICR guidelines prior to cancer diagnosis was also computed using data collected at cohort baseline in 1986.

Endpoint identification

Vital status of the cohort participants is updated annually via linkage with the State Health Registry of Iowa, supplemented with the National Death Index (National Center for Health Statistics). A total of 461 deaths were identified from 2004 to 2009 among the cancer survivors included in this study. For each death, the date and cause of death were obtained. The 2 most common causes of death were cancer ($n = 184$) and CVD ($n = 145$). Person-years of follow-up time for each cancer survivor was computed from January 1, 2004 through the date of death, the date on which the participant moved out of Iowa, or December 31, 2009, whichever occurred first.

Analysis and statistical methods

Demographic and lifestyle characteristics of the cancer survivors and characteristics of their cancers were compared by quartiles of the WCRF/AICR adherence score using a Student t test and a χ^2 test for continuous and categorical variables, respectively. Age-adjusted risk of all-cause mortality was compared by demographic and lifestyle factors and cancer characteristics using Cox proportional hazards regression to determine confounders. Multivariable-adjusted HRs and 95% confidence intervals (CI) for all-cause, cancer-specific, and CVD-specific mortality across the WCRF/AICR adherence score quartiles were computed using Cox proportional hazards regres-

sion. Covariates in the final analytic models included confounders that were statistically significantly associated with both adherence score quartiles and all-cause mortality [total number of comorbid conditions, current smoking (yes/no), perceived general health (excellent/good or fair/poor), and cancer type] as well as risk factors for death (i.e., factors which were statistically significantly associated with all-cause mortality including age at the 2004 survey, cancer stage (localized, regional, or distant), current cancer treatment at the time of the 2004 survey (yes/no), surgery and chemotherapy as a first course of cancer therapy (yes/no), and subsequent cancer before 2004 (yes/no). Person-years from cancer diagnosis through the end of 2003 were also included as a covariate because survivors' behavior and mortality might be affected by time since diagnosis. In addition, we adjusted the analysis for adherence to the recommendations prior to cancer diagnosis based on the data from the 1986 baseline questionnaire to isolate the effect of postdiagnosis recommendation adherence on mortality outcomes. We further evaluated whether the associations between WCRF/AICR recommendation adherence and all-cause or disease-specific mortality differed by cancer type, that is, breast, colorectal, gynecologic (cervical, endometrial, ovarian, and other female genital organ cancers), and other cancers.

To evaluate the effect of each component of the WCRF/AICR guidelines (body weight, physical activity, and diet) on mortality independent of the effects of the other 2 components, all-cause, and disease-specific mortality were also compared by adherence to each component of the guidelines while adjusting for adherence to the other components of the guidelines. We created a series of spline curves describing the multivariable-adjusted hazard ratio for the association between BMI and 3 mortality outcomes to evaluate inflection points for the risk. Statistical significance was defined as $P < 0.05$.

Results

Table 2 shows characteristics of cancer survivors and their cancers for all survivors and by levels of adherence to the WCRF/AICR guidelines. At the time of the 2004 follow-up survey, the average age of the IWHS cancer survivors was 78.9 years ($SD = 3.9$ years; range = 72–88 years). The average time since cancer diagnosis was 8.6 years ($SD = 4.8$ years). A total comorbidity count ranged from 0 to 11 with a median of 2. The 3 most common cancer types among the study subjects were breast ($n = 938$), colorectal ($n = 380$), and gynecologic cancers ($n = 262$). Compared to survivors of breast or gynecologic cancers, more colon cancer survivors reported excellent or good general health whereas more survivors of "other cancers" reported fair or poor perceived general health. Among the 215 women who reported current treatment for cancer in the 2004 survey, 62% were survivors for 2–<5 years. Among the 244 women who had experienced more than 1 primary cancer, 51% had survived their first cancer for at least 10 years (data not shown). Survivors who had higher

Table 1. The 2007 WCRF/AICR recommendations for cancer prevention and adherence score assignment among cancer survivors in the IWHS

	WCRF/AICR recommendation	IWHS 2004 data	Operationalization	Score	n	%	
1.	Be as lean as possible without becoming underweight.	BMI	18.5–<25	1	756	37.5	
			25–<30	0.5	741	36.7	
			≥30	0	520	25.8	
2.	Be physically active, for at least 30 minutes every day.	Physical activity level	High	1	447	22.2	
			Moderate	0.5	517	25.6	
			Low	0	1,053	52.2	
3.	(1) Limit consumption of energy-dense foods. (2) Avoid sugary drinks.	(1) Not included ^a	–	–	–	–	
			(2) High sugar beverage intake	0 g/d	1	137	6.8
				<250 g/d	0.5	925	45.9
4.	Eat more of a variety of vegetables, fruits, whole grains, and legumes such as beans.	(1) Total fruit and vegetable intake frequency	≥5 servings/d	1	1,239	61.4	
			3–<5 servings/d	0.5	575	28.5	
			<3 servings/d	0	203	10.1	
		(2) Daily dietary fiber intake	≥25 g/d	1	642	31.8	
			12.5–<25 g/d	0.5	1,109	55.0	
			<12.5 g/d	0	266	13.2	
5.	Limit consumption of red meats (such as beef, pork, and lamb) and avoid processed meats.	Daily red meat and processed meat intake (RP) and processed meat intake (P)	<500 g/d RP and 3 g/d P	1	382	18.9	
			<500 g/d RP and 3–<50 g/d P	0.5	1,286	63.8	
			≥500 g/d RP or ≥50 g/d P	0	349	17.3	
6.	Limit alcoholic drinks to 2 for men and 1 for women a day, if consumed at all.	Daily alcohol intake	≤10 g/d	1	1,863	92.4	
			>10–20 g/d	0.5	98	4.8	
			>20 g/d	0	56	2.8	
7.	Limit consumption of salty foods and foods processed with salt.	Daily sodium intake	≤1,500 mg/d	1	550	27.3	
			>1,500–2,400 mg/d	0.5	959	47.5	
			>2,400 mg/d	0	508	25.2	
8.	Do not use supplements to protect against cancer.	Not included ^a	–	–	–	–	
9.	It is best for mothers to breastfeed exclusively for up to 6 months.	Not applicable for this analysis	–	–	–	–	
10.	Cancer survivors should follow the recommendations for cancer prevention (after treatment).						

Abbreviations: WCRF, World Cancer Research Fund; AICR, American Institution for Cancer Research; IWHS, Iowa Women's Health Study.

^aSufficient information not available.

education level, smaller number of comorbid conditions, were less likely to be smokers, and perceived excellent or good general health reported higher adherence to the WCRF/AICR guidelines ($P_{\text{trend}} < 0.01$ for all). The distributions of age and marital status were not different by levels of recommendation adherence. Cancer characteristics, except for cancer type, did not differ by levels of recommendation adherence; more colorectal cancer survivors reported greater adherence to the guidelines whereas more gynecologic cancer survivors

reported poorer adherence. Survivors who reported current cancer treatment in the 2004 questionnaire were more likely to have poorer adherence to the guidelines ($P_{\text{trend}} = 0.08$).

The mean follow-up time from 2004 to 2009 was 5.4 years. Survivors who reported older age, a greater number of comorbid conditions, current smoking, and fair or poor perceived general health condition were at higher risk of death compared to survivors without these factors (data not shown). Although risk of death did not differ among

Table 2. Characteristics of cancer survivors by the 2007 WCRF/AICR recommendation adherence score quartile

	Recommendation adherence score					<i>p</i> ^c
	All	Q1 (1.5–4.0)	Q2 (4.5)	Q3 (5.0–5.5)	Q4 (6.0–8.0)	
<i>N</i>	2,017	505	356	744	412	
Age (mean ± SD)	78.9 ± 3.9	78.6 ± 3.9	79.2 ± 4.0	79.0 ± 3.9	78.8 ± 3.9	0.37
Education level (%) ^a						
< High school	13.9	17.0	17.4	12.9	9.0	0.0001
High school	42.2	44.2	39.0	44.4	38.6	
Some college	43.9	38.8	43.6	42.7	52.4	
Marital status (%)						
Married	45.3	45.4	40.7	46.9	46.1	0.46
Widowed	47.7	46.4	52.3	46.6	47.1	
Divorced/separated	4.7	5.8	5.3	4.5	3.6	
Never married	2.3	2.4	1.7	2.0	3.2	
Number of comorbid conditions (%) ^b						
None	14.6	10.5	15.2	14.1	20.2	<0.0001
1	25.6	24.2	23.0	24.7	30.8	
2	26.7	25.9	28.1	28.6	23.0	
≥3	33.1	39.4	33.7	32.6	26.0	
Current smoking (%)	3.0	5.4	3.4	1.8	1.9	0.002
Perceived general health (%)						
Excellent or good	76.9	71.9	73.0	77.6	85.0	<0.0001
Fair or poor	23.1	28.1	27.0	22.4	15.0	
Age at cancer diagnosis (mean ± SD)	70.3 ± 6.1	69.9 ± 6.0	70.9 ± 5.9	70.1 ± 6.1	70.3 ± 6.4	0.62
Cancer type (%)						
Breast	46.5	43.6	51.1	48.4	42.7	0.007
Colorectal	18.8	18.6	17.7	17.7	22.1	
Gynecologic	13.0	17.4	12.1	12.1	10.0	
Other	21.7	20.4	19.1	21.8	25.2	
Cancer stage (%)						
Localized	71.1	72.1	70.5	70.3	71.8	0.43
Regional	20.8	20.0	20.8	20.6	22.1	
Distant	6.0	5.1	5.9	7.5	4.4	
Unknown	2.1	2.8	2.8	1.6	1.7	
Cancer treatment						
Surgery (%)	93.4	93.2	93.5	93.0	94.6	0.73
Chemotherapy (%)	17.0	15.9	17.5	16.8	18.4	0.79
Radiation (%)	22.3	21.3	25.4	22.9	19.6	0.24
Immunotherapy (%)	2.4	3.0	1.1	2.6	2.2	0.34
Hormone therapy (%)	22.9	22.0	25.4	22.7	22.3	0.67
Time since diagnosis (%)						
2–<5 y	29.2	27.7	30.1	29.2	30.3	0.71
5–10 y	31.8	34.3	32.3	29.8	31.8	
>10 y	39.0	38.0	37.6	41.0	37.9	
Current cancer treatment (%)	10.7	13.1	12.1	9.4	8.7	0.08
Subsequent cancer (%)	12.2	12.9	10.7	12.2	12.1	0.81
Recommendation adherence score (mean ± SD)	4.9 ± 0.9	3.7 ± 0.5	4.5 ± 0.0	5.2 ± 0.2	6.3 ± 0.5	<0.0001

^aData collected at baseline (1986); other data were collected at the 2004 follow-up.

^bAccumulated comorbid conditions up to 2004, including diabetes, hypertension, heart disease, heart attack, stroke, hip fracture, rheumatoid arthritis, and Parkinson's disease.

^c*P* values from χ^2 test for categorical variables and *P* values for trend from *t*-test for continuous variables.

Table 3. HR and 95% confidence intervals (CI)^a for all-cause, cancer-specific, and CVD-specific mortality by the WCRF/AICR recommendation adherence score quartile

	N	Death	Adherence summary score				P _{trend}
			Q1 (1.5–4.0)	Q2 (4.5)	Q3 (5.0–5.5)	Q4 (6.0–8.0)	
<i>All-cause mortality</i>							
All survivors	2,017	461	1.0	1.06 (0.81–1.39)	0.91 (0.72–1.15)	0.67 (0.49–0.90)	0.03
Breast cancer	938	203	1.0	0.93 (0.63–1.38)	0.73 (0.52–1.05)	0.61 (0.39–0.96)	0.01
Colorectal cancer	380	82	1.0	1.17 (0.59–2.32)	1.13 (0.62–2.06)	1.19 (0.59–2.43)	0.64
Gynecologic cancer	262	50	1.0	1.17 (0.47–2.94)	1.15 (0.54–2.45)	0.96 (0.34–2.69)	0.94
Other cancer	437	126	1.0	1.26 (0.73–2.19)	1.10 (0.70–1.73)	0.55 (0.30–1.01)	0.12
<i>Cancer-specific mortality</i>							
All survivors	2,017	184	1.0	1.21 (0.79–1.87)	1.10 (0.76–1.59)	0.63 (0.39–1.04)	0.21
Breast cancer	938	75	1.0	1.43 (0.74–2.74)	1.06 (0.57–1.99)	0.88 (0.41–1.91)	0.65
Colorectal cancer	380	23	1.0	1.04 (0.27–3.92)	1.04 (0.32–3.31)	1.16 (0.33–4.12)	0.84
Gynecologic cancer	262	19	1.0	0.82 (0.18–3.77)	1.04 (0.32–3.35)	N/A ^b	0.38
Other cancer	437	67	1.0	1.20 (0.54–2.67)	1.21 (0.66–2.23)	0.49 (0.21–1.15)	0.25
<i>CVD-specific mortality</i>							
All survivors	2,017	145	1.0	0.74 (0.45–1.22)	0.67 (0.44–1.03)	0.92 (0.57–1.47)	0.40
Breast cancer	938	66	1.0	0.55 (0.27–1.14)	0.50 (0.27–0.93)	0.67 (0.33–1.37)	0.10
Colorectal cancer	380	31	1.0	2.05 (0.62–6.83)	1.54 (0.49–4.87)	2.61 (0.78–8.71)	0.19
Gynecologic cancer	262	16	1.0	N/A ^b	0.46 (0.12–1.71)	1.05 (0.27–4.15)	0.83
Other cancer	437	32	1.0	1.20 (0.40–3.58)	0.74 (0.29–1.89)	0.78 (0.25–2.39)	0.49

^aAdjusted for age, total number of comorbid conditions (accumulated, 1986–2004), perceived general health and current smoking, cancer stage, cancer type, cancer treatment (surgery, chemotherapy), subsequent cancer diagnosis before 2004, current cancer treatment, and person-years since cancer diagnosis.

^bNo cancer death in this category.

survivors of the 3 common cancers (breast, colorectal, and gynecologic), survivors of cancers other than these 3 common cancers were at higher risk of death (HR = 1.47; 95% CI, 1.18–1.83 vs. breast cancer survivors, data not shown).

Survivors who reported greater adherence to the WCRF/AICR guidelines were at lower risk of death ($P_{\text{trend}} = 0.003$; Table 3). Compared with survivors who scored 4 or less out of 8 for recommendation adherence, survivors who scored 6 or above were at 33% lower risk of death. Interactions between adherence to the guidelines and cancer type on the mortality outcomes were not statistically significant. When stratified by cancer type, lower risk of death was observed among survivors of breast cancers ($P_{\text{trend}} = 0.01$), but not among survivors of colorectal and gynecologic cancers. Albeit not statistically significant, survivors of other cancers who scored 6 or above out of 8 for recommendation adherence were at lower risk for dying compared to those who scored 4 or less (HR = 0.55; 95% CI, 0.30–1.01). Similarly, although the trend was weaker, women who reported greater adherence to the guidelines were at lower risk for dying from cancer among survivors of breast cancer and cancer other than the 3 common cancers. The level of recommendation adherence was not associated with risk of CVD-specific mortality overall or by cancer type. None of the observed associations changed by further adjusting for prediagno-

sis WCRF/AICR recommendation adherence (data not shown).

Adherence to the physical activity recommendation was associated with the body weight and dietary recommendations ($P < 0.0001$), whereas adherence to the dietary recommendations was not associated with the body weight recommendation. For any of the 3 mortality outcomes, survivors who adhered to the physical activity recommendation were at decreased risk (26–40% reduction) compared to those who did not adhere, regardless of adjustment for BMI and adherence to the dietary recommendations (Table 4). Risk of death from any cause, cancer, or CVD among survivors with complete vs. no adherence to the physical activity recommendation were 38%, 28%, and 40% lower, respectively. Survivors who met more dietary recommendations were at lower risk of all-cause mortality only ($P_{\text{trend}} < 0.05$). In contrast, survivors who met the recommendation to maintain a normal body weight had 34% higher risk of death compared to those who did not. The spline curves show that the risk peaked at normal range BMI (21–24) for all 3 mortality outcomes and constantly decreased up to 35% at BMI above 24 (Fig. 1). Further adjustment for survivors' prediagnosis adherence to each of 3 components of the guidelines did not change the observed associations between adherence to the physical activity or body weight recommendation and mortality outcomes (data not shown). The

Table 4. HR and 95% confidence intervals (CI) for all-cause, cancer-specific, and CVD-specific mortality by the WCRF/AICR body weight, physical activity, and dietary recommendation adherence scores

	Physical activity recommendation adherence score			<i>P</i> _{trend}
	0	0.5	1.0	
All-cause mortality				
Model 1 ^a	1.0	0.64 (0.50–0.81)	0.64 (0.48–0.85)	0.0001
Model 2 ^b	1.0	0.62 (0.48–0.79)	0.62 (0.47–0.83)	<0.0001
Cancer-specific mortality				
Model 1 ^a	1.0	0.63 (0.43–0.92)	0.74 (0.49–1.11)	0.05
Model 2 ^b	1.0	0.61 (0.42–0.91)	0.72 (0.47–1.10)	0.04
CVD-specific mortality				
Model 1 ^a	1.0	0.70 (0.46–1.09)	0.63 (0.37–1.07)	0.04
Model 2 ^b	1.0	0.68 (0.44–1.05)	0.60 (0.35–1.03)	0.03
	Dietary recommendation adherence score ^c			
	<4.0	4.0	>4.0	<i>P</i> _{trend}
All-cause mortality				
Model 1 ^a	1.0	0.94 (0.75–1.18)	0.77 (0.62–0.96)	0.02
Model 2 ^b	1.0	0.95 (0.76–1.19)	0.80 (0.64–1.00)	0.046
Cancer-specific mortality				
Model 1 ^a	1.0	0.84 (0.59–1.20)	0.74 (0.52–1.05)	0.09
Model 2 ^b	1.0	0.86 (0.60–1.23)	0.76 (0.53–1.09)	0.14
CVD-specific mortality				
Model 1 ^a	1.0	0.84 (0.55–1.30)	0.97 (0.66–1.43)	0.91
Model 2 ^b	1.0	0.84 (0.55–1.30)	1.00 (0.68–1.46)	1.00
	Body weight recommendation adherence score			
	0	0.5	1.0	<i>P</i> _{trend}
All-cause mortality				
Model 1 ^a	1.0	0.92 (0.72–1.19)	1.22 (0.96–1.55)	0.06
Model 2 ^b	1.0	0.98 (0.76–1.27)	1.34 (1.05–1.72)	0.009
Cancer-specific mortality				
Model 1 ^a	1.0	0.90 (0.60–1.38)	1.16 (0.79–1.70)	0.35
Model 2 ^b	1.0	0.93 (0.62–1.39)	1.26 (0.85–1.86)	0.18
CVD-specific mortality				
Model 1 ^a	1.0	0.92 (0.59–1.45)	1.14 (0.74–1.75)	0.47
Model 2 ^b	1.0	0.98 (0.62–1.54)	1.25 (0.81–1.94)	0.27

^aAdjusted for age, total number of comorbid conditions (accumulated, 1986–2004), perceived general health and current smoking, cancer stage, cancer type, cancer treatment (surgery, chemotherapy), subsequent cancer diagnosis before 2004, current cancer treatment and person years since cancer diagnosis.

^bAdditional adjustment for the other 2 components of the adherence score (e.g., adherence to the physical activity and dietary recommendations for the analysis of the body weight recommendation adherence).

^cSum of adherence scores for the 6 dietary recommendations (range: 0–6).

inverse association between adherence to the dietary recommendations and risk of all-cause mortality was attenuated and no longer statistically significant by additional adjustment for prediagnosis adherence to the dietary recommendations ($P_{\text{trend}} = 0.10$).

Discussion

This is one of the first studies to report that overall health behaviors included in the evidence-based cancer

prevention guidelines may be beneficial to improve survival after cancer diagnosis. We found that older female cancer survivors who met a greater number of WCRF/AICR guidelines for cancer prevention were at lower risk of all-cause mortality, possibly also cancer-specific mortality, but not CVD-specific mortality. Among the 3 components of the WCRF/AICR guidelines (body weight, physical activity, and diet), adherence to the physical activity recommendation was the strongest factor

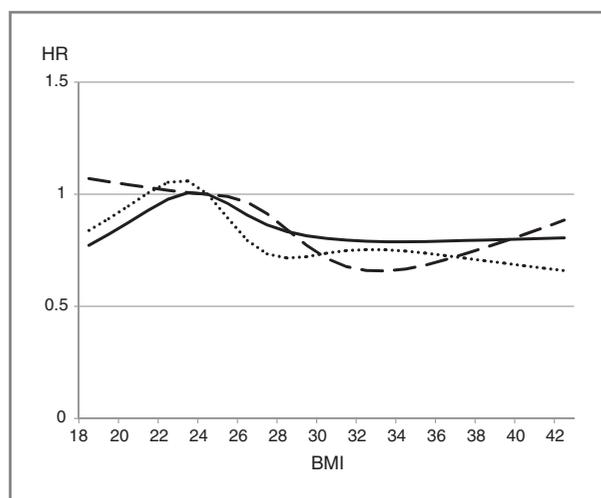


Figure 1. Body mass index (BMI) and all-cause, cancer-specific, and cardiovascular disease (CVD)-specific mortality among all cancer survivors. Solid line: all cause-mortality, dashed line: cancer-specific mortality, wider dashed line: CVD-specific mortality. Spline lines indicate HR with BMI of 24 as a reference. Adjusted for age, total number of comorbid conditions (accumulated, 1986–2004), perceived general health and current smoking, cancer stage, cancer type, cancer treatment (surgery, chemotherapy), subsequent cancer diagnosis before 2004, current cancer treatment, and person-years since cancer diagnosis.

associated with lower risk of each mortality outcome. Adherence to the dietary recommendations was also associated with lower risk of all-cause mortality but not cancer-specific and CVD-specific mortality, whereas adherence to the body weight recommendation was associated with higher risk of all-cause mortality. Our results indicate that, despite prediagnosis health behaviors, leading a healthy lifestyle after a cancer diagnosis may be important for better survival among older cancer survivors.

There is a growing body of literature evaluating the effect of individual health behavior (e.g., physical activity, weight loss, and healthy diet) interventions on health outcomes among cancer survivors (31–34). Current evidence indicates that physical activity interventions improve fitness, strength, physical function, cardiopulmonary fitness, and cancer-related psychosocial status, whereas dietary interventions improve diet quality and thus nutrition-related biomarkers and body weight among cancer survivors (35, 36). Physical activity and dietary interventions have also resulted in improved biomarkers associated with disease progression and overall survival, such as insulin levels and tumor proliferation rates (35). We found that survivors who engaged in moderate, rather than vigorous, physical activity were at somewhat lower risk for dying from cancer. These findings are consistent with a previous report that found moderate-intensity physical activity intervention reduced oxidative DNA damage, whereas high-intensity physical activity increased DNA damage among colorectal cancer survivors (37). Further research focusing on physical activity intensity among older survivors is needed to confirm these findings.

A healthy diet is thought to impact health outcomes via weight management, but the mechanisms are likely more complex. In our study, adherence to the dietary and body weight recommendations were not associated, and adjusting for adherence to the body weight recommendation did not change the association between adherence to the dietary recommendations and mortality outcomes (data not shown). However, adjusting for adherence to the physical activity recommendation weakened the associations between adherence to the dietary recommendations and all-cause or disease-specific mortality. In a previous RCT, increased intake of fruits and vegetables improved survival among breast cancer survivors, but their weight did not change (38).

Weight control has consistently been found to be a key factor in the prevention of many chronic diseases via changes in hormones, growth factors, immune system function, and inflammation (35, 36). Historically, cancer has been associated with cachexia because of the profound wasting coupled with anorexia that can occur, especially at the advanced stage. However, given that cancer is now often diagnosed at earlier stages, obesity (rather than underweight) is more likely to be an issue among cancer survivors. Increasing evidence indicates that being obese may increase risk of cancer recurrence and comorbidities such as CVD and diabetes, and worsen overall survival among cancer survivors (39–42). Suggested mechanisms of the association between body weight and cancer outcomes include alterations in circulating hormones, genomic instability, dysregulated growth signaling and cellular energetics, inhibition of apoptosis and immune surveillance, angiogenesis, insulin and insulin-like growth factor-1 signaling, and inflammatory modulation by adipokines (43).

However, in our older cancer survivor population, women having normal body weight were at higher risk of death compared to those being obese. An "obesity paradox"—where the prognosis of overweight and obese individuals seems to be better than the prognosis of normal weight subjects—has been identified among older adults and individuals with chronic diseases such as CVD (44–49). Lower body weight in older cancer survivors is likely to reflect unintentional weight loss from cancer, side effects of cancer treatment, and other age-related chronic health conditions. Although intentional weight loss may have beneficial health effects (50), unintentional weight loss may be a sign of deteriorating health status and malnutrition and may increase the risk of death (51–53). In this study, we were unable to distinguish intentional and unintentional weight loss after cancer diagnosis, based on data collected in the 2004 follow-up survey. However, we excluded underweight cancer survivors (BMI < 18.5) who were most likely to have lost weight unintentionally as a result of cancer and other health conditions. Moderate weight gain may be beneficial for older cancer survivors.

A cancer diagnosis may provide a "teachable moment" (a life event that is accompanied by self-reflection; ref. 54)

for cancer survivors to make positive changes in their health behaviors (55, 56). Making positive changes in multiple health behaviors may be most effective in prolonging life after cancer diagnosis. Healthier behaviors often coexist. In fact, adherence to the physical activity and dietary recommendations and current smoking status were associated each other in our study. However, evidence supporting the combined effect of multiple health behaviors on survival after a cancer diagnosis, as we provide here, is scarce. Following the WCRF/AICR guidelines for cancer prevention has been shown to be associated with lower risk for dying from, as well as developing, cancer in prospective studies of healthy individuals. In a previous IWHS analysis, cancer-free women who followed 0 or 1 versus 6–9 of the 1997 WCRF/AICR recommendations were at a 35% higher risk for cancer incidence and a 43% higher risk for cancer-specific mortality (57). Similarly, each additional 2007 WCRF/AICR guideline recommendation met was associated with a 5% lower risk for developing cancer in the European Prospective Investigation into Cancer and Nutrition study (58). Concordance to the ACS cancer prevention guidelines, which are similar to the WCRF/AICR guidelines, has also been associated with lower risk of death from cancer, CVD, or any cause among cancer-free individuals in the Cancer Prevention Study-II Nutrition Cohort study (59). Here, for the first time, we report findings from a large population-based study supporting that adherence to evidence-based guidelines for cancer prevention may also be beneficial to improve survival among cancer survivors.

The prospective study design is an important strength of this study. Anthropometry and health behaviors were assessed before (at cohort baseline) and after (in the 2004 follow-up) cancer diagnosis. Therefore, we could measure participants' adherence to all 3 components (body weight, physical activity, and diet) of the WCRF/AICR guidelines before and after cancer diagnosis. We were able to identify that pre- and postdiagnosis adherence to the recommendations were reasonably correlated (correlation coefficient, $r = 0.43$) in our older cancer survivor population, and further adjust analysis for prediagnosis adherence to the recommendations. Another strength is a large number of cohort participants. After the 18 years of follow-up, we could identify more than 2,000 survivors of multiple cancer types and almost 500 deaths among these cancer survivors during the subsequent 6-year follow-up. The analysis focused specifically on older cancer survivors, which is a rapidly expanding population that has been understudied. Data on factors that may affect the association between recommendation adherence and mortality, such as demographics, health behaviors, comorbidities as well as cancer characteristics were available for inclusion as covariates in the analysis. All analyses were adjusted for current smoking, which is a well-known risk factor for death (2). Residual confounding is likely to be minimal considering the extremely low prevalence (3%) of current smoking.

One limitation of our study is the reliance on death records to determine the cause of death. There were limited numbers of deaths attributed to cancer and CVD, which might have limited statistical power to detect associations of adherence to the WCRF/AICR recommendations and its interactions with cancer type on the risk of disease-specific mortality. In our scoring algorithm, the 8 recommendations contribute equal weight to the total adherence score. Because the total adherence score consists of 6 dietary recommendations, the dietary component contributes more weight to the total adherence score than the body weight and physical activity components. To overcome this limitation, we evaluated the associations of adherence to each of the body weight, physical activity, and dietary recommendations and mortality individually. The current study included only women who had survived until the 2004 follow-up questionnaire and were able to complete the questionnaire, thus survival bias may be an issue. All study subjects were older women and the majority (99.6%) was white, which limits the generalizability of our findings to young and middle-aged adults, men, or ethnic minority groups. Potential residual confounding by measured and/or unmeasured cancer characteristics and comorbid conditions cannot be ruled out.

In summary, cancer survivors with greater overall adherence to the evidence-based cancer prevention guidelines for health behaviors, including maintaining an ideal body weight, staying physically active and eating a healthy diet, were at lower risk of death among older female cancer survivors. Our results support that the WCRF/AICR's recommendation for cancer survivors to follow its cancer prevention guidelines. Staying physically active seems to be a key health behavior to prolong life after cancer diagnosis among older female cancer survivors. More research needs to be done to understand how diet and obesity influence health outcomes among cancer survivors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M. Inoue-Choi, 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, K. Robien, D. Lazovich

Writing, review, and/or revision of the manuscript: M. Inoue-Choi, K. Robien, D. Lazovich

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Robien, D. Lazovich, M. Inoue-Choi
Study supervision: K. Robien, D. Lazovich

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Adherence to the WCRF/AICR Guidelines for Cancer Prevention Is Associated with Lower Mortality among Older Female Cancer Survivors

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