Published OnlineFirst June 18, 2013; DOI: 10.1158/1055-9965.EPI-13-0210

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Adherence to WCRF/AICR Cancer Prevention Recommendations and Risk of Postmenopausal Breast Cancer

Theresa A. Hastert[1,2], Shirley A.A. Beresford[1,2], Ruth E. Patterson[3], Alan R. Kristal[1,2], and Emily White[1,2]

Abstract

Background: In 2007, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) released eight recommendations related to body fatness, physical activity, and diet aimed at preventing the most common cancers worldwide. However, limited information exists on the association between meeting these recommendations and risks of specific cancers, including breast cancer.

Methods: We operationalized six recommendations (related to body fatness, physical activity, foods that promote weight gain, plant foods, red and processed meats, and alcohol) and examined their association with invasive breast cancer incidence over 6.7 years of follow-up in the Vitamins and Lifestyle (VITAL) study cohort. Participants included 30,797 postmenopausal women, ages 50–76 years at baseline in 2000–2002 with no history of breast cancer. Breast cancers ($n = 899$) were tracked through the Western Washington Surveillance, Epidemiology, and End Results database.

Results: Breast cancer risk was reduced by 60% in women who met at least five recommendations compared with those who met none [HR: 0.40; 95% confidence interval (CI): 0.25–0.65; $P_{trend} < 0.001$]. Further analyses that sequentially removed individual recommendations least associated with reduced risk suggested that this reduction is due to meeting recommendations related to body fatness, plant foods, and alcohol (HR for meeting vs. not meeting these three recommendations: 0.38; 95% CI: 0.25–0.58; $P_{trend} < 0.001$).

Conclusions: Meeting the WCRF/AICR cancer prevention recommendations, specifically those related to alcohol, body fatness, and plant foods, is associated with reduced postmenopausal breast cancer incidence.

Impact: Increased adherence to the WCRF/AICR cancer prevention recommendations could substantially reduce postmenopausal breast cancer risk in U.S. women. *Cancer Epidemiol Biomarkers Prev; 22(9); 1498–508. ©2013 AACR.*

Introduction

Several diet-quality indexes have been developed on the basis of recommendations aimed at preventing chronic disease. In previous studies, most diet indexes have not predicted total cancer incidence (1–5) or total cancer mortality (6, 7), with some exceptions (8–10). However, in most cases, lifestyle indexes that add other modifiable risk factors such as body weight, physical activity, and smoking have been found to predict total cancer incidence (11–14) and mortality (10, 11, 15–19).

Because the association between modifiable risk factors and cancer outcomes differs by cancer site (20), looking at total cancer incidence or mortality may mask associations for individual cancers. Although breast cancer risk is associated with several modifiable risk factors including alcohol consumption and body weight (20, 21), evidence is mixed as to whether other individual dietary behaviors (22–25), diet indexes (13), or lifestyle indexes (13, 16) are associated with breast cancer incidence. Several diet-quality indexes have failed to predict total breast cancer risk and mortality (23, 26, 27); however, associations between diet and breast cancer may differ by menopausal status (26). Similarly, the association between body mass index (BMI) and breast cancer risk differs for pre- and postmenopausal women (20). In addition, if not all of the behaviors considered are associated with reduced risk of breast cancer, weighting each equally when assessing the association between a group of behaviors and breast cancer incidence will yield misleading results.

On the basis of a comprehensive literature review, in 2007 the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) released 8 recommendations related to body fatness, diet, and physical activity aimed at reducing incidence of the most common cancers worldwide (20). One recent study

Authors' Affiliations: [1]Fred Hutchinson Cancer Research Center; [2]Department of Epidemiology, University of Washington, Seattle, Washington; and [3]Moores Cancer Center, University of California, San Diego, San Diego, California

Corresponding Author: Theresa A. Hastert, University of Michigan, Center for Social Epidemiology and Population Health, 1415 Washington Heights, SPH Tower, Room 3622, Ann Arbor, MI 48109-2029. Phone: 734-615-9214; Fax: 734-763-5706; Email: thastert@umich.edu

doi: 10.1158/1055-9965.EPI-13-0210

©2013 American Association for Cancer Research.

Downloaded from cebp.aacrjournals.org on May 24, 2019. © 2013 American Association for Cancer Research.

Published OnlineFirst June 18, 2013; DOI: 10.1158/1055-9965.EPI-13-0210

examined the association between these recommendations and total and site-specific cancer incidence and reported a statistically significant 16% reduction in risk of breast cancer in women with the highest concordance with the recommendations compared with women with the lowest concordance in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (12). However, combining pre- and postmenopausal women may have attenuated their results because several of the recommendations were developed on the basis of findings for postmenopausal breast cancer.

The purpose of this study is to assess whether an index of behaviors related to body fatness, physical activity, and diet based on the 2007 WCRF/AICR cancer prevention recommendations is associated with reduced breast cancer incidence in a cohort of postmenopausal women in the United States and, if so, to evaluate which recommendations are most strongly associated with reduced risk.

Materials and Methods

Study cohort

The Vitamins and Lifestyle (VITAL) study is a prospective cohort study designed to investigate the associations between use of dietary supplements and cancer risk and has previously been described in detail (28). Participants were eligible to join the cohort if they were between the ages of 50 and 76 and lived in one of the 13 counties in the Western Washington Surveillance, Epidemiology and End Results (SEER) cancer registry at baseline. Recruitment of women into the VITAL cohort is described below.

Using names purchased from a commercial mailing list, baseline questionnaires were mailed to 168,953 women between October 2000 and December 2002 and followed by reminder postcards. A total of 41,157 questionnaires were returned and 40,337 passed quality control checks. Overall, 30,797 women were included in our analyses after excluding women with a history of breast cancer or with incomplete baseline medical history ($n = 3,164$); premenopausal women ($n = 1,356$); those who were missing BMI ($n = 1,619$) or physical activity ($n = 509$) data; those whose food frequency questionnaires (FFQ) had less than 5 items completed on a single page ($n = 2,334$) or whose estimated energy consumption was less than 600 calories ($n = 1,477$) or more than 4,000 calories per day ($n = 137$); and women diagnosed with rare histologic types of breast cancer (e.g., sarcoma, lymphoma, phyllodes) postbaseline ($n = 9$; numbers of exclusions reported are not mutually exclusive).

The Institutional Review Board at the Fred Hutchinson Cancer Research Center approved this research.

Data collection

Baseline questionnaires included medical history, self-reported height and weight, physical activity over the previous 10 years, reproductive history, medication use, and a 126-item FFQ covering diet in the year before baseline.

The FFQ was adapted from the questionnaire developed for use in the Women's Health Initiative and other studies. The University of Minnesota's Nutrition Coding Center database was used to convert food frequency information into nutrients (29). Number of servings was calculated on the basis of frequency of intake and whether respondents indicated their usual portion size was small, medium, or large compared with a provided sex-specific medium portion size of each food and beverage. Validity studies of similar FFQs have reported correlation coefficients of 0.41 for servings of fruits and vegetables compared with food records and 0.57 to 0.61 compared with dietary recalls (30, 31), 0.50 to 0.59 for measures of red and processed meat intake compared with diet records (32), and 0.89 for alcohol consumption compared with a combination of diet recalls and food records (33).

Physical activity was assessed by a one-page questionnaire that asked about walking (including usual pace) and other moderate and strenuous recreational activities done at least once per week in the previous 10 years. The questionnaire included categorical questions on minutes per day, days per week, and number of years they participated in each activity. Estimates of metabolic equivalent task (MET)-hours per week were validated against a detailed in-person interview on 10-year recreational physical activity among a subsample of VITAL respondents (age-adjusted correlation coefficient among women: 0.70; ref. 34).

Body fatness was assessed using self-reported height and weight at baseline. Estimates of overweight status on the basis of self-reported height and weight have been found to have 84% to 95% sensitivity and 96% to 99% specificity among women ages 50 to 79 (35).

Operationalization of the WCRF/AICR recommendations

The main exposures of this study were whether or not respondents met each individual WCRF/AICR cancer prevention recommendation and the number of recommendations met. The recommendations include 8 broad guidelines, with between 1 and 4 more specific personal recommendations and public health goals for each. An expert panel of 4 nutritional epidemiologists (R.E. Patterson, Alan R. Kristal, S.A.A. Beresford, and E. White) with knowledge of the VITAL cohort data made recommendations on the operationalization of 6 of the 8 recommendations. The key components of each recommendation were identified (noted in italics in Table 1) and specific cutoffs for meeting the key components were selected on the basis of information provided in the recommendations or from external sources (e.g., the World Health Organization; ref. 36). The recommendation to limit salt-preserved foods and moldy cereals and legumes was not operationalized because those exposures are not common in the food supply in the United States and data were not available in VITAL. The recommendation to meet nutritional needs through diet alone was not operationalized because, while it did not recommend using dietary supplements, it also did not recommend against supplement use. Detail about

Downloaded from cebp.aacrjournals.org on May 24, 2019. © 2013 American Association for Cancer Research.

Published OnlineFirst June 18, 2013; DOI: 10.1158/1055-9965.EPI-13-0210

Table 1. WCRF/AICR cancer prevention recommendations (20), their operationalization in this study, and percentage who met each recommendation

WCRF/AICR recommendation	Associated personal recommendations	Met/did not meet recommendation in this study if:	VITAL cohort ($N = 30,797$) *N* (%)	Breast cancer cases ($N = 899$) *N* (%)
1. Body fatness: *Be as lean as possible within the normal range of body weight*	• Ensure that weight through childhood and adolescent growth projects toward the lower end of the normal BMI range at age 21 • Maintain body weight within the normal range from age 21 • Avoid weight gain and increases in waist circumference throughout adulthood	**Met:** 18.5 kg/m^2 $\leq$ BMI <25 kg/m^2	11,946 (38.8)	327 (36.4)
		Did not meet: BMI <18.5 kg/m^2 or BMI $\geq$25 kg/m^2	18,851 (61.2)	572 (63.6)
2. Physical activity: Be physically active as part of everyday life	• *Be moderately physically active, equivalent to brisk walking, for at least 30 minutes every day* • As fitness improves, aim for 60 minutes or more of moderate, or for 30 minutes or more of vigorous, physical activity every day • Limit sedentary habits such as watching television	**Met:** $\geq$30 minutes per day of moderate or fast walking and/or moderate or strenuous activity on at least 5 days per week in at least 7 of the past 10 years	5,288 (17.2)	155 (17.2)
		Did not meet: <30 minutes per day or <5 days per week or <7 of the previous 10 years of moderate or fast walking and/or moderate or strenuous activity	25,509 (82.8)	744 (82.8)
3. Energy density: Limit consumption of energy dense foods; avoid sugary drinks	• *Consume energy-dense foods sparingly* • *Avoid sugary drinks* • Consume 'fast foods' sparingly, if at all	**Met:** Energy density of diet <125 kcal per 100 g and <1 sugary drink per week	7,657 (24.9)	227 (25.3)
		Did not meet: Energy density of diet $\geq$125 kcal per 100 g or $\geq$1 sugary drink per week	23,140 (75.1)	672 (74.8)
4. Plant foods: Eat mostly foods of plant origin	• *Eat at least five portions/servings (at least 400 g or 14 oz) of a variety of non-starchy vegetables and of fruits every day* • *Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal* • Limit refined starchy foods • People who consume starchy roots or tubers as staples also to ensure intake of sufficient non-starchy vegetables, fruits, and pulses (legumes)	**Met:** $\geq$5 servings of fruits and vegetables and $\geq$1 serving of whole grains and/or legumes per day	4,565 (14.8)	114 (12.7)
		Did not meet: <5 servings of fruits and vegetables and/or <1 serving of whole grains and/or legumes per day	26,232 (85.2)	785 (87.3)
5. Red meat: Limit intake of red meat and avoid processed meat	• *People who eat red meat to consume less than 500 g (18 oz) a week, very little if any to be processed*	**Met:** <18 oz red and/or processed meat per week	22,648 (73.5)	653 (72.6)
		Did not meet: $\geq$18 oz red and/or processed meat per week	8,149 (26.5)	246 (27.4)
6. Alcohol: Limit alcoholic drinks	• *If alcoholic drinks are consumed, limit consumption to no more than two drinks a day for men and one drink a day for women*	**Met:** $\leq$1 drink per day	26,639 (86.5)	719 (80.0)
		Did not meet: >1 drink per day	4,158 (13.5)	180 (20.0)

(Continued on the following page)

Downloaded from cebp.aacrjournals.org on May 24, 2019. © 2013 American Association for Cancer Research.

Published OnlineFirst June 18, 2013; DOI: 10.1158/1055-9965.EPI-13-0210

Table 1. WCRF/AICR cancer prevention recommendations (20), their operationalization in this study, and percentage who met each recommendation (Cont'd)

WCRF/AICR recommendation	Associated personal recommendations	Met/did not meet recommendation in this study if:	VITAL cohort ($N = 30,797$) *N* (%)	Breast cancer cases ($N = 899$) *N* (%)
7. Salt-preserved foods: Limit consumption of salt; avoid moldy grains or legumes	• Avoid salt-preserved, salted, or salty foods; preserve foods without using salt • Limit consumption of processed foods with added salt to ensure an intake of less than 6 g (2.4 g sodium) a day • Do not eat moldy cereals (grains) or pulses (legumes)	**Not operationalized**	— —	— —
8. Supplements: Aim to meet nutritional needs through diet alone	• Dietary supplements are not recommended for cancer prevention	**Not operationalized**	— —	— —

NOTE: *Italicized text* indicates portions of the WCRF/AICR recommendations operationalized in this study. These represent the key components of the recommendations selected by an expert panel.

the operationalization of the remaining recommendations is below.

Body fatness. The recommendation to be as lean as possible within the normal range of body weight was operationalized as having a BMI of at least 18.5 but less than 25 kg/m^2 on the basis of height and weight reported at baseline. This range was based on that set by the World Health Organization (36) as normal weight, as suggested in the recommendation (20).

For women with missing weight at baseline but who reported BMI at age 45 ($n = 685$), BMI at baseline was imputed by calculating the average annual change in BMI within 18 age- and race/ethnicity-specific strata (<60, 60–69, and 70+ for age; white, Hispanic, African-American, American Indian/Alaska Native, Asian, or Pacific Islander, and other for race/ethnicity), multiplying that value by the difference between baseline age of respondents and 45, and adding the product to their BMI at age 45.

Physical activity. The recommendation to be physically active as a part of everyday life (equivalent to brisk walking for at least 30 minutes every day) was operationalized as engaging in moderate or fast walking and/or other moderate or strenuous activity for an average of at least 30 minutes per day, at least 5 days per week, and in at least 7 of the past 10 years. Respondents who were missing data for this constructed variable but whose physical activity responses were complete enough to estimate their MET-hours per week of walking and/or moderate/strenuous physical activity ($n = 1,950$) were categorized as meeting this recommendation if they engaged in an average of at least 10 MET hours of walking and/or moderate/strenuous physical activity per week (using an estimate of 4.0 METs/hour × 0.5 hours/day × 5 days/week) over the previous 10 years.

Energy density. The recommendation to limit consumption of energy-dense foods and to avoid sugary drinks was operationalized as consuming a diet where the energy density of foods consumed was less than 125 kcal per 100 g on the basis of responses to the FFQ and also consuming less than 1 serving of regular (not diet) soda, fruit drinks, and/or cranberry juice per week. Fruit juices which typically do not have added sugar (e.g., orange juice) were not counted as sugary drinks. The energy density cutoff was based on a public health goal included in the WCRF/AICR recommendation that the average energy density of diets should be lowered toward 125 kcal per 100 g.

Plant foods. The recommendation to eat mostly foods of plant origin, specifically the personal recommendations to eat at least 5 servings of a variety of non-starchy vegetables and fruits every day and to eat relatively unprocessed grains and/or legumes with every meal, were operationalized as consuming at least 5 servings of fruits and/or non-starchy vegetables and also at least 1 serving of whole grains and/or legumes per day. Servings of fruits and non-starchy vegetables included 25 foods or food groups, adjusted by portion size and by summary questions on total numbers of fruits and vegetables eaten to reduce overestimation by participants. It excluded fruit juices and potatoes. Because the VITAL FFQ only included 5 items on whole grains (covering breads and breakfast cereals) and, therefore, failed to fully separate whole grains from other grains (e.g., brown rice from white rice), we used a cutoff of 1 serving per day rather than per meal to represent those who habitually eat whole grains and/or

Downloaded from cebp.aacrjournals.org on May 24, 2019. © 2013 American Association for Cancer Research.

Published OnlineFirst June 18, 2013; DOI: 10.1158/1055-9965.EPI-13-0210

legumes. Legume servings included 3 items on bean dishes and one item on tofu and tempeh.

Red meat. The recommendation to limit intake of red meat and to avoid processed meat was operationalized as consuming less than 18 ounces of red or processed meat per week. Red and processed meat from mixed dishes in the FFQ were also included by assuming that red or processed meat accounted for one-quarter of their weight.

Alcohol. The recommendation to limit alcoholic drinks was operationalized as consuming no more than one alcoholic beverage per day on average, where a drink was classified as a 12-ounce bottle or can of beer; 4-ounce glass of red, white, or rosé wine; or one shot (1.5 ounces) of liquor or one mixed drink.

Case ascertainment and censoring

Incident primary breast cancers were ascertained through December 31, 2008 by annual linkage with the Western Washington SEER cancer registry. All incident cancers diagnosed in the 13 counties of the Western Washington SEER registry (except for nonmelanoma skin cancers) are reported to SEER by all area hospitals and by offices of pathologists, oncologists, and radiotherapists. Linkage between VITAL and SEER is largely automated and based on ranking agreement between items common to both sets of data, such as Social Security number, name, and date of birth. Matches with high concordance are linked automatically. Visual inspection is used to adjudicate incomplete matches. A total of 899 incident invasive breast cancers were identified among the women eligible for this analysis in an average of 6.7 years of follow-up.

Participants who did not develop breast cancer were right-censored at the earliest of the following events: date they requested removal from the study ($n = 12$), date they moved out of the Western Washington SEER catchment area ($n = 1{,}617$), date of death ($n = 1{,}318$), or December 31, 2008 ($n = 26{,}712$). Because *in situ* breast cancers are commonly treated and not all would be expected to progress to invasive disease, women diagnosed with *in situ* breast cancer ($n = 239$) were not considered as meeting the case definition and were censored at the date of diagnosis. Moves out of the SEER catchment area were identified through linkage with the National Change of Address System and deaths occurring in Washington State were ascertained via linkage with the Washington State death file using linkage procedures similar to that for linkage to SEER.

Statistical analyses

HRs and 95% confidence intervals (CI) of incident, invasive breast cancer associated with meeting (vs. not meeting) each individual recommendation and for the number of recommendations met (vs. meeting none) were estimated using Cox proportional hazards models. We used participant age as the time scale, with participants entering the analysis at the age they completed the baseline questionnaire and exiting at age at diagnosis of invasive breast cancer or age at censoring event. Proportional hazards assumptions were examined using scaled Schoenfeld residuals. No significant ($P < 0.05$) deviations from proportionality were observed. P_{trend} values were calculated using the Wald test associated with modeling the number of recommendations met as a continuous variable. All statistical tests were two-sided.

Multivariate analyses included adjustment for potential confounders selected *a priori*, including known risk factors for breast cancer. These analyses included categorical variable adjustment for education, race, age at menarche, age at birth of first child, years of combined estrogen plus progestin hormone therapy use, age at menopause, receipt of a mammogram in the 2 years before baseline, and history of breast cancer in a first-degree relative using the categories in Table 2, as well as adjustment for kilocalories of average daily energy intake (continuous). Participants with missing data were treated as their own category for each potential confounder.

In additional analyses, binary variables indicating whether respondents met each of the 6 recommendations were included in one model with the potential confounders. The least-protective recommendation (the one with the largest HR) was subsequently removed, the model was run again, and the process was repeated until only the most protective recommendation remained. Each subset of recommendations identified through this process was evaluated in relation to breast cancer risk. Analyses were conducted using Stata 12.1 (StataCorp LP).

Results

Table 1 gives the proportion of women in the VITAL cohort and those diagnosed with breast cancer during follow-up who met each recommendation. More than 70% of the women in the cohort and of cases met the recommendations to limit consumption of alcohol and of red and processed meat. Less than 40% met the recommendations on body fatness, consumption of energy dense foods and sugary drinks, plant foods, and physical activity.

The average age at baseline was 61.3 years for women in the cohort and 63.2 for cases. Table 2 gives baseline characteristics of women in the overall study population and those diagnosed with invasive breast cancer during follow-up. Women in both groups were predominantly white, and more than one-third of each group completed college. Compared with the cohort as a whole, a larger proportion of women diagnosed with breast cancer reported having at least one first-degree relative with a history of breast cancer and reported using hormone therapy for at least 5 years ($P < 0.05$ for both).

Table 3 gives HRs and 95% CIs associated with meeting (vs. not meeting) each individual recommendation. In covariate-adjusted analyses, meeting the recommendation to limit alcohol to no more than 1 drink per day was associated with a 37% reduction in breast cancer risk compared with consuming more than one drink per day (HR, 0.63; 95% CI, 0.54–0.75) and meeting the recommendation to consume mostly plant foods was associated

Downloaded from cebp.aacrjournals.org on May 24, 2019. © 2013 American Association for Cancer Research.

Published OnlineFirst June 18, 2013; DOI: 10.1158/1055-9965.EPI-13-0210

Table 2. Baseline characteristics of the study population and of breast cancer cases

Characteristic	VITAL cohort (*N* = 30,797) *N* (%)	Breast cancer cases (*N* = 899) *N* (%)
Age		
50–54	6,981 (22.7)	112 (12.5)
55–59	7,648 (24.8)	200 (22.3)
60–64	5,725 (18.6)	189 (21.0)
65–69	4,810 (15.6)	177 (19.7)
70 or older	5,633 (18.3)	221 (24.6)
Education		
High school graduate/GED or below	6,996 (22.7)	210 (23.4)
Some college/technical school	12,791 (41.5)	366 (40.7)
College graduate	6,866 (22.3)	207 (23.0)
Advanced degree	4,012 (13.0)	111 (12.4)
Missing	132 (0.4)	5 (0.6)
Race		
White	28,762 (93.4)	858 (95.4)
Non-white	1,922 (6.2)	37 (4.1)
Missing	113 (0.4)	4 (0.4)
Mammogram in 2 years before baseline		
No	2,606 (8.5)	73 (8.1)
Yes	28,090 (91.2)	824 (91.7)
Missing	101 (0.3)	2 (0.2)
Family history of breast cancer (first degree)		
No	25,738 (83.6)	683 (76.0)
Yes	4,626 (15.0)	192 (21.4)
Missing	433 (1.4)	24 (2.7)
Age at menarche		
11 or younger	5,736 (18.6)	182 (20.2)
12	9,129 (29.6)	288 (32.0)
13	8,966 (29.1)	238 (26.5)
14	3,984 (12.9)	110 (12.2)
15 or older	2,716 (8.8)	77 (8.6)
Missing	266 (0.9)	4 (0.4)
Age when first child born		
19 or younger	5,413 (17.6)	135 (15.0)
20–24	12,557 (40.8)	396 (44.1)
25–29	5,999 (19.5)	155 (17.2)
30–34	2,019 (6.6)	52 (5.8)
35 or older	629 (2.0)	26 (2.9)
No children	3,883 (12.6)	128 (14.2)
Missing	297 (1.0)	7 (0.8)
Years of combined estrogen and progestin hormone therapy use		
None or less than 1	18,002 (58.5)	472 (52.5)
1–4	4,092 (13.3)	92 (10.2)
5–9	3,366 (10.9)	123 (13.7)
10 or more	3,581 (11.6)	157 (17.5)
Missing	1,756 (5.7)	55 (6.1)
Age at menopause		
39 or younger	2,909 (9.5)	70 (7.8)
40–44	4,041 (13.1)	124 (13.8)
45–49	8,208 (26.7)	237 (26.4)
50–54	10,826 (35.2)	333 (37.0)
55 or older	1,698 (5.5)	60 (6.7)
Perimenopausal at baseline	978 (3.2)	19 (2.1)
Missing	2,137 (6.9)	56 (6.2)

Downloaded from cebp.aacrjournals.org on May 24, 2019. © 2013 American Association for Cancer Research.

Published OnlineFirst June 18, 2013; DOI: 10.1158/1055-9965.EPI-13-0210

Table 3. HRs and 95% CIs for invasive breast cancer associated with meeting (vs. not meeting) each WCRF/AICR recommendation

Recommendation	Age-adjusted HR (95% CI)	Covariate-adjusted[a] HR (95% CI)	Fully adjusted[b] HR (95% CI)
Body fatness	0.89 (0.78–1.02)	0.87 (0.76–1.00)	0.85 (0.74–0.98)
Physical activity	0.98 (0.82–1.16)	0.95 (0.80–1.13)	0.97 (0.81–1.16)
Energy density	1.00 (0.86–1.17)	0.98 (0.84–1.15)	1.04 (0.88–1.22)
Plant foods	0.81 (0.67–0.99)	0.79 (0.64–0.97)	0.82 (0.66–1.02)
Red meat	0.94 (0.81–1.09)	0.90 (0.77–1.06)	0.94 (0.80–1.11)
Alcohol	0.62 (0.52–0.73)	0.63 (0.54–0.75)	0.63 (0.53–0.74)

NOTE: Age is used as the timeline in the Cox proportional hazards models. All models included 30,797 women and 899 incident breast cancers.

[a]Adjusted for age (as the timeline in the Cox model), education, race, mammography, family history of breast cancer, age at menarche, age at first birth, age at menopause, and years of estrogen plus progestin hormone therapy use using categories in Table 2 and daily energy intake (kcal).

[b]Adjusted for the factors in the covariate-adjusted model as well as for whether respondents met each of the other recommendations.

with a 21% reduction in risk (HR, 0.79; 95% CI, 0.64–0.97) compared with not meeting the recommendation. Breast cancer risk was 13% lower in women whose BMI was in the normal range at baseline relative to those with BMIs above or below the normal range (HR, 0.87; 95% CI, 0.76–1.00). After also adjusting for whether respondents met each of the other recommendations, the recommendations related to body fatness and alcohol remained associated with significant reductions in breast cancer risk.

Table 4 gives HRs and 95% CIs associated with the number of recommendations met. After adjusting for potential confounders, each additional recommendation met was associated with an 11% (95% CI, 5%–16%) reduction in breast cancer risk ($P_{trend} < 0.001$). In adjusted analyses, compared with meeting no recommendations, meeting one recommendation was associated with a marginally significant 32% reduction in breast cancer risk, meeting 2 to 4 recommendations was associated with a statistically significant 44% to 48% reduction in risk, and meeting 5 to 6 recommendations was associated with a 60% reduction in risk (HR, 0.40; 95% CI, 0.25–0.65; $P_{trend} = 0.001$).

Sensitivity analyses excluding women missing BMI and physical activity data rather than imputing their values did not alter our results (data not shown).

To identify specific subsets of recommendations most associated with reduced breast cancer risk, additional

Table 4. HRs and 95% CIs for invasive breast cancer associated with number of WCRF/AICR recommendations met at baseline

Recommendations met	VITAL cohort ($N = 30,797$) N (%)	Breast cancer cases ($N = 899$) N (%)	Age-adjusted HR (95% CI)	Covariate-adjusted[a] HR (95% CI)
None	571 (1.9)	28 (3.1)	1.00	1.00
1	5,025 (16.3)	166 (18.5)	0.67 (0.45–1.00)	0.68 (0.46–1.02)
2	10,324 (33.5)	300 (33.4)	0.57 (0.39–0.84)	0.56 (0.38–0.83)
3	8,616 (28.0)	239 (26.6)	0.54 (0.36–0.80)	0.53 (0.35–0.78)
4	4,405 (14.3)	125 (13.9)	0.55 (0.36–0.83)	0.52 (0.34–0.79)
5–6	1,856 (6.0)	41 (4.6)	0.42 (0.26–0.68)	0.40 (0.25–0.65)
Per recommendation			0.91 (0.86–0.96)	0.89 (0.84–0.95)
P_{trend}[b]			0.001	<0.001

NOTE: Age is used as the timeline in the Cox proportional hazards models. All models included 30,797 observations and 899 incident breast cancers.

[a]Adjusted for age (as the timeline in the Cox model), education, race, mammography, family history of breast cancer, age at menarche, age at first birth, age at menopause, and years of estrogen plus progestin hormone therapy use using categories in Table 2 and daily energy intake (kcal).

[b]HRs, 95% CIs, and *P* values were calculated using a two-sided test for linear trend modeling categories as a continuous variable (0–6).

Downloaded from cebp.aacrjournals.org on May 24, 2019. © 2013 American Association for Cancer Research.

Published OnlineFirst June 18, 2013; DOI: 10.1158/1055-9965.EPI-13-0210

Table 5. HRs and 95% CIs for invasive breast cancer associated with subsets of WCRF/AICR cancer prevention recommendations met at baseline after sequentially eliminating the recommendation least associated with a reduction in breast cancer risk

Recs. included:	Physical activity, meat, body fatness, plant foods, alcohol (removed energy density)		Meat, body fatness, plant foods, alcohol (removed physical activity)		Body fatness, plant foods, alcohol (removed meat)		Plant foods, alcohol (removed body fatness)	
Recs. met	No. of cases	HR (95% CI)[a]	No. of cases	HR (95% CI)[a]	No. of cases	HR (95% CI)[a]	No. of cases	HR (95% CI)[a]
None	31	1.00	32	1.00	82	1.00	160	1.00
1	176	0.65 (0.44–0.95)	194	0.71 (0.49–1.03)	504	0.69 (0.54–0.87)	645	0.63 (0.53–0.76)
2	370	0.58 (0.40–0.84)	424	0.66 (0.46–0.95)	283	0.57 (0.44–0.73)	94	0.52 (0.40–0.67)
3	245	0.52 (0.35–0.75)	225	0.53 (0.36–0.77)	30	0.38 (0.25–0.58)		
4	68	0.43 (0.28–0.66)	24	0.35 (0.21–0.59)				
5	9	0.31 (0.15–0.65)						
Per rec.		0.86 (0.80–0.92)		0.82 (0.76–0.89)		0.77 (0.70–0.85)		0.70 (0.62–0.80)
P_{trend}[b]		<0.001		<0.001		<0.001		<0.001

[a]Adjusted for age (as the timeline in the Cox model), education, race, mammography, family history of breast cancer, age at menarche, age at first birth, age at menopause, and years of estrogen plus progestin hormone therapy use using categories in Table 2 and daily energy intake (kcal). Models included 30,797 observations and 899 incident breast cancers.

[b]HRs, 95% CIs, and *P* values were calculated using a two-sided test for linear trend modeling categories as a continuous variable.

analyses were conducted in which the fully adjusted model presented in Table 3 was repeated with the recommendation least associated with reduction in breast cancer risk sequentially removed. Results given in Table 5 suggest that, compared with meeting no recommendations, the reduction in breast cancer risk observed for women meeting the recommendations related to body fatness, plant foods, and alcohol intake (HR, 0.38; 95% CI, 0.25–0.58 vs. meeting none of the three) is at least as great as for meeting any combination of 5 to 6 of all of the recommendations considered (HR, 0.40; 95% CI, 0.25–0.65; Table 4). Modest additional benefit is achieved from also meeting the recommendations related to red and processed meat and physical activity.

Results appeared to be somewhat stronger for estrogen-receptor (ER)-negative breast cancer (per-recommendation HR, 0.84; 95% CI, 0.72–0.99) than for ER-positive breast cancer (per-recommendation HR, 0.90; 95% CI, 0.85–0.96). As for all breast cancer cases, body fatness, plant foods, and alcohol accounted for most of the association with reduced ER-positive breast cancer risk, where red and processed meat, body fatness, and alcohol accounted for most of the association with ER-negative breast cancer (data not shown).

Discussion

In this cohort of postmenopausal women, meeting at least 5 of the WCRF/AICR recommendations was associated with a 60% reduction in breast cancer risk compared with meeting no recommendations (HR: 0.40; 95% CI, 0.25–0.65). Further analyses suggest that this association is primarily due to meeting recommendations related to body fatness, plant foods, and alcohol (HR for meeting all vs. none of these recommendations: 0.38; 95% CI, 0.25–0.58). The results based on counts of the 6 recommendations are somewhat misleading, as each recommendation does not have the same impact on breast cancer risk; rather, as the number of recommendations met increases, the likelihood that a woman has met the three key recommendations increases.

In the previous study that examined the association between concordance with the WCRF/AICR recommendations and overall and site-specific cancer incidence in the EPIC cohort, each additional point on a recommendation score was associated with a 5% (95% CI, 3%–7%) reduction in breast cancer risk and a recommendation score of 5 points or more was associated with a HR for breast cancer incidence of 0.84 (95% CI, 0.78–0.90) compared with a score of 3 points or less (12).

Although we cannot directly compare the much larger risk reduction for our highest versus our lowest recommendation group to that reported previously due to differences in operationalizing the recommendations and in defining the high and low groups, our result of an 11% decreased risk per recommendation met (HR, 0.89; 95% CI, 0.84–0.94) is more than twice as large a reduced risk as in the EPIC cohort. Several differences between our study and the EPIC study may have contributed to the different magnitude of our findings. Previous research suggests that both the strength and the direction of the association between modifiable risk factors and breast cancer differ in

Downloaded from cebp.aacrjournals.org on May 24, 2019. © 2013 American Association for Cancer Research.

Published OnlineFirst June 18, 2013; DOI: 10.1158/1055-9965.EPI-13-0210

pre- and postmenopausal women (e.g., body fatness is inversely associated with breast cancer risk in premenopausal women, but positively associated in postmenopausal women; ref. 20). Thus, the results of the previous study may have been attenuated by including premenopausal women (33.4% of women were premenopausal at baseline; ref. 12). In addition, the EPIC study included the WCRF/AICR special recommendation that mothers should aim to breastfeed exclusively for 6 months (12), although this difference would have made the EPIC findings stronger relative to ours (breastfeeding data were not available in VITAL). Furthermore, the current study operationalized recommendations as being met or not met but, in the previous study, respondents received partial points for near-adherence (12).

To our knowledge, only two other studies of lifestyle indexes (i.e., those that include modifiable risk factors such as body weight and physical activity as well as diet) and cancer incidence have reported results for breast cancer in subanalyses (13, 16). Heidemann and colleagues examined the association between a diabetes risk score (including waist circumference, height, physical activity, age, hypertension, smoking, and intake of alcohol, red meat, whole-grain bread, and coffee) and breast cancer incidence (HR for breast cancer associated with $\geq$10% vs. <1% 5-year probability of developing diabetes: 1.3; 95% CI, 0.6–2.7; $P_{trend} = 0.85$); however, this estimate is based on only 9 breast cancer cases in the highest-risk group (16). In a study of the association between an index representing adherence to the Dietary Guidelines for Americans (including dietary behaviors, BMI and physical activity) and total and site-specific cancer incidence, Harnack and colleagues reported a HR for breast cancer of 0.76 (95% CI, 0.65–0.89) for women ages 55–69 in the highest quintile of adherence compared with women in the lowest quintile (13). When BMI and physical activity were removed from the index, leaving only the dietary behaviors, the association attenuated to a HR of 0.86 (95% CI, 0.73–1.00; ref. 13).

Strengths of this study include its large sample size, prospective design, and the detailed information collected at baseline that allowed us to operationalize 6 of the WCRF/AICR cancer prevention recommendations and control for several potential confounding factors. Linkage with the SEER database provided accurate and near-complete ascertainment of breast cancer outcomes. In additional analyses, we were able to identify the specific recommendations associated with reduction in postmenopausal breast cancer risk.

Another feature of our study was the use of an expert panel to operationalize the recommendations. Although this was designed to be a strength, our results might have differed had we used different interpretations. Therefore, we conducted sensitivity analyses using stricter standards for the recommendations related to body fatness (BMIs of 21–23 at baseline) and physical activity (60+ minutes/day on 5–7 days/week in all 10 years) on the basis of additional information in the recommendations. In adjusted analyses, meeting the stricter recommendations related to body fatness and physical activity was more strongly associated with reductions in breast cancer risk compared with the original classifications (HR for body fatness: 0.75; 95% CI, 0.61–0.93; HR for physical activity, 0.90; 95% CI, 0.72–1.12). In further analyses of the per-recommendation association with breast cancer risk using the stricter version of these two recommendations, each additional recommendation met was associated with a 14% reduction in breast cancer risk (HR, 0.86; 95% CI, 0.81–0.92), a somewhat stronger association compared with the original interpretation.

One limitation of our study is that those who chose to join the VITAL cohort may have had more positive health behaviors than the general population. Compared with women in Washington State, a larger proportion of VITAL participants were white, college-educated, maintained BMIs in the normal range, and consumed at least 1 alcoholic drink per day, and a lower proportion were current smokers (37). However, selection bias is not likely to affect results in a prospective study where future disease status is unknown at baseline. In addition, although analyses controlled for many potential confounding factors, residual confounding may exist due to missing or misspecified confounders. Measurement error in our assessment of meeting individual recommendations and the combined score would act to bias results toward the null. Finally, we did not have the data to include the special recommendation related to breastfeeding, which has been found to be protective against breast cancer (20). Therefore, the effect of the WCRF/AICR recommendations on breast cancer risk may be even greater than that found in this study.

This study is the first to examine adherence to the WCRF/AICR cancer prevention recommendations related to body fatness, diet, and physical activity and cancer risk in a U.S. population, and to examine the association between meeting the recommendations and risk of postmenopausal breast cancer. These results indicate that meeting the WCRF/AICR cancer prevention recommendations related to body fatness, plant foods, and alcohol is associated with substantial reductions in risk of invasive breast cancer in postmenopausal women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: T.A. Hastert, A.R. Kristal, E. White
Development of methodology: T.A. Hastert, S.A.A. Beresford, R.E. Patterson, A.R. Kristal, E. White
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.E. Patterson, A.R. Kristal, E. White
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T.A. Hastert, S.A.A. Beresford, R.E. Patterson, A.R. Kristal, E. White
Writing, review, and/or revision of the manuscript: T.A. Hastert, S.A.A. Beresford, R.E. Patterson, A.R. Kristal, E. White
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E. White
Study supervision: E. White

Downloaded from cebp.aacrjournals.org on May 24, 2019. © 2013 American Association for Cancer Research.

Published OnlineFirst June 18, 2013; DOI: 10.1158/1055-9965.EPI-13-0210

Grant Support

This work was financially supported by the Biobehavioral Cancer Prevention and Control Training Program at the University of Washington funded by the National Cancer Institute R25CA92408 (to T. A. Hastert) and by the National Cancer Institute and the National Institutes of Health Office of Dietary Supplements K05CA154337 (to E. White).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received March 1, 2013; revised April 30, 2013; accepted May 13, 2013; published OnlineFirst June 18, 2013.

References

1. McCullough ML, Feskanich D, Rimm EB, Giovannucci EL, Ascherio A, Variyam JN, et al. Adherence to the Dietary Guidelines for Americans and risk of major chronic disease in men. Am J Clin Nutr 2000;72:1223–31.
2. McCullough ML, Feskanich D, Stampfer MJ, Rosner BA, Hu FB, Hunter DJ, et al. Adherence to the Dietary Guidelines for Americans and risk of major chronic disease in women. Am J Clin Nutr 2000;72:1214–22.
3. McCullough ML, Willett WC. Evaluating adherence to recommended diets in adults: the Alternate Healthy Eating Index. Public Health Nutr 2006;9:152–7.
4. McCullough ML, Feskanich D, Stampfer MJ, Giovannucci EL, Rimm EB, Hu FB, et al. Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. Am J Clin Nutr 2002;76:1261–71.
5. von Ruesten A, Illner AK, Buijsse B, Heidemann C, Boeing H. Adherence to recommendations of the German food pyramid and risk of chronic diseases: results from the EPIC–Potsdam study. Eur J Clin Nutr 2010;64:1251–9.
6. Seymour JD, Calle EE, Flagg EW, Coates RJ, Ford ES, Thun MJ. Diet Quality Index as a predictor of short-term mortality in the American Cancer Society Cancer Prevention Study II Nutrition Cohort. Am J Epidemiol 2003;157:980–8.
7. Kaluza J, Hakansson N, Brzozowska A, Wolk A. Diet quality and mortality: a population-based prospective study of men. Eur J Clin Nutr 2009;63:451–7.
8. Kant AK, Schatzkin A, Graubard BI, Schairer C. A prospective study of diet quality and mortality in women. JAMA 2000;283:2109–15.
9. van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB. Combined impact of lifestyle factors on mortality: prospective cohort study in US women. BMJ 2008;337:a1440.
10. Knoops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O, Menotti A, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. JAMA 2004;292:1433–9.
11. Cerhan JR, Potter JD, Gilmore JM, Janney CA, Kushi LH, Lazovich D, et al. Adherence to the AICR cancer prevention recommendations and subsequent morbidity and mortality in the Iowa Women's Health Study cohort. Cancer Epidemiol Biomarkers Prev 2004;13:1114–20.
12. Romaguera D, Vergnaud AC, Peeters PH, van Gils CH, Chan DS, Ferrari P, et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. Am J Clin Nutr 2012;96:150–63.
13. Harnack L, Nicodemus K, Jacobs DR Jr., Folsom AR. An evaluation of the Dietary Guidelines for Americans in relation to cancer occurrence. Am J Clin Nutr 2002;76:889–96.
14. Ford ES, Bergmann MM, Kroger J, Schienkiewitz A, Weikert C, Boeing H. Healthy living is the best revenge: findings from the European Prospective Investigation Into Cancer and Nutrition-Potsdam study. Arch Intern Med 2009;169:1355–62.
15. McCullough ML, Patel AV, Kushi LH, Patel R, Willett WC, Doyle C, et al. Following cancer prevention guidelines reduces risk of cancer, cardiovascular disease, and all-cause mortality. Cancer Epidemiol Biomarkers Prev 2011;20:1089–97.
16. Heidemann C, Boeing H, Pischon T, Nothlings U, Joost HG, Schulze MB. Association of a diabetes risk score with risk of myocardial infarction, stroke, specific types of cancer, and mortality: a prospective study in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort. Eur J Epidemiol 2009;24:281–8.
17. Khaw KT, Wareham N, Bingham S, Welch A, Luben R, Day N. Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. PLoS Med 2008;5:e12.
18. Kvaavik E, Batty GD, Ursin G, Huxley R, Gale CR. Influence of individual and combined health behaviors on total and cause-specific mortality in men and women: the United Kingdom health and lifestyle survey. Arch Intern Med 2010;170:711–8.
19. Nechuta SJ, Shu XO, Li HL, Yang G, Xiang YB, Cai H, et al. Combined impact of lifestyle-related factors on total and cause-specific mortality among Chinese women: prospective cohort study. PLoS Med 2010;7:e1000339.
20. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR, 2007.
21. Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA 1998;279:535–40.
22. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295:629–42.
23. Fung TT, Hu FB, McCullough ML, Newby PK, Willett WC, Holmes MD. Diet quality is associated with the risk of estrogen receptor-negative breast cancer in postmenopausal women. J Nutr 2006;136:466–72.
24. Fung TT, Hu FB, Holmes MD, Rosner BA, Hunter DJ, Colditz GA, et al. Dietary patterns and the risk of postmenopausal breast cancer. Int J Cancer 2005;116:116–21.
25. Fung TT, Hu FB, Hankinson SE, Willett WC, Holmes MD. Low-carbohydrate diets, dietary approaches to stop hypertension-style diets, and the risk of postmenopausal breast cancer. Am J Epidemiol 2011;174:652–60.
26. Cade JE, Taylor EF, Burley VJ, Greenwood DC. Common dietary patterns and risk of breast cancer: analysis from the United Kingdom Women's Cohort Study. Nutr Cancer 2010;62:300–6.
27. Mai V, Kant AK, Flood A, Lacey JV Jr., Schairer C, Schatzkin A. Diet quality and subsequent cancer incidence and mortality in a prospective cohort of women. Int J Epidemiol 2005;34:54–60.
28. White E, Patterson RE, Kristal AR, Thornquist M, King I, Shattuck AL, et al. VITamins And Lifestyle cohort study: study design and characteristics of supplement users. Am J Epidemiol 2004;159:83–93.
29. Schakel SF, Buzzard IM, Gebhardt SE. Procedures for estimating nutrient values for food composition databases. J Food Composition Anal 1997;10:102–14.
30. Kristal AR, Vizenor NC, Patterson RE, Neuhouser ML, Shattuck AL, McLerran D. Precision and bias of food frequency-based measures of fruit and vegetable intakes. Cancer Epidemiol Biomarkers Prev 2000;9:939–44.
31. Thompson FE, Kipnis V, Midthune D, Freedman LS, Carroll RJ, Subar AF, et al. Performance of a food-frequency questionnaire in the US NIH-AARP (National Institutes of Health-American Association of Retired Persons) Diet and Health Study. Public Health Nutr 2008;11:183–95.
32. Hu FB, Rimm E, Smith-Warner SA, Feskanich D, Stampfer MJ, Ascherio A, et al. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. Am J Clin Nutr 1999;69:243–9.
33. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Ann Epidemiol 1999;9:178–87.

Downloaded from cebp.aacrjournals.org on May 24, 2019. © 2013 American Association for Cancer Research.

Published OnlineFirst June 18, 2013; DOI: 10.1158/1055-9965.EPI-13-0210

34. Littman AJ, White E, Kristal AR, Patterson RE, Satia-Abouta J, Potter JD. Assessment of a one-page questionnaire on long-term recreational physical activity. Epidemiology 2004;15:105–13.
35. Kuczmarski MF, Kuczmarski RJ, Najjar M. Effects of age on validity of self-reported height, weight, and body mass index: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. J Am Diet Assoc 2001;101:28–34; quiz 5–6.
36. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:i-xii, 1–253.
37. Behavioral Risk Factor Surveillance System Washington State Data Report 2001. Centers for Disease Control and Prevention; 2001. Available from: http://www.doh.wa.gov/Portals/1/Documents/5300/BRFSSWA01SDRP.pdf.

Downloaded from cebp.aacrjournals.org on May 24, 2019. © 2013 American Association for Cancer Research.

Published OnlineFirst June 18, 2013; DOI: 10.1158/1055-9965.EPI-13-0210

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Adherence to WCRF/AICR Cancer Prevention Recommendations and Risk of Postmenopausal Breast Cancer

Theresa A. Hastert, Shirley A.A. Beresford, Ruth E. Patterson, et al.

Cancer Epidemiol Biomarkers Prev 2013;22:1498-1508. Published OnlineFirst June 18, 2013.

Updated version Access the most recent version of this article at: doi:10.1158/1055-9965.EPI-13-0210

Cited articles This article cites 35 articles, 11 of which you can access for free at: http://cebp.aacrjournals.org/content/22/9/1498.full#ref-list-1

Citing articles This article has been cited by 13 HighWire-hosted articles. Access the articles at: http://cebp.aacrjournals.org/content/22/9/1498.full#related-urls

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link http://cebp.aacrjournals.org/content/22/9/1498. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.

Downloaded from cebp.aacrjournals.org on May 24, 2019. © 2013 American Association for Cancer Research.