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ORIGINAL REPORT

Greater Survival After Breast Cancer in Physically Active Women With High Vegetable-Fruit Intake Regardless of Obesity

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ABSTRACT

Purpose
Single-variable analyses have associated physical activity, diet, and obesity with survival after breast cancer. This report investigates interactions among these variables.

Patients and Methods
A prospective study was performed of 1,490 women diagnosed and treated for early-stage breast cancer between 1991 and 2000. Enrollment was an average of 2 years postdiagnosis. Only seven women were lost to follow-up through December 2005.

Results
In univariate analysis, reduced mortality was weakly associated with higher vegetable-fruit consumption, increased physical activity, and a body mass index that was neither low weight nor obese. In a multivariate Cox model, only the combination of consuming five or more daily servings of vegetables-fruits, and accumulating 540+ metabolic equivalent tasks-min/wk (equivalent to walking 30 minutes 6 d/wk), was associated with a significant survival advantage (hazard ratio, 0.56; 95% CI, 0.31 to 0.98). The approximate 50% reduction in risk associated with these healthy lifestyle behaviors was observed in both obese and nonobese women, although fewer obese women were physically active with a healthy dietary pattern (16% *v* 30%). Among those who adhered to this healthy lifestyle, there was no apparent effect of obesity on survival. The effect was stronger in women who had hormone receptor–positive cancers.

Conclusion
A minority of breast cancer survivors follow a healthy lifestyle that includes both recommended intakes of vegetables-fruits and moderate levels of physical activity. The strong protective effect observed suggests a need for additional investigation of the effect of the combined influence of diet and physical activity on breast cancer survival.

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INTRODUCTION

Dietary pattern and moderate levels of physical activity (PA) have each been linked separately to survival after breast cancer in some[1-5] but not all[6,7] studies. Given that both diet and PA have each been shown to modify circulating gonadal hormone concentrations,[8,9] their effect on survival after breast cancer may not be independent, and combining both may provide the optimal survival benefit. There is considerable scope for improving dietary pattern and PA, given that only half of breast cancer survivors report at least 9 metabolic equivalent tasks (MET) -h/wk[3] and another half eat at least five daily servings of vegetables-fruits (VF).[10]

In this study, we examined the interactions between selected lifestyle factors and mortality in breast cancer survivors who might change lifestyle to improve prognosis. These women volunteered for a diet trial within 4 years of diagnosis and were randomly assigned to the comparison group of the ongoing Women's Healthy Eating and Living Study. Our goal was to establish a parsimonious set of lifestyle predictors for use in the final analysis of the Women's Healthy Eating and Living Study, which is investigating the effect of a plant-based diet on additional breast cancer events. First, we looked for univariate effects on survival of lifestyle variables measured at baseline and, using only variables with significant associations, we developed a combined lifestyle variable. We

tested the combined variable in a multivariate model controlling for obesity and cancer and treatment characteristics.

PATIENTS AND METHODS

Study Population

This study considers 1,490 women, age ≤ 70 years at diagnosis of early-stage breast cancer (average age, 50 years), who resided in California, Oregon, Arizona, and Texas. All were originally diagnosed between 1991 and 2000, and randomly assigned to the control group in a dietary trial within 48 months of diagnosis (average, 24 months) between March 1995 and November 2000.[10] Breast cancer stage from American Joint Committee on Cancer (6th edition)[11] was as follows: 40% stage I (≥ 1 cm), 45% stage II, and 15% stage III, and all had completed primary therapy, although the majority were still taking tamoxifen. Medical records relating to the primary diagnosis provided details regarding tumor characteristics and treatment. Baseline questionnaires included information regarding adjuvant therapies. Institutional review board approval and written participant consent was obtained for conduct of the research.

Outcome Ascertainment

All participants were judged cancer free by an oncologist within 6 months of enrollment. A health status questionnaire was completed at each of five clinic visits scheduled during 6 years, and semiannual phone calls sought details on any health events.[10] Social security numbers and contact information from friends/relatives were obtained to minimize loss to follow-up. The study's medical director (B.P.) reviewed medical records of all cancer events and death certificates. The national death index and other sources were searched for end points for participants who were out of study contact. This report includes information collected through December 1, 2005, a minimum of 5 years and a maximum of 11 years of follow-up after study enrollment. We could not verify health status for seven participants as of this date.

Lifestyle Assessments

Dietary pattern. At baseline, participants provided four 24-hour dietary recalls on random days during a 3-week period, stratified for weekend versus weekdays.[10] As described previously,[12] the telephone-based dietary assessment used the multipass software-driven recall protocol in the Nutrition Data System for Research, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN (Food and Nutrient Database 31, version 4.03, released November 2000). In this analysis, quantified vegetable and fruit servings did not include iceberg lettuce, white potatoes, or juices with little nutritional value, but they did include nutrient-rich fruit juices such as citrus fruit juices. Plasma carotenoid concentrations were used to validate reported vegetable and fruit intake.[12,13]

Physical activity. Physical activity was assessed at baseline using a nine-item questionnaire on usual PA,[14] previously demonstrated to be both reliable[15] and valid.[16] This questionnaire queries frequency, duration, and speed of walking outside the home and frequency and duration of participating in each of three intensity levels of exercise: strenuous, moderate, or mild (with example activities for each level). Activity levels were converted into METs in accordance with Ainsworth et al[17]: mild activity was assessed as three METs, moderate activity was assessed as five METs, and vigorous activity was assessed as eight METs. For walking, slow, average, fast, and very fast were assessed as two, three, four, and six METs, respectively. Total energy expenditure for an activity was estimated as the product of time spent in activity (minutes) times METs.[17]

Other assessments. Height and weight were measured at a baseline clinic visit and body mass index (BMI; weight in kilograms/height in meters squared) was calculated. A short self-reported smoking history was collected at baseline.[14] Lifetime alcohol consumption was assessed on a baseline questionnaire. For ever drinkers (> 12 drinks lifetime), we report the number of drinks/mo estimated from the 24-hour dietary recalls.

Statistical Methods

To describe the study sample, we used standard categories for tumor characteristics.[11] We verified previous reports of a J-shaped relationship between BMI and mortality.[18,19] Exploratory data analysis indicated that a BMI of 20 was the low-risk inflection point, and adjusted the lowest standard category for BMI[20] to less than 20. Other variables were classified into categories or quartiles. Unadjusted Cox models examined univariate associations with mortality for all variables, and trends for continuous variables. We developed a combined dietary pattern–PA lifestyle variable from the components of each that were significant in the univariate analysis.

Initially, a multivariate model included all variables found to be significant in either the univariate categoric or the univariate trend analyses at the α level less than .10. Baseline VF intake and PA were included as independent variables in this model, and then tested for an interaction effect. To account for the up to 4 years (mean, 24 months) from time of diagnosis to study entry, we used a left-truncated Cox proportional hazard[21] regression model to examine the relationship of independent variables on survival. We report hazard ratios with their 95% CIs. In addition, a Kaplan-Meier survival graph showing survival after study entry, stratified by the lifestyle variable, was generated. Women who had not died were censored at the date of their most recent contact before December 1, 2005. All analyses were conducted using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Tumor and Treatment Characteristics and Mortality

The average follow-up interval between original breast cancer diagnosis and censor point was 8.7 years, with an average of 6.7 years of follow-up after baseline data collection. As of December 1, 2005, this study group (n = 1,490) had accumulated 9,665 person-years of observation, during which time there were 236 breast cancer events and 135 deaths: 118 were attributable to breast cancer, 10 were attributable to other cancers, and only seven were attributable to noncancer mortality.

In the univariate analysis (Table 1), as expected, tumor stage and grade were strongly related to mortality. Age, hormone receptor status, type of chemotherapy and adjuvant tamoxifen were not associated significantly with mortality.

Lifestyle Factors and Mortality

Tables 2 and 3 present the univariate analyses of mortality for all lifestyle factors considered in our model. Less than 5% of participants were current smokers, averaging 11 cigarettes/d, and nearly 60% had never smoked. Smoking status was not associated with mortality ($P = .45$). Less than one third (29%) of these breast cancer survivors were current drinkers, with 7% classified as heavy drinkers (60 drinks/mo). Alcohol consumption showed an inverse association with mortality ($P = .03$).

BMI was related to mortality ($P = .06$) with an apparent J-shaped relationship and no significant linear trend. Women categorized as low BMI (BMI < 20; n = 77) had twice the mortality (15.6% *v* 7.1%) as women with BMI 20 to 24.99 or categorized as overweight (BMI = 25 to 29.99). Women categorized as obese (BMI ≥ 30) had a higher mortality rate than normal-weight participants (12.4% *v* 7.1%; $P = .01$).

The median intake of VF was 4.93 servings/d. Consumption of VF was related to mortality ($P = .02$), although the trend was not linear ($P_{trend} = .08$). Women who consumed fewer than 3.43 VF servings/d (quartile 1) experienced the highest mortality rate (12.4%). Mortality seemed to decrease with increasing intake to 5 VF servings/d.

The mean reported energy intake was 1,722 kcal/d and was not associated with mortality. The median intake of fat was 28.5% of

Table 1. Mortality by Age and Clinical Characteristics of Original Tumor and Treatment, Using Unadjusted Categorical Cox Models

Treatment Category	No. of Patients	Mortality (%)	*P*
Age at enrollment, years			.27
< 40	116	8.6	
40-59	1,030	8.3	
≥ 60	344	11.6	
Stage AJCC			< .0001
I	581	4.3	
II	670	8.5	
IIIA, IIIC	239	22.2	
Tumor grade			.002
I	238	2.5	
II	594	9.1	
III	534	11.2	
Unspecified	124	12.1	
Receptor status			.23
ER positive/PR positive	917	7.5	
ER positive/PR negative	158	10.1	
ER negative/PR positive	75	13.3	
ER negative/PR negative	303	11.9	
Chemotherapy			.40
None	468	7.5	
Nonanthracycline	383	9.7	
Anthracycline	639	9.9	
Adjuvant tamoxifen			.57
Yes	623	10.3	
No	864	8.2	

Abbreviations: AJCC, American Joint Committee on Cancer (6th edition); ER, estrogen receptor; PR, progesterone receptor.

energy intake, with the highest quartile consuming more than 33% energy from fat and the lowest quartile consuming less than 24% energy from fat; however, mortality rates did not differ significantly across quartiles ($P = .6$), and a significant trend was not observed ($P_{trend} = .10$).

The lowest quartile of fiber consumption was less than 16 g/d and the highest was more than 25 g/d. The median fiber consumption was 20.2 g/d. Mortality did not differ across quartiles ($P = .15$) nor was there a linear trend ($P_{trend} = .12$).

The median level of PA was 636 MET-min/wk. Women who reported no PA (7.7%) had a mortality similar to other women in the lowest quartile and were combined with them. Mortality rates showed a linear trend ($P_{trend} = .02$), with the highest mortality in the lowest quartile (< 225 MET -min/wk) and reduced mortality, particularly in the highest two quartiles.

Composite Dietary Pattern-PA Variable

The correlation between the two continuous lifestyle variables, PA and VF, was 0.19. First, we made binary categories of each variable. For VF consumption, we used the recommendation of 5 servings a day as the cut point. In accordance with Holmes et al,[3] we chose 540 MET -min/wk to for the PA categorization. A total of 30% of study participants were in the high VF/high PA category (mean, 7.6 VF servings/d; 1,513 MET -min/wk) with a mortality of 4.8%. Twenty-two percent of the sample was classified as low VF/high PA (mean, 3.4 VF servings/d; 1,478 MET-min/wk) with a mortality of 10.4%. Another 18% were classified as high VF/low PA (mean, 7.2 VF servings/d; 224 MET-min/wk) with a mortality of 10.7%. Finally, 30% of the sample was classified as low VF/low PA (mean, 3.1 VF servings/d; 221 MET-min/wk) with a mortality of 11.5%. A difference in mortality observed across categories was statistically significant ($P = .01$), although the lifestyle variable did not differ by time since diagnosis.

Multivariate Regression Model of Mortality

Using our a priori criteria, an initial multivariate model included stage, grade, BMI, VF consumption, PA, and the combination VF-PA variable (Table 4). In the preliminary multivariate model, VF-PA interaction term reached statistical significance although neither main effect was significant. Accordingly, our final model included only the composite VF-PA variable from Table 3. Stage of original breast cancer was the major predictor of mortality: women with stage III cancers were 4.5 times more likely to die during the study period than were women with stage I disease. Tumor grade was also significantly associated with mortality. Adjusted for other variables, having low BMI (BMI < 20) at study entry (average 20 months postdiagnosis) was

Table 2. Univariate Associations of Baseline Lifestyle Factors With Subsequent Mortality in WHEL Study Comparison Group, Using Categoric and Continuous Cox Models: Smoking, Alcohol, and BMI (N = 1,490)

Factor	Category				$P_{categoric}$	P_{trend}
Smoking status	Never	Former	Smoker			
No. of patients in sample	828	590	72			
Mortality, %*	8.3	9.7	12.5			
Cox hazard	1.00	0.95	1.59		.45	NA*†
Alcohol consumption	Never	Former	Current 1-59 drinks/month	Current 60+ drinks/month		
No. of patients in sample	108	954	321	107		
Mortality, %*	13.0	9.2	8.7	4.7		
Cox hazard	1.70	1.00	0.88	0.47	.10	.03
BMI	< 20	20-24.99	25-29.99	≥ 30		
No. of patients in sample	77	575	458	380		
Mortality, %*	15.6	7.1	7.6	12.4		
Cox hazard	1.98	1.00	1.14	1.71	.06	.29

Abbreviations: WHEL, Women's Healthy Eating and Living Study; NA, not applicable; BMI, body mass index.
*Mortality percentage during the study period.
†For categorical variables.

Table 3. Univariate Associations of Baseline Lifestyle Factors With Subsequent Mortality in WHEL Study Comparison Group, Using Categoric and Continuous Cox Models: Diet and Physical Activity (N = 1,490)

Factor	Quartile 1	Quartile 2	Quartile 3	Quartile 4	$P_{categoric}$	P_{trend}
VF servings/d	0.33-3.43	3.43-4.93	4.93-6.94	6.94-19.96		
Mortality, %*	12.4	9.8	5.7	8.3		
Cox hazard	1.00	0.74	0.44	0.63	.02	.08
Energy intake, kcal/d*	584-1,435	1,435-1,686	1,686-1,981	1,981-3,553		
Mortality, %	11.1	8.9	7.0	9.1		
Cox hazard	1.00	0.75	0.55	0.74	.17	.24
Energy from fat, %	9.04-23.87	23.90-28.52	28.52-33.42	33.42-58.86		
Mortality, %*	8.8	7.9	9.3	10.2		
Cox hazard	1.00	1.08	1.27	1.39	.59	.10
Fiber, g/d	5.1-15.6	15.6-20.2	20.2-23.5	23.5-59.7		
Mortality, %*	11.6	8.2	8.0	8.4		
Cox hazard	1.00	0.63	0.63	0.61	.15	.12
PA, MET-min/wk	0-225	225-636	636-1,320	1,320-6,420		
Mortality, %*	11.4	10.5	8.2	6.0		1
Cox hazard	1.00	0.86	0.76	0.58	.24	.02
Composite VF-PA variable	Low VF, low PA	Low VF, high PA	High VF, low PA	High VF, high PA		
No. of patients in sample	436	327	271	456		
Mortality, %*	11.5	10.4	10.7	4.8		
Cox hazard	1.00	1.07	0.96	0.46	.01	NA†

Abbreviations: WHEL, Women's Healthy Eating and Living Study; NA, not applicable; BMI, body mass index.
*Mortality percentage during the study period.
†For categorical variables.

associated with almost a two-fold increase in mortality, although the subsample size was small and this was only marginally significant ($P = .08$). Overweight (BMI = 25 to 29.99) was not associated with an increased risk ($P > .9$) but obese women (BMI > 30) tended to have a higher death rate, although this relationship did not reach statistical significance ($P = .16$). No differences were observed in mortality for the first three combined VF-PA categories; however, compared with women in the low VF/low PA group, the hazard ratio for women in the high VF/high PA was 0.56 (95% CI, 0.31 to 0.98).

The strong protective association of high VF/high PA with improved survivorship is also evident in the Kaplan-Meier survival curves (Fig 1): survival data from study enrollment through the December 2005 follow-up illustrates an estimated 10-year survival rate

Table 4. Final Cox Proportional Hazard Ratios for Mortality by Four Diet and Physical Activity Categories: WHEL Comparison Group (N = 1,490)

Category	Hazard Ratio	95% CI	P
Stage			
I (reference)	1.0		
II	1.82	1.11 to 2.97	.02
III	4.49	2.67 to 7.53	< .0001
Grade			
I (reference)	1.0		
II	3.51	1.39 to 8.86	.01
III	2.96	1.15 to 7.61	.02
Unspecified grade	3.25	1.12 to 9.39	.03
BMI			
Normal weight, 20-24.99 (reference)	1.0		
Low, < 20	1.90	0.92 to 3.90	.08
Overweight, 25-29.99	1.00	0.62 to 1.64	.99
Obese, ≥ 30	1.42	0.87 to 2.31	.16
Diet and PA			
Low VF and low PA (reference)	1.0		
Low VF and high PA	1.22	0.75 to 1.97	.42
High VF and low PA	0.86	0.51 to 1.45	.57
High VF and high PA	0.56	0.31 to 0.98	.04

NOTE. Model is controlled for age, alcohol intake, tumor hormone receptor status, and time from diagnosis to study entry.
Abbreviations: WHEL, Women's Healthy Eating and Living Study; BMI, body mass index; VF, vegetables-fruits; PA, physical activity.

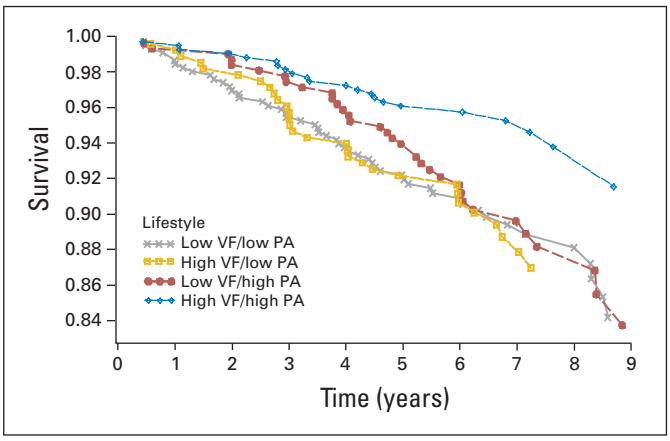

Fig 1. Kaplan-Meier survival after Women's Healthy Eating and Living (WHEL) Study enrollment by four diet and physical activity categories. Low vegetables-fruits (VF), less than 5 servings/d; high VF, ≥ 5 servings/d; low physical activity (PA), less than 540 metabolic equivalent task (MET) -min/wk; high PA, ≥ 540 MET-min/wk. Survival is plotted as a function of number of years enrolled in WHEL Study.

postdiagnosis of 93% in the high VF/high PA group, and 86% to 87% in the other three groups. Thus, the estimated absolute unadjusted mortality risk reduction was 6% to 7% at 10 years for women who achieved this pattern, compared with women who consumed fewer daily VF servings and/or performed less PA.

Figure 2 presents the mortality experience for categories of BMI and the composite VF-PA variable, comparing nonobese with obese women. For the nonobese group, there was no difference in mortality in the study period for women in any group other than the high VF/high PA group with estimated mortality percentage between 9.1% and 9.9%. Mortality among women in the high VF/high PA group (4.9%; 95% CI, 2.7% to 7.1%) was approximately half that of the other groups. For women who were obese, there was no difference in mortality in the same three study groups, with estimates from 12.7% to 14.2%. Again, there were significantly fewer deaths in the 16% of obese women classified in the high VF/high PA group (4.7%; 95% CI, 0% to 9.8%). Within each VF/PA category, women who were obese had an apparent increase in mortality compared with those who were not obese, except in the high VF/high PA group, where the observed mortality rates were comparable.

We also assessed whether the high VF/high PA lifestyle effect on survival was limited to women with hormone receptor–positive tumors (Fig 3), as might be expected if the mechanism of action was mediated by gonadal reproductive hormones. Univariate analysis showed no survival advantage for healthy lifestyle in estrogen receptor–negative, progesterone receptor–negative (ER negative, PR negative) group ($P = .4$), a borderline advantage for ER-negative, PR-positive group ($P = .09$), and significant advantages for ER-positive, PR-negative ($P = .04$) and ER-positive, PR-positive groups ($P = .01$).

Finally, we investigated cause of death and saw no difference in breast cancer versus other-cause mortality when stratified by the lifestyle variable ($P = .37$).

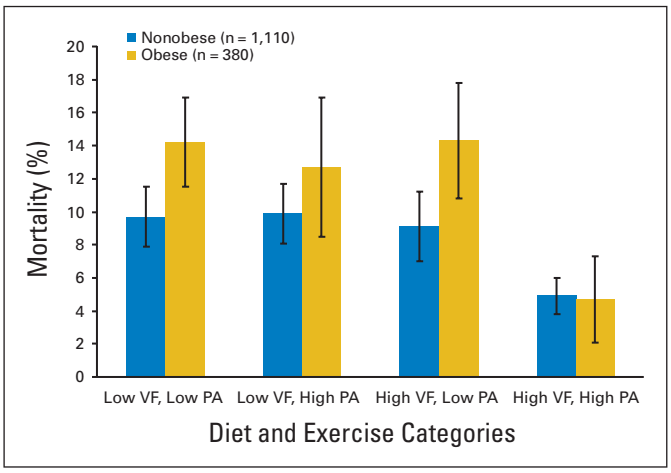

Fig 2. Mortality by diet and physical activity (PA) in Women's Healthy Eating and Living Study comparison group: body mass index (BMI) categories. Bars show proportion (SE) for all-cause mortality by baseline BMI category. Low vegetables-fruits (VF), less than 5 servings/d; high VF, ≥ 5 servings/d; low PA, less than 540 metabolic equivalent task (MET) -min/wk; high PA, ≥ 540 MET-min/wk. BMI was calculated as weight in kilograms/height in square meters.

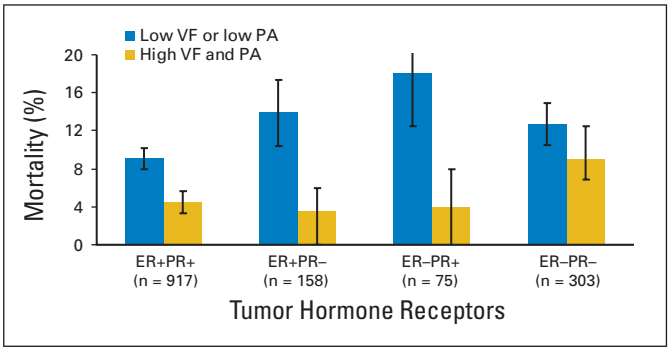

Fig 3. Mortality by tumor hormone receptor status and lifestyle in Women's Healthy Eating and Living Study comparison group. Bars show proportion (SE) for all-cause mortality by baseline tumor estrogen receptor (ER) and progesterone receptor (PR) status (+, positive; −, negative), dietary intake of vegetables-fruits (VF), and physical activity (PA). Low VF, less than 5 servings/d; high VF, ≥ 5 servings/d; low PA, less than 540 metabolic equivalent task (MET) -min/wk; high PA, ≥ 540 MET-min/wk.

DISCUSSION

In these breast cancer survivors who were interested in lifestyle change and were predominantly nonsmokers, the 30% of women who were physically active and consumed at least 5 servings of vegetables and fruits each day had an estimated 10-year mortality rate of 7%, approximately half that of any other combination of PA and dietary pattern. Of particular importance, this halving of risk was seen in women who were not obese as well as in those who were obese. Indeed, it appeared that both being physically active and having a healthy dietary pattern attenuated the increase in risk observed among the obese. It was noted, however, that obese women were approximately one half as likely as nonobese women to be both physically active and to have a healthy dietary pattern.

This study is not the first to suggest that a combination of healthy lifestyle behaviors is associated with improved survival, although it is the first, to our knowledge, in a population of breast cancer survivors. The European Healthy Aging study[22] of 70- to 90-year-old men and women noted that being a nonsmoker, adhering to a Mediterranean diet, being physically active, and consuming alcohol in moderation were associated with a 60% reduction in cancer deaths as well as 60% reduction in all-cause mortality. Similarly, the Nurses' Health Study[23] noted that 82% of coronary events could be attributed to lack of adherence to a similar combination of behaviors. Longitudinal follow-up of a population-based random survey of men and women in Hawaii demonstrated that a combination variable constructed from smoking status, BMI, dietary pattern, and alcohol use was strongly associated with mortality, including mortality from cancer.[24] Accordingly, most recent guidelines for chronic disease prevention, including cancer,[25] cardiovascular disease,[26] and obesity,[27] emphasize the importance of adhering to multiple lifestyle behaviors. Given that the number of cancer survivors is increasing, and breast cancer survivors make up the largest group of cancer survivors,[28] it is important to consider the potential impact on prognosis of lifestyle changes such as diet and PA on women who have survived initial treatment.

PA recommendations usually include duration (eg, 30 min/d), intensity (moderate, 3 to 6 METs; vigorous, 6+ METs) and frequency

(eg, vigorous, 3 times/wk; moderate, 5+ times/wk). Accordingly, the absolute minimum recommendation for moderate activity would require 450 MET-min/wk. In this study, we chose a level 20% higher than this absolute minimum for classifying a participant as physically active; this allowed us to use an equivalent cut point to that used in the Nurses' Health Study.[3] However, unlike the Nurses' Health Study, in the univariate analysis only, we found a significant linear association in which more activity was associated with increased benefit. It is important to note that the brief self-reported questionnaire has been shown to overestimate activity when compared with an accelerometer measure in our study population.[16]

The survival advantage for the high VF/high PA lifestyle was present in women who had ER-positive tumors, but not in those who were ER-negative, suggesting that the mechanism for action for this effect might be reproductive gonadal hormones, as has been suggested previously for each of the component lifestyle factors.[8,9] It is likely that this observed effect is not simply an effect of adjuvant tamoxifen, which was prescribed to 45% of the study sample.[10] The effect observed may vary in current populations because study participants were all diagnosed before the introduction of adjuvant aromatase inhibitor therapy.

In summary, breast cancer survivors who consume a healthy diet and are physically active may increase their years of survival after diagnosis. Specifically, we have shown that those who reported eating a minimum of 5 VF servings daily and performing weekly PA equivalent to 30 minutes of walking at a moderate pace for 6 days a week had a higher 10-year survival rate than those who did not adhere to these lifestyle practices. The improved survival rate was observed in women who were obese as well as those who were not obese. Adhering to these two health behaviors reduced the probability of death in the follow-up period by 50%, whereas this effect was not seen if breast cancer survivors were adherent to only PA or VF dietary pattern. These findings suggest the need for additional study of the combined protective effect of diet and PA on breast cancer survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Provision of study materials or patients: John P. Pierce
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REFERENCES

1. Rock CL, Flatt SW, Natarajan L, et al: Plasma carotenoids and recurrence-free survival in women with a history of breast cancer. J Clin Oncol 23: 6631-6638, 2005
2. Zhang S, Folsom AR, Sellers TA, et al: Better breast cancer survival for postmenopausal women who are less overweight and eat less fat: The Iowa Women's Health Study. Cancer 76:275-283, 1995
3. Holmes MD, Chen WY, Feskanich D, et al: Physical activity and survival after breast cancer diagnosis. JAMA 293:2479-2486, 2005
4. Bastarrachea J, Hortobagyi GN, Smith TL, et al: Obesity as an adverse prognostic factor for patients receiving adjuvant chemotherapy for breast cancer. Ann Intern Med 120:18-25, 1994
5. Obermair A, Kurz C, Hanzal E, et al: The influence of obesity on the disease-free survival in primary breast cancer. Anticancer Res 15:2265-2269, 1995
6. Rohan TE, Fu W, Hiller JE: Physical activity and survival from breast cancer. Eur J Cancer Prev 4:419-424, 1995
7. Kroenke CH, Fung TT, Hu FB, et al: Dietary patterns and survival after breast cancer diagnosis. J Clin Oncol 23:9295-9303, 2005
8. Rock CL, Demark-Wahnefried W: Nutrition and survival after the diagnosis of breast cancer: A review of the evidence. J Clin Oncol 20:3302-3316, 2002
9. Broocks A, Pirke KM, Schweiger U, et al: Cyclic ovarian function in recreational athletes. J Appl Physiol 68:2083-2086, 1990
10. Pierce JP, Faerber S, Wright FA, et al: A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: The Women's Healthy Eating and Living (WHEL) Study. Control Clin Trials 23:728-756, 2002
11. American Joint Committee on Cancer.Manual for Staging of Cancer (ed 6). New York, NY, Springer-Verlag, 2002
12. Pierce JP, Newman VA, Flatt SW, et al: Telephone counseling intervention increases intakes of micronutrient- and phytochemical-rich vegetables, fruit and fiber in breast cancer survivors. J Nutr 134:452-458, 2004
13. Natarajan L, Flatt SW, Sun X, et al: Validity and systematic error in measuring carotenoid consumption with dietary self-report instruments. Am J Epidemiol 163:770-778, 2006
14. Design of the Women's Health Initiative clinical trial and observational study: The Women's Health Initiative Study Group. Control Clin Trials 19:61-109, 1998
15. Langer RD, White E, Lewis CE, et al: The Women's Health Initiative Observational Study: Baseline characteristics of participants and reliability of baseline measures. Ann Epidemiol 13:S107-S121, 2003
16. Johnson-Kozlow M, Rock CL, Gilpin EA, et al: Validation of WHI brief physical activity questionnaire among women diagnosed with breast cancer. Am J Health Behav 31:193-202, 2007
17. Ainsworth BE, Haskell WL, Whitt MC, et al: Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc 32:S498-S504, 2000
18. Goodwin PJ, Ennis M, Pritchard KI, et al: Fasting insulin and outcome in early-stage breast cancer: Results of a prospective cohort study. J Clin Oncol 20:42-51, 2002
19. Suissa S, Pollak M, Spitzer WO, et al: Body size and breast cancer prognosis: A statistical explanation of the discrepancies. Cancer Res 49:3113-3116, 1989
20. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: Executive summary—Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. Am J Clin Nutr 68:899-917, 1998
21. Therneau TM, Grambsch PM: Modeling Survival Data: Extending the Cox Model, Statistics for Biology and Health. New York, NY, Springer-Verlag, 2000
22. Knoops KT, de Groot LC, Kromhout D, et al: Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: The HALE project. JAMA 292:1433-1439, 2004
23. Stampfer MJ, Hu FB, Manson JE, et al: Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 343:16-22, 2000
24. Meng L, Maskarinec G, Lee J, et al: Lifestyle factors and chronic diseases: Application of a composite risk index. Prev Med 29:296-304, 1999

25. Byers T, Nestle M, McTiernan A, et al: American Cancer Society guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 52:92-119, 2002

26. Krauss RM, Eckel RH, Howard B, et al: AHA Dietary Guidelines: Revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Circulation 102:2284-2299, 2000

27. USDHHS: Dietary Guidelines for Americans, 2005. Washington, DC, US Department of Health and Human Services, 2005

28. CDC: Cancer Survivorship—United States, 1971-2001. MMWR Morb Mortal Wkly Rep 53:526-529, 2004

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