The Effect of Resistance Exercise on All-Cause Mortality in Cancer Survivors

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Abstract

Objective: To examine the independent associations of leisure-time aerobic physical activity (PA) and resistance exercise (RE) on all-cause mortality in cancer survivors.

Patients and Methods: Patients included 2863 male and female cancer survivors, aged 18 to 81 years, who received a preventive medical examination between April 8, 1987, and December 27, 2002, while enrolled in the Aerobics Center Longitudinal Study in Dallas, Texas. Physical activity and RE were assessed by self-report at the baseline medical examination. Cox proportional hazards regression analysis was performed to determine the independent associations of PA and RE with all-cause mortality in participants who had a history of cancer.

Results: Physical activity in cancer survivors was not associated with a lower risk of all-cause mortality. In contrast, RE was associated with a 33% lower risk of all-cause mortality (95% CI, 0.45-0.99) after adjusting for potential confounders, including PA.

Conclusion: Individuals who participated in RE during cancer survival had a lower risk for all-cause mortality. The present findings provide preliminary evidence for benefits of RE during cancer survival. Future randomized controlled trials examining RE and its effect on lean body mass, muscular strength, and all-cause mortality in cancer survivors are warranted.

Cancer is the second leading cause of death and accounts for 23% of all deaths in the United States. In 2013, it was estimated that approximately 1.6 million new cancer cases would be diagnosed and 68% of survivors would live more than 5 years. The number of cancer survivors will continue to increase each year with improvements to early detection and treatment. Although commonly associated with the period after treatment, cancer survival is defined as the time between cancer diagnosis and mortality. Cancer survival is associated with a decrease in health status, and it increases the risk for all-cause mortality. Physical activity (PA) is a modifiable risk factor known to decrease the occurrence of disease and all-cause mortality and may improve a cancer survivor’s quantity and quality of life.

Individuals who receive a diagnosis of cancer have an approximately 50% higher risk of noncancer mortality than the general population. There is growing evidence to suggest that PA is beneficial for individuals who received a diagnosis of cancer. Regular PA during cancer survival can lead to the maintenance of and/or improvements in body composition, physical function, and overall quality of life. In addition, PA after diagnosis reduces the risk of cancer-specific mortality in breast cancer survivors and decreases all-cause mortality in colorectal and prostate cancer survivors. It is rational to think that resistance exercise (RE) training may also have similar benefits in cancer survivors as in healthy populations; however, there is limited research on the effect of RE on all-cause mortality in cancer survivors. Furthermore, many questions remain on which type of PA may be most beneficial for cancer survivors. Therefore, the purpose of this study was to examine the effects of leisure-time aerobic PA and RE on all-cause mortality in cancer survivors. It was hypothesized that both PA and RE would be associated with a decreased risk of all-cause mortality in cancer survivors.
PATIENTS AND METHODS

Study Population

Between April 8, 1987, and December 27, 2002, 3388 men and women aged 18 to 81 years with a previous diagnosis of cancer received a comprehensive preventive medical examination at the Cooper Clinic in Dallas, Texas, and were enrolled in the Aerobics Center Longitudinal Study, a prospective epidemiological investigation. It should be noted that specific information related to cancer diagnosis and treatment (ie, type, stage, and location) was not available at the time of baseline examination and therefore anyone who responded positively to the question “have you had any type of cancer” was included in the present analysis. Detailed information about the study population has been published previously.20 Participants were sent to the clinic by their employers for examination, referred by their personal physician, or self-referred. Participants were volunteers and did not receive monetary assistance for participation. The study protocol was approved annually by the institutional review board of the Cooper Institute.

Participants were excluded from the final analysis if they were underweight (body mass index [BMI] < 18.5 kg/m²; n = 101); had myocardial infarction (n = 127) or stroke (n = 32); died during first year of follow-up (n = 115); or had missing data on PA (n = 78) or PA (n = 72). These criteria resulted in 2863 participants (859 women), who were followed until the date of death or December 31, 2003. Participants were predominantly white, well-educated, and within the middle to upper socioeconomic strata.21

Baseline Examination

Participants completed a comprehensive medical examination that included a physical evaluation by a physician, personal and family medical history questionnaire, anthropometry, blood pressure, and fasting blood chemistry. Detailed procedures regarding baseline measurements have been described previously.20Height and weight were measured, and BMI was computed as weight per square meter. Resting blood pressure was measured by trained technicians using standard auscultatory methods in a seated position and was recorded as the first and fifth Korotkoff sounds, respectively. Two readings separated by 1 minute were averaged. Overnight fasting serum concentrations of total cholesterol, triglyceride, and glucose were analyzed using standardized automated bioassays at the Cooper Clinic chemistry laboratory.

Baseline medical conditions were determined as having a physician diagnosis or measured phenotypes that met clinical thresholds. Hypercholesterolemia was defined as having total cholesterol levels of 240 mg/dL (6.2 mmol/L) or higher or physician diagnosis. Diabetes was defined as having fasting glucose levels of 126 mg/dL (7.0 mmol/L) or higher, the use of insulin, or physician diagnosis. Hypertension was defined as having a resting systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or physician diagnosis. Parental history of cancer, smoking habits (current smoker or not), and alcohol intake (number of drinks per week) were obtained from the medical questionnaire. Heavy drinking was defined as consuming 7 drinks or more per week for women and 14 drinks or more per week for men.

Leisure-Time Aerobic PA

Self-reported PA during the past 3 months was obtained from the medical questionnaire at baseline examination. Detailed procedures regarding the assessment of PA have been described previously.22 In brief, a metabolic equivalent of task (MET) value was assigned to each PA contained within the medical questionnaire and then multiplied by the frequency and duration of each PA performed. Physical activity values were summated and represent the total volume of PA, which is expressed as the total MET-minutes per week. Meeting the current PA guidelines was defined as performing 500 or more MET-minutes/wk. In addition, we grouped participants into physically active and inactive on the basis of walking and jogging because they were the most common activities for the Aerobics Center Longitudinal Study population.23

Resistance Exercise

Resistance exercise was assessed by self-report on the medical history questionnaire. Participants were asked to provide yes or no answers to the following questions: (1) Are you currently involved in a muscle-strengthening program? (2) Can you specify the muscle-strengthening activity as “Calisthenics,” “Free weights,” “Weight training machines,” or “Other”? (3) How many
days per week do you do these exercises? Those who responded “Yes” to free weights or weight training and had exercised at least 1 day/wk were classified as positive for RE.

**Mortality Surveillance**

Study participants were followed up for all-cause mortality from baseline examination through the end of December 2003. Official death certificates were obtained from the National Death Index and recorded throughout the analysis. The National Death Index has been established to be an accurate method of ascertaining deaths in observational studies, having high sensitivity (96%) and specificity (100%).

**Statistical Analyses**

Continuous variables were summarized using mean ± SD, and categorical variables were summarized using frequency (percentage). Continuous variables were compared using the Student t test, and categorical variables were compared using the $\chi^2$ test. Follow-up time was computed as the difference between the date of the baseline examination and the date of death for decedents or through the end of 2003 for survivors. Cox proportional hazards regression analysis was used to compute hazard ratios (HRs) and 95% CIs for all-cause mortality according to categories of RE or leisure-time aerobic PA to quantify the strength of these associations. Adjusted models were used to control for potential confounding factors at baseline examination. Model 1 was adjusted for age, sex, and examination year, and model 2 was adjusted for variables in model 1 plus BMI, current smoking (yes or no), heavy drinking (yes or no), hypertension (present or not), diabetes (present or not), hypercholesterolemia (yes or no), and parental history of cancer (yes or no). Model 3 was adjusted for variables in model 2 plus leisure-time aerobic PA (MET-minutes per week when RE was the exposure) or RE (yes or no when aerobic activity was the exposure). The Kaplan-Meier method was used to calculate survival curves. The log-rank test was used to compare survival between RE and no-RE groups. Finally, we conducted stratified analysis to test the PA-related interaction on the association between RE and all-cause mortality by using the interaction term. All the statistical analyses were performed using SAS software (SAS Institute), and all the P values were 2 sided, with an α level of .05.

**RESULTS**

Among 2863 men and women with cancer, there were a total of 121 deaths (4%) during a mean follow-up duration of 7.3 years. The baseline characteristics of the study population are summarized in Table 1. Participants were middle aged (54±11 years), mostly men (2004; 70%), slightly overweight (BMI, 25.9±4.1 kg/m²), predominantly active (1746; 61%), and nonsmokers (2611; 91%). Participants who performed RE had lower values for BMI, total cholesterol, triglycerides, fasting blood glucose; lower incidence of hypercholesterolemia; and lower hypertension (Table 1). In addition, cancer survivors who performed RE engaged in more PA than did their counterparts who did not perform RE.

Table 2 presents the independent association between PA and all-cause mortality in cancer survivors. The association between PA and all-cause mortality was examined using 3 different models. For all 3 models, PA was not associated with a decreased risk of all-cause mortality in cancer survivors. The fully adjusted model exhibited a 1% nonsignificant higher risk ($P=.97$) of mortality in participants who performed 500 or more MET-minutes/wk of PA than those who did not.

Table 3 presents the independent association between RE and all-cause mortality in cancer survivors. The risk of all-cause mortality was lower in participants who performed RE than in those who did not. After adjustment for covariates (age, sex, examination year, smoking status, alcohol intake, BMI, chronic conditions, and family history of cancer), participants who performed RE ($\geq$1 day/wk) had a 33% reduction in all-cause mortality compared with those who did not ($P<.05$). Additional adjustment for PA did not materially change the above association. The Kaplan-Meier survival curves also indicate that cancer survivors who performed RE had higher survival probability as compared with those who did not (Figure 1). Additional analysis was performed to examine whether PA moderated the association between RE and all-cause mortality (Figure 2). Indeed, there was an inverse relationship between RE and all-cause mortality in those who were physically active ($P=.04$) whereas this association was not observed in those who were physically inactive ($P=.82$).
DISCUSSION

With improvements in cancer diagnosis and treatment, the number of individuals living with cancer will continue to increase in forthcoming years. Identifying modifiable factors that increase the quality of life and reduce all-cause mortality risk during cancer survival is of great importance. Increased levels of PA have been found to improve health outcomes after cancer diagnosis; however, the type of PA that is most beneficial for long-term cancer survival is not known. In the present study, cancer survivors who reported performing RE at least 1 day of the week had a 33% reduction in all-cause mortality compared with individuals who did not report participation in RE.

### TABLE 1. Baseline Characteristics of Cancer Survivors in the Aerobics Center Longitudinal Study, 1987-2002a,b,c

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N=2863)</th>
<th>Resistance exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=1612)</td>
<td>Yes (n=1251)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>54.4±10.5</td>
<td>54.5±10.5</td>
</tr>
<tr>
<td>Sex: female</td>
<td>859 (30.0)</td>
<td>516 (32.0)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.9±4.1</td>
<td>26.5±4.4</td>
</tr>
<tr>
<td>Lipid profile (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>204±38.5</td>
<td>207±39.0</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>127.3±88.4</td>
<td>135.7±89.1</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>99.4±17.0</td>
<td>100.4±19.3</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124±17</td>
<td>125±17</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81±10</td>
<td>82±10</td>
</tr>
<tr>
<td>Leisure-time aerobic physical activity (MET-min/wk)</td>
<td>1019.4±13132</td>
<td>748.5±1048.7</td>
</tr>
<tr>
<td>Meet current guidelinesd</td>
<td>1746 (61.0)</td>
<td>788 (48.9)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>252 (8.8)</td>
<td>157 (9.7)</td>
</tr>
<tr>
<td>Heavy drinkere</td>
<td>389 (13.6)</td>
<td>202 (12.5)</td>
</tr>
<tr>
<td>Baseline medical conditionsf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesteremia</td>
<td>1053 (36.8)</td>
<td>634 (39.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>188 (6.6)</td>
<td>116 (7.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1100 (38.4)</td>
<td>650 (40.3)</td>
</tr>
<tr>
<td>Parental history of cancer</td>
<td>282 (9.9)</td>
<td>150 (9.3)</td>
</tr>
</tbody>
</table>

aMET = metabolic equivalent of task.
bTo convert mg/dL values to mmol/L, multiply by 0.0259.
cValues are reported as mean±SD for continuous variables or as No. (percentage) for categorical variables.
dDefined as performing ≥500 MET-min/wk.
eDefined as consuming ≥7 drinks/wk for women and ≥14 drinks/wk for men.
fDefined as the presence of hypercholesterolemia (history of physician diagnosis or total cholesterol level ≥240 mg/dL [6.20 mmol/L]), diabetes (history of physician diagnosis, use of insulin, or fasting glucose level ≥126 mg/dL [7.0 mmol/L]), or hypertension (history of physician diagnosis, resting systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg).

### TABLE 2. Hazard Ratios (HRs) and 95% CIs for All-Cause Mortality Stratified by Leisure-Time Aerobic Physical Activity (PA) Levels in Cancer Survivorsa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of deaths/total</th>
<th>Model 1b</th>
<th>Model 2c</th>
<th>Model 3d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leisure-time aerobic PA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500 MET-min/wk</td>
<td>46/1117</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≥500 MET-min/wk</td>
<td>75/1746</td>
<td>0.91 (0.63-1.32)</td>
<td>0.99 (0.67-1.46)</td>
<td>1.01 (0.68-1.49)</td>
</tr>
<tr>
<td>P value</td>
<td>.62</td>
<td>.95</td>
<td>.97</td>
<td></td>
</tr>
</tbody>
</table>

aMET = metabolic equivalent of task.
bAdjusted for age, sex, and examination year.
cAdjusted for variables in model 1 plus body mass index, current smoking (yes or no), heavy drinking (yes or no), hypertension (present or not), diabetes (present or not), hypercholesterolemia (yes or no), and parental history of cancer (yes or no).
dAdjusted for variables in model 2 plus resistance exercise (d/wk).
Furthermore, there was an inverse relationship between RE and all-cause mortality in those who were physically active, but not in those who were physically inactive. Although leisure-time PA was not associated with decreased all-cause mortality, the present results support the benefits of RE and PA during cancer survival. By identifying the effect of PA and RE on all-cause mortality after cancer diagnosis, clinicians may be more likely to promote these practices after cancer diagnosis.

To our knowledge, this is the first prospective study to examine the associations between RE and all-cause mortality in cancer survivors. Previous reports have found positive relationships between muscular strength and decreased risk of cancer mortality in healthy men. These benefits may translate into increased survival; however, future research is needed to address this important question in cancer survivors. The present results reveal that RE was associated with a reduction in all-cause mortality, which should be considered when providing advice to cancer survivors.

With improvements in cancer treatment after diagnosis, many cancer survivors are now living more than 65 years. It is well established that aging is associated with musculoskeletal perturbations (ie, osteoporosis and sarcopenia), and therefore patients may experience age-related decrease in health status at the time of or after diagnosis. In addition, decrease in bone mineral density and skeletal muscle mass can be observed during cancer treatment, which may lead to an even higher risk of all-cause mortality in older cancer survivors. Therefore, behavioral modifications that promote overall health and reduce adverse effects of the treatment are of utmost importance during cancer survival.

Several mechanisms may be responsible for a reduced risk of all-cause mortality with RE during cancer survival. One primary benefit of RE training and muscle strengthening activities is increased loading to bone and skeletal muscle tissue. The musculoskeletal system has the ability to translate mechanical forces into biochemical signals in a process known as mechanotransduction. This response results in enhanced bone formation and muscle protein accretion after loading. When mechanical loading is continued over time, as with exercise training, it can lead to the maintenance and/or increase in bone mineral density and skeletal muscle mass. Thus, the adaptive response to

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**TABLE 3. Hazard Ratios (HRs) and 95% CIs for All-Cause Mortality Stratified by Resistance Exercise in Cancer Survivors**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of deaths/total</th>
<th>HR (95% CI)</th>
<th>Model 1a</th>
<th>Model 2b</th>
<th>Model 3c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Model 1a</td>
<td>Model 2b</td>
<td>Model 3c</td>
</tr>
<tr>
<td>Resistance exercise</td>
<td></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>82/1612</td>
<td>0.67 (0.46-0.99)</td>
<td>0.67 (0.45-0.99)</td>
<td>0.67 (0.45-0.99)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39/1251</td>
<td>0.67 (0.46-0.99)</td>
<td>0.67 (0.45-0.99)</td>
<td>0.67 (0.45-0.99)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.045</td>
<td>.04</td>
<td>.049</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aAdjusted for age, sex, and examination year.

bAdjusted for variables in model 1 plus body mass index, current smoking (yes or no), heavy drinking (yes or no), hypertension (present or not), diabetes (present or not), hypercholesterolemia (yes or no), and parental history of cancer (yes or no).

cAdjusted for variables in model 2 plus leisure-time aerobic physical activity (in MET-minutes/week; MET = metabolic equivalent of task).

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RE is associated with improved muscle mass and muscular strength, which can translate into improved physical function and quality of life in cancer patients. Research has established a positive relationship between muscle strength and physical function in cancer survivors. Interestingly, these benefits can occur independently of changes in endocrine or immune function, exhibiting a unique role of mechanical loading and muscle contraction in the regulation of muscle plasticity during wasting conditions. Collectively, the importance of RE training for improvements in physical function in cancer survivors cannot be understated.

Additional biological mechanisms associated with decreased all-cause mortality with RE training may be related to modifications in glucose homeostasis, insulin and insulin-like growth factor 1 signaling, and inflammation. It has been reported that more than one-third of the patients with cancer exhibit glucose intolerance and insulin resistance, which may contribute to increased comorbidities and mortality in cancer survivors. In addition, insulin resistance may contribute to muscle wasting owing to a decreased anabolic state of skeletal muscle. A single bout of physical exercise increases skeletal muscle glucose uptake independent of insulin action, and exercise training is associated with improved insulin sensitivity in cancer survivors. In addition, elevated systemic inflammation during cancer contributes to muscle wasting and decreased survival. There is a strong inverse relationship between circulating inflammation and both cancer-specific and noncancer survival. On the basis of the current body of literature, treatment modalities promoting the preservation of skeletal muscle mass and function are associated with improvements in cardiovascular risk factors and improved health outcomes and may decrease an individual’s risk of all-cause mortality during cancer survival.

Interestingly, self-reported PA was not associated with decreased all-cause mortality in the present cohort of cancer survivors. This finding is in contrast to previous studies reporting positive benefits of PA and exercise during cancer survival. For example, Haydon et al found improved disease-specific (HR, 0.73; 95% CI, 0.54-1.00, \( P = .05 \)) and overall (HR, 0.77; 95% CI, 0.58-1.03, \( P = .08 \)) survival in patients with colorectal cancer who participated in exercise before diagnosis. In addition, Meyerhardt et al found significant trends for post-diagnosis PA and improved disease-free (\( P \) for trend = .01), recurrence-free (\( P \) for trend = .03), and overall survival (\( P \) for trend = .01) in patients with stage III colon cancer. Furthermore, a reduced risk of cancer-specific death (>9 MET-hours/wk) and all-cause mortality (\( \geq 8.75 \) MET-hours/wk) has been reported in breast cancer survivors and colorectal cancer survivors, respectively.

In the present study, approximately 61% of the study population had reasonable PA at the time of examination. In addition, the small number of deaths, relatively small sample size, and self-report nature of PA status of the current cohort might limit the ability to detect considerable changes, and thus the results reported here should be interpreted with caution. Taken collectively, there is sufficient evidence in the literature to support beneficial effects of PA on cancer recurrence and survival, and PA should be recommended to improve health outcomes in cancer survivors.

The present study has several limitations that should be addressed. The primary limitations were the small sample size and the assessment
of PA and RE through self-report. As previously discussed, the relatively small number of deaths and sample size limited our ability to examine several factors such as the overall PA dose or the effect of sex on PA associations. Furthermore, it is well established that self-reported exercise habits are subject to recall bias and are often overreported or misclassified. Our observation of an inverse relation between RE and mortality rates in only physically active participants may reflect more precise reporting in this subgroup. Future studies should use objective measures, such as accelerometry or strength measurements, to provide proper classification and minimize subject bias. In addition, the volume and intensity of RE activities was not quantified in this study. It is known that manipulations to training intensity can result in different musculoskeletal, cardiovascular, and metabolic adaptations. Thus, further research should establish optimal training parameters for the maintenance or improvement of clinically important outcomes during cancer survival. Moreover, dietary habits were not included in the present analysis and should be considered in subsequent studies. Furthermore, the present population consisted of well-educated men and women, of middle to upper class socioeconomic status, with relatively high PA, which limits the generalization of the present findings. Owing to the limited information, we were unable to determine the types of cancer. It has been suggested that certain types of cancer may be more sensitive to changes in PA status. Finally, and probably most importantly, we were unable to find whether the association between higher reported RE and improved mortality was causal or whether selection bias (ie, healthier and stronger cancer survivors may be more likely to perform and/or report higher levels of RE) was responsible for this powerful association, which even appeared to be totally independent of leisure-time aerobic PA. Future research is needed to include this information to clearly establish the effect of RE and PA on longevity in cancer survivors.

CONCLUSION
This study provides initial evidence that RE at least 1 day/wk was associated with a reduced risk of all-cause mortality in cancer survivors. The present findings along with previous evidence provides additional clinical significance and rationale for the integration of RE during cancer survival. If these findings are replicated in other studies, medical practitioners and clinicians should be aware of these benefits and discuss the importance of PA, particularly RE, during and after cancer treatment. The mechanisms associated with these benefits are yet to be clearly defined, and further research on this issue is needed. In addition, it is necessary to determine whether a specific type of PA may be more beneficial for certain cancers. Therefore, future prospective randomized controlled trials should be designed to address potential mechanisms between RE and health outcomes, including all-cause and disease-specific mortality, during cancer survival.

ACKNOWLEDGMENTS
We thank the Cooper Clinic physicians and technicians for collecting the baseline data as well as staff at the Cooper Institute for data entry and data management.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Abbreviations and Acronyms: BMI = body mass index; HR = hazard ratio; MET = metabolic equivalent of task; PA = physical activity; RE = resistance exercise

Grant Support: The work was supported by grants AG06945, HL62508, and DK088195 from the US National Institutes of Health.

Potential Competing Interests: Dr Archer’s Post-Doctoral Fellowship was supported by an unrestricted research grant to Dr Blair from The Coca-Cola Company. Dr Blair has received research funding from Technogym, and also has served on their Advisory Board.

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REFERENCES
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