JAMA Oncology | Original Investigation

Association of Sedentary Behavior With Cancer Mortality in Middle-aged and Older US Adults

Susan C. Gilchrist, MD, MS; Virginia J. Howard, PhD; Tomi Akinyemiju, PhD; Suzanne E. Judd, PhD; Mary Cushman, MD, MS; Steven P. Hooker, PhD; Keith M. Diaz, PhD

IMPORTANCE Sedentary behavior is associated with several health outcomes, including diabetes, cardiovascular disease, and all-cause mortality. Less is known about the association between objectively measured sedentary behavior and cancer mortality, as well as the association with physical activity.

OBJECTIVE To examine the association between accelerometer-measured sedentary behavior (total volume and accrual in prolonged, uninterrupted bouts) and cancer mortality.

DESIGN, SETTING, AND PARTICIPANTS A prospective cohort study conducted in the contiguous US included 8002 black and white adults aged 45 years or older enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. The present analysis was performed from April 18, 2019, to April 21, 2020.

EXPOSURES Sedentary time, light-intensity physical activity (LIPA), and moderate- to vigorous-intensity physical activity (MVPA) were measured using a hip-mounted accelerometer worn for 7 consecutive days.

MAIN OUTCOMES AND MEASURES Cancer mortality.

RESULTS Of the 8002 study participants, 3668 were men (45.8%); mean (SD) age was 69.8 (8.5) years. Over a mean (SD) follow-up of 5.3 (1.5) years, 268 participants (3.3%) died of cancer. In multivariable-adjusted models, including MVPA, greater total sedentary time was associated with a greater risk of cancer mortality (tertile 2 vs tertile 1: hazard ratio [HR], 1.45; 95% CI, 1.00-2.11; tertile 3 vs tertile 1: HR, 1.52; 95% CI, 1.01-2.27). Longer sedentary bout duration was not significantly associated with greater cancer mortality risk: after adjustment for MVPA (tertile 2 vs tertile 1: HR, 1.26; 95% CI, 0.90-1.78; tertile 3 vs tertile 1: HR, 1.36; 95% CI, 0.96-1.93). Replacing 30 minutes of sedentary time with LIPA was significantly associated with an 8% (per 30 minutes: HR, 0.92; 95% CI, 0.86-0.97) lower risk of cancer mortality; MVPA was significantly associated with a 31% (per 30 minutes: HR, 0.69; 95% CI, 0.48-0.97) lower risk of cancer mortality.

CONCLUSIONS AND RELEVANCE In this cohort study, greater sedentary time, as measured with accelerometry, appeared to be independently associated with cancer mortality risk. Replacing sedentary time with either LIPA or MVPA may be associated with a lower risk of cancer mortality. These findings suggest that the total volume of sedentary behavior is a potential cancer mortality risk factor and support the public health message that adults should sit less and move more to promote longevity.

JAMA Oncol. doi:10.1001/jamaoncol.2020.2045
Published online June 18, 2020.

Author Audio Interview

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Susan C. Gilchrist, MD, MS, MD Anderson Cancer Center, Clinical Cancer Prevention, 1155 Pressler Dr, Unit 1360, Houston, TX 77030 (sgilchrist@mdanderson.org).

Cancer is a leading cause of death in US adults, although more than 50% of cancer deaths are preventable through healthy lifestyle choices.[1] Being physically active is a key lifestyle behavior associated with reductions in both the risk of incident cancer and the risk of death from cancer,[2,3] with guidelines recommending at least 150 minutes of moderate- to vigorous-intensity physical activity (MVPA) weekly as an ideal goal for the primary and secondary prevention of cancer.[4] However, adherence to physical activity recommendations is poor, with less than 25% of US adults meeting guidelines.[5] Epidemiologic evidence has indicated that sedentary behavior is associated with all-cause and cardiovascular mortality, particularly among individuals who are not achieving recommended amounts of MVPA.[6] Thus, sedentary behavior is now thought to represent a clinically important aspect of a person's physical activity profile and could represent an alternative and potentially more achievable target for prevention of cancer deaths.[7]

A systematic review and meta-analysis from 2015 reported an association between sedentary behavior and cancer mortality, with a summary hazard ratio (HR) of 1.13 (95% CI, 1.05-1.21).[6] However, studies reporting associations between sedentary behavior and cancer mortality have relied on self-reported sedentary time; this method is subject to reporting bias and measurement error.[6,7] Prospective studies using more objective measures (eg, accelerometry) may help improve the precision of measurement and better elucidate the association between sedentary behavior and cancer mortality risk. Furthermore, as some evidence suggests, sedentary time is associated with health risks, particularly when accumulated in prolonged, uninterrupted bouts (eg, sitting for hours at a time).[8,9] More specific guidance is needed regarding sedentary behavior (eg, targeted reductions in total sedentary time or interruptions of prolonged sedentary bouts) to guide patients and complement a recommendation to meet guideline-based levels of physical activity.

To address this gap in knowledge, the purpose of this study was to examine the associations between accelerometer-measured total sedentary time and prolonged sedentary bouts with cancer mortality risk in a national cohort of US middle-aged and older adults enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study.[8] In addition, to inform what type of activity should be substituted for sedentary time to impart health benefit, we assessed the association of replacing sedentary time with light-intensity physical activity (LIPA) and MVPA and cancer mortality risk in this population.

Key Points

Question Is sedentary behavior as determined by accelerometry associated with future risk of cancer mortality in middle-aged and older US adults?

Findings In this cohort study of 8002 adults, a greater amount of sedentary time was associated with a higher risk of cancer mortality. Replacing sedentary time with light- or moderate- to vigorous-intensity physical activity was associated with reduced cancer mortality risk.

Meaning The findings of this cohort study suggest that less time in sedentary behavior and more time in physical activity may help to reduce the risk of cancer death.

Methods

Participants

The REGARDS study includes 30 239 black and white US adults aged 45 years or older from across the contiguous states, recruited between 2003 and 2007, with an oversampling of black adults, and involves a prospective follow-up to ascertain health outcomes. Individuals receiving active cancer treatment were excluded from participation. The study design has been described in detail elsewhere.[10] Briefly, demographic and cardiovascular risk factor data were collected by telephone interview and an in-home physical assessment on enrollment. A detailed summary of baseline measures is provided in the eMethods in the Supplement. Accelerometer measures of sedentary behavior were collected from active REGARDS participants from May 12, 2009, to December 31, 2012 (mean [SD] time from enrollment, 5.7 [1.5] years; range, 1.9-9.5 years). In the present study, 8002 participants with adherent accelerometer wear (≥4 days with accelerometer wear ≥10 hours) and follow-up data for mortality were included, and data analysis was performed from April 18, 2019, to April 21, 2020. Characteristics of participants who agreed to wear the accelerometer vs those who declined and of participants with adherent vs nonadherent wear have been reported elsewhere.[8,10,11] Briefly, participants who agreed to complete the accelerometer protocol had a higher socioeconomic status compared with those who did not, and participants with nonadherent wear were more likely to be female, black, and obese compared with those with adherent wear.

The REGARDS study was approved by institutional review boards of all participating universities, and all participants provided written informed consent; participants did not receive financial compensation. The present study was approved by the Columbia University Medical Center Institutional Review Board. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Accelerometer Data

Methods for accelerometer data collection were previously described.[10] Briefly, participants wore an accelerometer (Actical, Philips Respironics) secured to their right hip using a nylon belt and were instructed to wear the device during waking hours for 7 consecutive days. The Actical accelerometer has been validated for measurement of physical activity and sedentary behavior and has acceptable reliability.[12-14]

Activity counts were summed over 1-minute epochs. Nonwear periods were defined as at least 150 consecutive minutes of 0 activity counts. This nonwear algorithm was previously validated against daily log sheets in REGARDS participants.[15] As determined in a laboratory-based calibration study, measurements of 0 to 49 counts/min were de-

fined as sedentary behavior; 50 to 1064 counts/min, LIPA; and at least 1065 counts/min, MVPA.[16] A sedentary bout was defined as consecutive minutes in which the accelerometer registered fewer than 50 counts/min. A sedentary break was defined as at least 1 minute in which 50 or more counts/min were registered after a sedentary bout. Both sedentary bouts and breaks were exclusively continuous periods, with no interruptions or nonwear intervals allowed in the definition. Sedentary and physical activity variables were summed across each adherent day (≥10 hours of wear) and then the mean was determined across all of a participant's adherent days to derive per-day values.

Cancer Mortality Outcome

Methods to obtain cancer mortality outcomes in the REGARDS study were published.[17] Mortality was identified through biannual follow-up, linkage with the Social Security Death Index and the National Death Index and death information from participants' proxies. Time to death was identified based on death certificates, the Social Security Death Index, and the National Death Index, and final cause of death was defined after adjudication by REGARDS clinical investigators. Cancer deaths through December 31, 2016, were included in the analysis.

Statistical Analysis

Because of a high correlation between wear time and total sedentary time, we corrected for wear time by standardizing total sedentary time to 16 hours per day of wear time using the residuals obtained when regressing total sedentary time on wear time as previously described.[8] Participants were stratified into tertiles according to total sedentary time and, separately, mean sedentary bout duration (a measure of overall prolonged, uninterrupted sedentary behavior). Cox proportional hazards cause-specific models were used to calculate the HR for cancer mortality associated with tertiles of total sedentary time and, separately, mean sedentary bout length.[18] Crude HRs were initially calculated. Subsequent HRs were calculated after adjustment for age, race, sex, region of residence, educational level, and season the accelerometer was worn (model 1), with further adjustment for current smoking, alcohol use, body mass index, diabetes, hypertension, dyslipidemia, history of coronary heart disease, history of stroke, and MVPA expressed as a continuous variable (model 2).

Tests for linear trend across tertiles were conducted by including the tertile for each participant as an ordinal variable in regression models. Because some evidence suggests that the associations of sedentary behavior with health outcomes vary according to MVPA level,[19] the above analyses were repeated in a fully adjusted model, testing the interaction for MVPA category (<150 min/wk and ≥150 min/wk). Because breaks in sedentary time have received interest as a potentially important adjunct to physical activity guidelines, as a tertiary analysis we examined the association between sedentary breaks (expressed as total number per day; standardized to 16 hours of wear) and risk for cancer mortality using the above-described analytic approach.

To evaluate whether LIPA and MVPA are healthier alternatives to sedentary behavior, isotemporal substitution models were used to estimate the theoretical effect of substituting total sedentary time with another type of activity (LIPA, MVPA) for the same amount of time while holding accelerometer wear time constant.[20] A description of the isotemporal substitution models is provided in the eMethods in the Supplement. Briefly, in the isotemporal model, LIPA, MVPA, and wear time were included in a single Cox proportional hazards cause-specific regression model (each expressed continuously in 30-minute units) that included adjustment for the above-listed covariates. Sedentary time was not included in this model (ie, it was eliminated), and resulting HRs estimated the associations for replacing 30 minutes of sedentary time with an equal amount of time in a given type of activity (LIPA or MVPA). To better understand results from the isotemporal analyses, we also fitted Cox proportional hazards cause-specific regression models (ie, partition models) that represented the association of each intensity category (sedentary time, LIPA, and MVPA) with mortality (1) without mutual adjustment for other activity categories (single-factor models), (2) with adjustment for selected activity categories (2-factor models), and (3) with mutual adjustment for all activity categories simultaneously (3-factor models). Isotemporal substitution analyses were also conducted expressing sedentary time, LIPA, and MVPA in 10-minute units. Since its first application in physical activity epidemiologic research in 2009,[20] isotemporal substitution has become widely adopted as a means to account for time displacement (eg, reduced time spent in one activity increases time in other activities) and estimate the health benefits incurred when reallocating time from one activity to another, keeping time in other activities fixed.[21] Isotemporal substitution is considered by some to be the standard time-use statistical method for physical activity epidemiologic research.[22]

As a secondary analysis, the continuous dose-response association between each sedentary characteristic and cancer mortality was evaluated in a fully adjusted model (model 3). We examined possible nonlinear associations nonparametrically with restricted cubic splines.[23] Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term with the model with the linear and cubic spline terms. No nonlinear associations were identified (*P* values for nonlinear associations were .85 and .92 for total sedentary time and mean sedentary bout duration, respectively). Therefore, linear models were used. We conducted a sensitivity analysis examining whether the HRs of later years (eg, after the first year) differed from the HRs in the first year by testing a model that allows for a change in the HR after 1 year vs a model that does not (eg, HR unchanged over time). Analyses were conducted using SAS, version 9.4 (SAS Institute Inc). Statistical significance, determined using 2-tailed testing, was set at $P < .05$, with significant interactions defined as those at $P < .10$. All models showed no evidence for multicollinearity (variance inflation factor <4) with the exception of the 2-factor model that simultaneously adjusted for sedentary time and LIPA (variance inflation factor >10).

Table 1. Characteristics of 8002 REGARDS Accelerometer Study Participants by Cancer Death Status

Characteristic	Death		*P* value
	No (n = 7734)	Yes (n = 268)	
Baseline data[a]			
Age, mean (SD), y	63.4 (8.5)	68.2 (8.1)	<.001
Male, No. (%)	3511 (45.4)	157 (58.6)	<.001
Black race, No. (%)	2444 (31.6)	68 (25.4)	.03
Region of residence, No. (%)			
No belt or buckle	3519 (45.5)	126 (47)	.71
Stroke buckle	1663 (21.5)	44 (16.4)	
Stroke belt	2552 (33)	98 (36.6)	
Educational level, No. (%)			
Less than high school	480 (6.2)	17 (6.3)	.50
High school graduate	1732 (22.4)	57 (21.3)	
Some college	2057 (26.6)	87 (32.5)	
College graduate	3465 (44.8)	107 (39.9)	
Current smoker, No. (%)	804 (10.4)	45 (16.8)	.001
Alcohol consumption, No. (%)			
None	4339 (56.1)	147 (54.7)	.20
Moderate	3032 (39.2)	100 (37.4)	
Heavy	356 (4.6)	21 (7.9)	
BMI, mean (SD)	28.7 (5.7)	28.5 (5.8)	.63
Diabetes, No. (%)	1121 (14.5)	44 (16.3)	.40
Hypertension, No. (%)	3983 (51.5)	147 (54.9)	.29
Dyslipidemia, No. (%)	4463 (57.7)	157 (58.5)	.80
CHD history, No. (%)	990 (12.8)	51 (19.0)	.002
Stroke history, No. (%)	263 (3.4)	15 (5.6)	.06
Accelerometer data			
Age at time of accelerometer testing, mean (SD), y	69.6 (8.7)	74.6 (8.2)	<.001
Season accelerometer worn, No. (%)			
Summer	1934 (25)	70 (26.1)	.61
Autumn	1879 (24.3)	72 (26.9)	
Winter	1794 (23.2)	49 (18.3)	
Spring	2127 (27.5)	77 (28.7)	
Wear time, mean (SD), min/d	890.4 (102.6)	870.8 (102.9)	.002
Valid wear, No. (%), d			
4-5	835 (10.8)	31 (11.6)	.87
6-7	6899 (89.2)	237 (88.4)	
Total sedentary time, mean (SD), min/d[b]	741.8 (84.1)	777.3 (76.7)	<.001
Sedentary bout duration, mean (SD), min/bout	11.4 (8.3)	14.0 (12.7)	<.001
Sedentary breaks, mean (SD), No.[c]	75.4 (18.8)	69.6 (19.1)	<.001
Physical activity, mean (SD), min/d			
LIPA	189.2 (78.3)	154.8 (70.0)	<.001
MVPA	13.4 (17.8)	7.9 (15.0)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; LIPA, light-intensity physical activity; MVPA, moderate- to vigorous-intensity physical activity; REGARDS, Reasons for Geographic and Racial Differences in Stroke.

[a] Demographic data, cardiovascular risk factors, chronic disease status, and medical history data were collected at original baseline (eMethods in the Supplement).

[b] Corrected for wear time and expressed as the estimated minutes of sedentary time per day given a standardized 16 hours of accelerometer wear (eMethods in the Supplement).

[c] Corrected for wear time and expressed as the estimated sedentary breaks per day given a standardized 16 hours of accelerometer wear (eMethods in the Supplement).

Results

Of the 8002 study participants, 3668 were men (45.8%); mean (SD) age was 69.8 (8.5) years. Over a mean (SD) follow-up of 5.3 (1.5) years, 268 participants (3.3%) died of cancer. Participant characteristics stratified by cancer death (no/yes) are presented in **Table 1.** Participants who died from cancer vs those who survived were older (68.2 [8.1] vs 63.4 [8.5] years) and more likely to be men (157 [58.6%] vs 3511 [45.4%]), to be current smokers (45 [16.8%] vs 804 [10.4%]), and to have a history of coronary heart disease (51 [19.0%] vs 990 [12.8%]). In

Table 2. Risk of Cancer Mortality by Total Sedentary Time and Mean Sedentary Bout Duration Tertiles in the REGARDS Study

Variable	Hazard ratio (95% CI)[a]			*P* value for trend[b]
	Tertile 1 (n = 2667)	Tertile 2 (n = 2668)	Tertile 3 (n = 2667)	
Total sedentary time				
No. of deaths	46	93	129	
Unadjusted	1 [Reference]	1.62 (1.13-2.32)	1.82 (1.27-2.60)	<.001
Model 1[c]	1 [Reference]	1.70 (1.19-2.43)	2.03 (1.41-2.92)	<.001
Model 2[d]	1 [Reference]	1.45 (1.00-2.11)	1.52 (1.01-2.27)	.07
Sedentary bout duration				
No. of deaths	55	88	125	
Unadjusted	1 [Reference]	1.33 (0.95-1.87)	1.61 (1.16-2.24)	.005
Model 1[c]	1 [Reference]	1.32 (0.94-1.85)	1.62 (1.16-2.27)	.004
Model 2[d]	1 [Reference]	1.26 (0.90-1.78)	1.36 (0.96-1.93)	.10

Abbreviation: REGARDS, Reasons for Geographic and Racial Differences in Stroke.

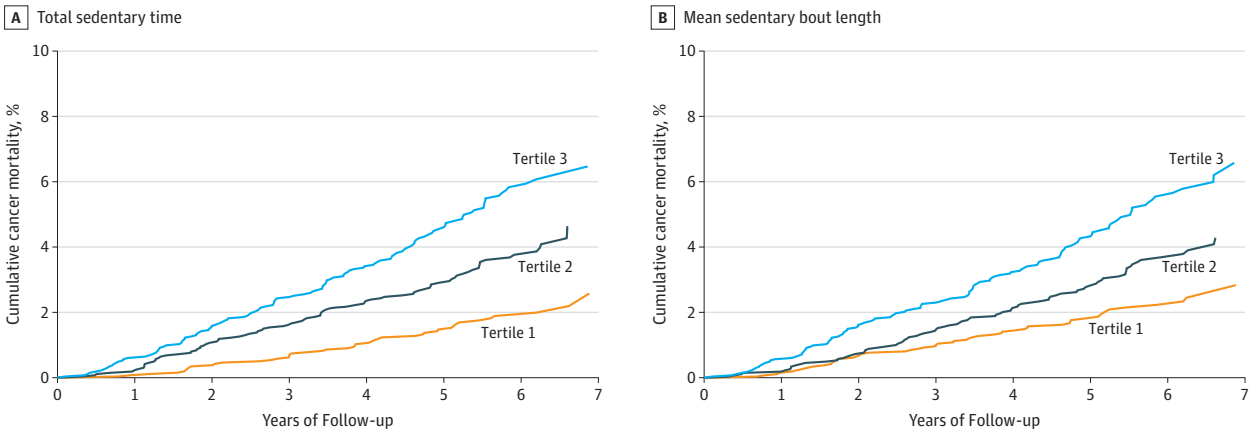
[a] The tertile cutoff points were less than 709.7, greater than or equal to 709.7 to less than 782.6, and greater than or equal to 782.6 min/16-h day for total sedentary time and less than 8.3, greater than or equal to 8.3 to less than 11.3, and greater than or equal to 11.3 min/bout for sedentary bout duration.

[b] *P* value from linear trend test when tertiles were treated as an ordinal variable in the Cox proportional hazards model.

[c] Adjusted for age, race, sex, region of residence, educational level, and season the accelerometer was worn.

[d] Adjusted for covariates in model 1 plus current smoking, alcohol use, body mass index, diabetes, hypertension, dyslipidemia, history of coronary heart disease, history of stroke, and moderate- to vigorous-intensity physical activity.

Figure 1. Cumulative Cancer Mortality

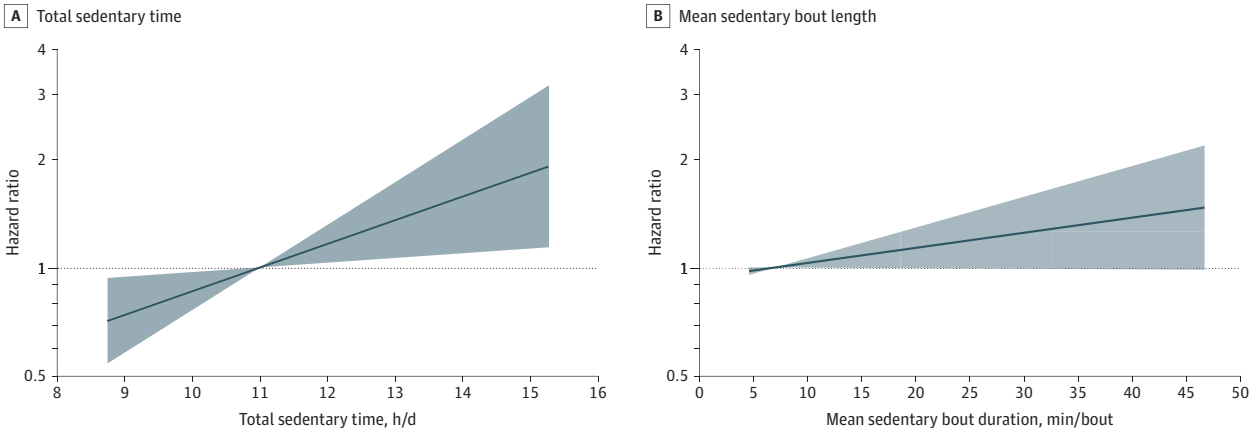


Cumulative mortality by tertiles of total sedentary time (A) and mean sedentary bout length (B).

addition, those who died had higher levels of total mean (SD) sedentary time (777.3 [76.7] vs 741.8 [84.1] min/d), longer mean (SD) sedentary bout duration (14.0 [12.7] vs 11.4 [8.3] min/bout), fewer mean (SD) sedentary time breaks (69.6 [19.1] vs 75.4 [18.8]), and lower mean (SD) levels of LIPA (154.8 [70.0] vs 189.2 [78.3] min/d) and MVPA (7.9 [15.0] vs 13.4 [17.8] min/d).

When expressed in tertiles, greater time spent in sedentary behavior and longer mean sedentary bout duration were each associated with an increased risk of cancer mortality in unadjusted and partially adjusted models (**Table 2**; **Figure 1**). For example, participants in tertile 3 of total sedentary time and sedentary bout duration had an 82% (HR, 1.82; 95% CI, 1.27-2.60) and 61% (HR, 1.61; 95% CI, 1.16-2.24) higher risk of cancer mortality, respectively, compared with participants in tertile 1. Adjustment for additional covariates and MVPA attenuated these associations, but for total sedentary time, participants in the middle and uppermost tertiles still had a significantly greater risk of cancer mortality compared with those in the lowest tertile (tertile 3 vs tertile 1; HR, 1.52; 95% CI, 1.01-2.27). Mean sedentary bout duration was no longer significantly associated with cancer mortality after adjustment for additional covariates and MVPA (tertile 2 vs tertile 1: HR, 1.26; 95% CI, 0.90-1.78); tertile 3 vs tertile 1: HR, 1.36; 95% CI, 0.96-1.93). Similar results were observed for sedentary breaks (eTable 1 in the Supplement). We did not detect a statistically significant interaction between total sedentary time and MVPA for cancer mortality (Wald $\chi^2 = 0.17$, $P = .68$ for interaction) (eTable 2 in the Supplement). The mean sedentary bout × MVPA category interaction was not statistically significant (Wald $\chi^2 = 2.64$, $P = .11$ for interaction) (eTable 3 in the Supplement), although a trend was observed wherein the association between mean sedentary bout duration and risk of cancer mortality was significant only for participants who did not meet MVPA guidelines (eTable 3 in the Supplement).

Figure 2. Dose-Response Association Between Cancer Mortality and Total Sedentary Time and Mean Sedentary Bout Length



Data on total sedentary time (A) and mean sedentary bout length (B) were fitted using a linear model (P = .01 for total sedentary time; P = .06 for mean sedentary bout duration) with results reported as hazard ratios (dark blue lines) and 95% CIs (shaded areas). The referent was the approximate median of the lowest tertile (total sedentary time, 11.0 h per 16-h day; mean sedentary bout duration, 7.0 min/bout). Models were adjusted for age, race, sex, region of residence, educational level, season the accelerometer was worn, current smoking, alcohol use, body mass index, diabetes, hypertension, dyslipidemia, history of coronary heart disease, history of stroke, and moderate- to vigorous-intensity physical activity.

Table 3. Risk of Cancer by Sedentary Time, LIPA, and MVPA in the REGARDS Study

	Hazard ratio (95% CI)		
Model[a]	Sedentary time	LIPA	MVPA
Single-factor[b]	1.12 (1.06-1.18)	0.89 (0.84-0.95)	0.58 (0.41-0.82)
2-Factor[c]	1.09 (1.03-1.16)	0.92 (0.86-0.97)	NA
2-Factor[d]	1.46 (1.03-2.06)	NA	0.69 (0.48-0.97)
Partition[e]	0.98 (0.94-1.02)	0.89 (0.84-0.96)	0.67 (0.47-0.95)
Isotemporal[f]	NA	0.92 (0.86-0.97)	0.69 (0.48-0.97)

Abbreviations: LIPA, light-intensity physical activity; MVPA, moderate- to vigorous-intensity physical activity; NA, not applicable; REGARDS, Reasons for Geographic and Racial Differences in Stroke.

[a] All variables expressed in 30-minute units. All models adjusted for age, race, sex, region of residence, educational level, season the accelerometer was worn, current smoking, alcohol use, body mass index, diabetes, hypertension, dyslipidemia, history of coronary heart disease, history of stroke, and accelerometer wear time.

[b] Results from separate models for each activity variable (sedentary time, LIPA, and MVPA), adjusted for covariates.

[c] Results from separate models for each activity variable, adjusted for covariates and MVPA.

[d] Results from separate models for each activity variable, adjusted for covariates and LIPA.

[e] Results from a single model that includes sedentary time, LIPA, MVPA, and covariates.

[f] Results from a single model wherein sedentary time is omitted from the model (but LIPA, MVPA, and wear time are included along with covariates); thus, resulting HRs estimate associations for replacing 30 minutes of sedentary time with an equal amount in a given type of activity (LIPA or MVPA).

Figure 2 shows the dose-response association for risk of cancer mortality when total sedentary time and mean sedentary bout length were expressed continuously. Total sedentary time was significantly associated with the risk of cancer mortality in a linear, dose-response fashion (HR per 1 hour/d increase in total sedentary time: 1.16; 95% CI, 1.03-1.31; P = .01). A trend for an association was observed for mean sedentary bout duration and risk of cancer mortality (HR per 1-minute/bout increase in mean sedentary bout duration: 1.01; 95% CI, 1.00-1.02; P = .06). Detailed data shown in Figure 2 are presented in eTable 4 and eTable 5 in the Supplement.

Table 3 presents single-factor, 2-factor, partition, and isotemporal substitution models for the associations between activity categories (sedentary time, LIPA, and MVPA; each expressed in 30-minute units) and risk of cancer mortality. In single- and 2-factor models, sedentary time was associated with a greater risk of cancer mortality; conversely, LIPA and MVPA were associated with a lower risk of cancer mortality. In a partition model that mutually adjusted for all activity categories simultaneously, LIPA and MVPA, but not sedentary time, remained significantly associated with cancer mortality risk. In isotemporal substitution models, replacing 30 minutes of sedentary time with 30 minutes of MVPA was associated with a 31% (HR, 0.69; 95% CI, 0.48-0.97) lower risk of cancer mortality. Replacing 30 minutes of sedentary time with 30 minutes of LIPA was associated with an 8% (HR, 0.92; 95% CI, 0.86-0.97) lower risk of cancer mortality. Results expressing activity categories in 10-minute units are reported in eTable 6 in the Supplement.

In sensitivity analyses, the HRs in the first year did not differ significantly from the HRs in later years for total seden-

tary time (P = .49 comparing HRs in the first year vs later years; for example: tertile 3 vs tertile 1 in first year: 1.49; 95% CI, 0.99-2.23; tertile 3 vs tertile 1 in later years: 1.87; 95% CI, 0.98-3.56) and mean sedentary bout duration (P = .43 comparing HRs in the first year vs later years; for example: tertile 3 vs tertile 1 in first year: 1.33; 95% CI, 0.94-1.91; tertile 3 vs tertile 1 in later years: 1.61; 95% CI, 0.87-3.00) (eTable 7 in the Supplement).

Discussion

Data from this US national cohort study of 8002 middle-aged and older adults provide information on the association between sedentary behavior and cancer mortality. Our main finding was that the total time spent in sedentary behavior, measured by accelerometry, was associated with an increased risk of cancer mortality, independent of MVPA. Using isotemporal substitution modeling, we also observed that replacing sedentary time with either LIPA or MVPA was associated with reductions in cancer mortality risk.

Mixed findings have been reported in previous studies examining associations between sedentary time and cancer mortality. In a meta-analysis, sedentary time was associated with a 13% increased risk of cancer mortality (HR, 1.13; 95% CI, 1.05-1.21).[6] Furthermore, in an evaluation of the current literature, the 2018 Physical Activity Guidelines Advisory Committee determined that there was limited evidence suggesting a direct association between sedentary behavior and cancer mortality, with only 5 of the 13 studies identified in their systematic review reporting a significant association.[7] However, those findings were based solely on self-reported sedentary time—such data are prone to measurement error, which may underestimate the magnitude of the association between sedentariness and health risk. Thus, the present study findings add to the literature by showing a possible association between accelerometer-measured sedentary time and cancer mortality in a national cohort including both black and white participants.

Our results address several recommendations from the 2019 American College of Sports Medicine roundtable on physical activity, sedentary behavior, and cancer prevention and control that called for observational research using device-based measurement of physical activity and accounting for sedentary behavior when assessing cancer outcomes.[24] Results from the present study that address this gap include our finding that replacing 30 minutes of sedentary time with MVPA may reduce the risk of cancer mortality by 31%. We also found an association suggesting that, when sedentary behavior was substituted for LIPA, replacing 30 minutes of sedentary time with LIPA would reduce the risk of cancer mortality by 8%. These results provide data on the benefits of more modest levels of physical activity to improve cancer outcomes and underscore a public health message that movement in itself (eg, sit less and move more), irrespective of intensity, is beneficial.

With use of accelerometry, studies have been able to add insights into the potential clinical importance of prolonged, uninterrupted bouts of sedentary behavior. Cross-sectional studies have reported associations between the total number of breaks in sedentary time per day (the reciprocal to mean sedentary bout length) and cardiometabolic risk factors.[25,26] These findings led to the prolonger vs breaker hypothesis, which postulates that it is not only the amount of sedentary time that is important for cardiometabolic health but also the manner in which the time is accumulated.[27] More recently, prolonged sedentary bouts were found to be associated with a greater risk of cardiovascular disease and all-cause mortality.[8,28] In the present study, we extended this previous work and, to our knowledge, suggest for the first time that mean sedentary bout length is also associated with a risk of cancer mortality, suggesting that interrupting sedentary time may represent an opportunity to mitigate excess mortality across different conditions beyond just cardiometabolic-related diseases. However, this association was not independent of and varied by MVPA levels.

Limitations

Our study has several limitations. First, data on cancer treatment and tumor characteristics were not collected and could confound the observed associations. Second, information concerning site-specific cancer deaths was not available. Previous evidence using self-report data suggests that physical activity and sedentary behavior affect the risk for some, but not all, cancers. Thus, the reported findings may vary for deaths associated with specific cancer subtypes. Third, the relatively short follow-up period may have led to confounding. Fourth, the definition of sedentary behavior was based only on intensity because the accelerometer used cannot distinguish between sitting and standing postures. Thus, time spent in sedentary behavior may be overestimated. Fifth, baseline risk factors (covariates) were obtained approximately 6 years before the accelerometer capture. Thus, residual confounding is possible owing to misclassification (eg, change in hypertension status). Sixth, REGARDS participants who did not enroll in the accelerometer substudy or did not have valid accelerometer wear had a greater risk factor burden (eg, older age and higher prevalence of diabetes) and lower survival rates.[8] Thus, participants included in the present study likely reflect a healthier sample.

Conclusions

In a geographically diverse, population-based sample of middle-aged and older black and white adults in the US, our data suggest an independent association between sedentary time and cancer mortality. To mitigate the risks incurred from sedentary behavior, our results suggest that replacing sedentary time with either LIPA or MVPA is associated with a lower cancer mortality risk. These findings add to growing evidence in cancer research on the importance of reducing sedentary behavior and support the public health message that adults should sit less and move more to promote health and longevity.

ARTICLE INFORMATION

Accepted for Publication: April 20, 2020.

Published Online: June 18, 2020. doi:10.1001/jamaoncol.2020.2045

Author Affiliations: Department of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center, Houston (Gilchrist); Department of Cardiology, The University of Texas MD Anderson Cancer Center, Houston (Gilchrist); Department of Epidemiology, University of Alabama School of Public Health, Birmingham (Howard); Department of Population Health Sciences, Duke University School of Medicine, Durham, North Carolina (Akinyemiju); Department of Biostatistics, University of Alabama School of Public Health, Birmingham (Judd); Vermont Cancer Center, Department of Medicine, Larner College of Medicine, University of Vermont, Burlington (Cushman); College of Health and Human Services, San Diego State University, San Diego, California (Hooker); Center for Behavioral Cardiovascular Health, Department of Medicine, Columbia University Medical Center, New York, New York (Diaz).

Author Contributions: Dr Diaz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Gilchrist, Howard, Akinyemiju, Judd, Hooker, Diaz.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Gilchrist, Akinyemiju, Diaz.
Critical revision of the manuscript for important intellectual content: Gilchrist, Howard, Akinyemiju, Judd, Cushman, Hooker.
Statistical analysis: Akinyemiju, Diaz.
Obtained funding: Howard, Judd, Hooker.
Administrative, technical, or material support: Howard, Akinyemiju, Cushman.
Supervision: Gilchrist, Howard.

Conflict of Interest Disclosures: Dr Gilchrist reported serving as a consultant for Outcomes4Me. Dr Judd reported receiving grants from the National Institutes of Health (NIH) during the conduct of the study. Dr Cushman reported receiving grants from the NIH during the conduct of the study and in-kind laboratory assay support from Sphingotec GmBh. Dr Hooker reported receiving grants from the NIH and Coca-Cola Company during the conduct of the study. No other disclosures were reported.

Funding/Support: This research project was supported by cooperative agreement U01 NS041588 co-funded by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging, NIH, and investigator-initiated grant R01NS061846 from the NINDS. Additional funding was provided by grant R01 HL080477 from the National Heart, Lung, and Blood Institute and an unrestricted research grant from the Coca-Cola Company.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the other investigators, staff, and participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study for their valuable contributions.

Additional Information: A full list of participating REGARDS investigators and institutions can be found at https://www.uab.edu/soph/regardsstudy/.

REFERENCES

1. Anand P, Kunnumakkara AB, Sundaram C, et al. Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res*. 2008;25(9):2097-2116. doi:10.1007/s11095-008-9661-9

2. Moore SC, Lee IM, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med*. 2016;176(6):816-825. doi:10.1001/jamainternmed.2016.1548

3. Arem H, Moore SC, Park Y, et al. Physical activity and cancer-specific mortality in the NIH-AARP Diet and Health Study cohort. *Int J Cancer*. 2014;135(2):423-431. doi:10.1002/ijc.28659

4. Kushi LH, Doyle C, McCullough M, et al; American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society guidelines on nutrition and physical activity for cancer prevention. *CA Cancer J Clin*. 2012;62(1):30-67. doi:10.3322/caac.20140

5. Katzmarzyk PT, Lee IM, Martin CK, Blair SN. Epidemiology of physical activity and exercise training in the United States. *Prog Cardiovasc Dis*. 2017;60(1):3-10. doi:10.1016/j.pcad.2017.01.004

6. Biswas A, Oh PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults. *Ann Intern Med*. 2015;162(2):123-132. doi:10.7326/M14-1651

7. Katzmarzyk PT, Powell KE, Jakicic JM, Troiano RP, Piercy K, Tennant B; 2018 Physical Activity Guidelines Advisory Committee. Sedentary behavior and health. *Med Sci Sports Exerc*. 2019;51(6):1227-1241. doi:10.1249/MSS.0000000000001935

8. Diaz KM, Howard VJ, Hutto B, et al. Patterns of sedentary behavior and mortality in US middle-aged and older adults. *Ann Intern Med*. 2017;167(7):465-475. doi:10.7326/M17-0212

9. Diaz KM, Goldsmith J, Greenlee H, et al. Prolonged, uninterrupted sedentary behavior and glycemic biomarkers among US Hispanic/Latino adults. *Circulation*. 2017;136(15):1362-1373. doi:10.1161/CIRCULATIONAHA.116.026858

10. Howard VJ, Rhodes JD, Mosher A, et al. Obtaining accelerometer data in a national cohort of black and white adults. *Med Sci Sports Exerc*. 2015;47(7):1531-1537. doi:10.1249/MSS.0000000000000549

11. Diaz KM, Howard VJ, Hutto B, et al. Patterns of sedentary behavior in US middle-age and older adults. *Med Sci Sports Exerc*. 2016;48(3):430-438. doi:10.1249/MSS.0000000000000792

12. Esliger DW, Tremblay MS. Technical reliability assessment of three accelerometer models in a mechanical setup. *Med Sci Sports Exerc*. 2006;38(12):2173-2181. doi:10.1249/01.mss.0000239394.55461.08

13. Welk GJ, Schaben JA, Morrow JR. Reliability of accelerometry-based activity monitors. *Med Sci Sports Exerc*. 2004;36(9):1637-1645. doi:doi:10.1249/01.MSS.0000074670.03001.98

14. Van Remoortel H, Giavedoni S, Raste Y, et al; PROactive consortium. Validity of activity monitors in health and chronic disease. *Int J Behav Nutr Phys Act*. 2012;9:84. doi:10.1186/1479-5868-9-84

15. Hutto B, Howard VJ, Blair SN, et al. Identifying accelerometer nonwear and wear time in older adults. *Int J Behav Nutr Phys Act*. 2013;10:120. doi:10.1186/1479-5868-10-120

16. Hooker SP, Feeney A, Hutto B, et al. Validation of the Actical activity monitor in middle-aged and older adults. *J Phys Act Health*. 2011;8(3):372-381. doi:10.1123/jpah.8.3.372

17. Akinyemiju T, Moore JX, Pisu M, et al. A prospective study of obesity, metabolic health, and cancer mortality. *Obesity (Silver Spring)*. 2018;26(1):193-201. doi:10.1002/oby.22067

18. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 2016;133(6):601-609. doi:10.1161/CIRCULATIONAHA.115.017719

19. Ekelund U, Steene-Johannessen J, Brown WJ, et al; Lancet Physical Activity Series 2 Executive Committee; Lancet Sedentary Behaviour Working Group. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? a harmonised meta-analysis of data from more than 1 million men and women. *Lancet*. 2016;388(10051):1302-1310. doi:10.1016/S0140-6736(16)30370-1

20. Mekary RA, Willett WC, Hu FB, Ding EL. Isotemporal substitution paradigm for physical activity epidemiology and weight change. *Am J Epidemiol*. 2009;170(4):519-527. doi:10.1093/aje/kwp163

21. Grgic J, Dumuid D, Bengoechea EG, et al. Health outcomes associated with reallocations of time between sleep, sedentary behaviour, and physical activity. *Int J Behav Nutr Phys Act*. 2018;15(1):69. doi:10.1186/s12966-018-0691-3

22. Mekary RA, Ding EL. Isotemporal substitution as the gold standard model for physical activity epidemiology. *Int J Environ Res Public Health*. 2019;16(5):797. doi:10.3390/ijerph16050797

23. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med*. 1989;8(5):551-561. doi:10.1002/sim.4780080504

24. Patel AV, Friedenreich CM, Moore SC, et al. American College of Sports Medicine roundtable report on physical activity, sedentary behavior, and cancer prevention and control. *Med Sci Sports Exerc*. 2019;51(11):2391-2402. doi:10.1249/MSS.0000000000002117

25. Healy GN, Matthews CE, Dunstan DW, Winkler EA, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults. *Eur Heart J*. 2011;32(5):590-597. doi:10.1093/eurheartj/ehq451

26. Healy GN, Dunstan DW, Salmon J, et al. Breaks in sedentary time. *Diabetes Care*. 2008;31(4):661-666. doi:10.2337/dc07-2046

27. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population health science of sedentary behavior. *Exerc Sport Sci Rev*. 2010;38(3):105-113. doi:10.1097/JES.0b013e3181e373a2

28. Bellettiere J, LaMonte MJ, Evenson KR, et al. Sedentary behavior and cardiovascular disease in older women. *Circulation*. 2019;139(8):1036-1046. doi:10.1161/CIRCULATIONAHA.118.035312