Pan-Cancer Analysis of Postdiagnosis Exercise and Mortality

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ABSTRACT

PURPOSE The impact of postdiagnosis exercise on cause-specific mortality in cancer survivors and whether this differs on the basis of cancer site is unclear.

METHODS We performed an analysis of 11,480 patients with cancer enrolled in the Prostate, Lung, Colorectal, and Ovarian cancer screening trial. Patients with a confirmed diagnosis of cancer completing a standardized survey quantifying exercise after diagnosis were included. The primary outcome was all-cause mortality (ACM); secondary end points were cancer mortality and mortality from other causes. Cox models were used to estimate the cause-specific hazard ratios (HRs) for ACM, cancer, and noncancer mortality as a function of meeting exercise guidelines versus not meeting guidelines with adjustment for important clinical covariates.

RESULTS After a median follow-up of 16 years from diagnosis, 4,665 deaths were documented (1,940 due to cancer and 2,725 due to other causes). In multivariable analyses, exercise consistent with guidelines was associated with a 25% reduced risk of ACM compared with nonexercise (HR, 0.75; 95% CI, 0.70 to 0.80). Compared with nonexercise, exercise consistent with guidelines was associated with a significant reduction in cancer mortality (HR, 0.79; 95% CI, 0.72 to 0.88) and mortality from other causes (HR, 0.72; 95% CI, 0.66 to 0.78). The inverse relationship between exercise and cause-specific mortality varied by exercise dose. Exercise consistent with guidelines was associated with a reduced hazard of ACM for multiple cancer sites. Reduction in cancer mortality for exercisers was only observed in head and neck and renal cancer.

CONCLUSION In this pan-cancer sample of long-term cancer survivors, exercise consistent with guidelines was associated with substantial ACM benefit driven by both reductions in cancer and noncancer mortality. The cause-specific impact of exercise differed as a function of cancer site.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

Improvements in detection, risk stratification, and combination therapy have resulted in significant reductions in cancer mortality for patients diagnosed with early-stage disease.[1,2] However, significant challenges remain. First, even patients living 5 years beyond early diagnosis remain at high risk of distant recurrence and new primary malignanices.[1,2] Second, as a consequence of improvements in cancer mortality, a large and rapidly growing number of patients with cancer have sufficient longevity to be at elevated risk of noncancer, competing causes of mortality.[3] Certain adjuvant therapies can also lead to excess risk of comorbid conditions because of normal organ and tissue damage.[4-7] Strategies that complement contemporary therapeutic approaches to further reduce cancer mortality while simultaneously lowering risk of death from other causes are therefore needed to improve all-cause mortality (ACM) among cancer survivors.[8]

In cancer survivors, high levels of postdiagnosis exercise is associated with a significant ACM benefit for several cancer types. However, most previous studies have focused on single cancer site, typically breast cancer, with fewer studies in colorectal or prostate cancer.[9-11] The few available pan-cancer analyses of postdiagnosis exercise and cause-specific mortality are mostly characterized by small overall sample sizes,[12-15] resulting in a small number of patients in each cancer site, thereby limiting investigation of the clinically important question whether exercise benefit differs by cancer site. Finally, small sample sizes together with short duration of follow-up have resulted in a low number of ACM events; mortality from noncancer causes is rarely reported.[9] Thus, the impact of exercise on ACM and cause-specific mortality in cancer survivors is unclear. Such findings will facilitate recommendation and discussion of exercise in cancer survivor consultations.

CONTEXT

Key Objective

Does exercise affect cause-specific mortality in long-term cancer survivors?

Knowledge Generated

In pan-cancer analysis, exercise consistent with guidelines was associated with a significant reduction in the hazard of all-cause mortality (ACM) and the hazards for cancer mortality and mortality from other causes. The inverse relationship between exercise and cause-specific mortality varied by dose. For individual cancer sites, the ACM benefit of exercise was driven primarily by a reduction in death from other causes; the impact on cancer mortality differed as a function of cancer site.

Relevance *(C. Zimmermann)*

In this analysis of more than 11,000 patients participating in a cancer screening trial, exercise was associated with reduced ACM across cancer sites, whereas cancer-specific mortality differed by cancer site. Further prospective studies are necessary to investigate variability in tumor response to exercise across cancer sites.*

*Relevance section written by *JCO* Associate Editor Camilla Zimmermann, MD, PhD, FRCPC.

We leveraged data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial to conduct a pan-cancer analysis of postdiagnosis exercise with ACM and mortality from cancer and other causes in long-term cancer survivors.

METHODS

PLCO Cohort, Patients, and Setting

Full details are provided in the Data Supplement (Methods, online only). Details of the PLCO screening trial design, methods, and cohort characteristics have been reported previously.[16-18] In brief, between November 1993 and July 2001, 10 screening centers in the United States enrolled 76,678 men and 78,209 women between age 55 and 74 years and with no history of prostate, lung, colorectal, or ovarian cancer. The PLCO protocol was approved by the institutional review board at each participating center and all participants provided written informed consent. Between 2006 and 2008, a one-time supplemental questionnaire (SQX) that contained patient-reported items, including questions on exercise, was sent to participants a median of 9 years after initial trial randomization. Of the 154,887 participants enrolled in the PLCO trial, a total of 40,126 (26%) had a confirmed cancer diagnosis. Of those, 12,277 (31%) completed the SQX after diagnosis. Patients were further excluded because of incomplete or missing exercise data (n = 593) or completion of the SQX within 6 months of death (n = 203), or with missing cause of death data (n = 1), resulting in a final analytic cohort of 11,480 (Appendix Fig A1, online only). Compared with excluded survivors (n = 28,646), those included in this analysis were more likely to be diagnosed with breast cancer, prostate cancer, and localized disease, and less likely to be diagnosed with lung cancer or distant disease at diagnosis (Appendix Table A1).

Exercise Assessment

The SQX contained a total of 12 items estimating occupational and nonoccupational (ie, exercise) physical activity. In this study, only the four items estimating strenuous or moderate exercise were analyzed. Items assessing mild exercise were not included in the SQX. Frequency was evaluated by the following two items: Over the past 12 months, on average, how many days per week did you spend in (1) any physical activity strenuous enough to work up a sweat or to increase your breathing and heart rate to very high levels and (2) any moderate physical activity where you worked up a light sweat or increased your breathing and heart rate to moderately higher levels. Four discrete response options were provided: 0 or <1 day per week; 2-3 days per week; 4-5 days per week; and 6-7 days per week. Average duration was evaluated by the following: Over the past 12 months, on average, how long was each session of strenuous activity? The same question assessed the duration of moderate activity. Five discrete response options were provided: 0 to <15 minutes; 16-19 minutes; 20-29 minutes; 30-39 minutes; and 40 minutes or more. These items are similar to those included in the International Physical Activity Questionnaire (IPAQ).[19] Validity and reliability of the IPAQ have been established across multiple countries.[19]

For the primary analysis, exercise exposure was compared across two distinct categories: (1) *meeting national guidelines*: moderate-intensity exercise ≥4 days per week, with each session, on average, ≥30 minutes in duration and/or strenuous-intensity exercise ≥2 days per week, with each session, on average, ≥20 minutes in duration; and (2) *not meeting national guidelines*: any exercise below the criteria for meeting national guidelines, including 0 days of exercise per week. These exercise exposure classifications were

TABLE 1. Characteristics of the Patients

Characteristic	Overall	Exercise Classification[a]	
		Nonexercisers	Exercisers
Patients, No. (%)	11,480 (100)	7,106 (62)	4,374 (38)
Estimated time of moderate exercise per week, minutes, median (IQR)	44 (8-100)	19 (8-61)	100 (61-180)
Unknown	38	0	38
Estimated time of strenuous exercise per week, minutes, median (IQR)	19 (8-86)	8 (8-19)	100 (61-155)
Unknown	17	0	17
Exercise survey completion, age, median (IQR)	73 (68-77)	73 (69-78)	72 (68-76)
Diagnosis, age, median (IQR)	68 (64-72)	68 (64-73)	67 (63-71)
Interval between diagnosis and survey completion, years, median (IQR)	4.50 (2.09-6.98)	4.36 (2.02-6.92)	4.69 (2.25-7.07)
PLCO intervention arm	6,030 (53)	3,691 (52)	2,339 (53)
Female, No. (%)	4,567 (40)	2,992 (42)	1,575 (36)
Race/ethnicity, No. (%)			
Non-Hispanic White	10,461 (93)	6,467 (93)	3,994 (93)
Other group	807 (7.2)	495 (7.1)	312 (7.2)
Missing	212	144	68
BMI, kg/m^2			
0-18.5	55 (0.5)	41 (0.6)	14 (0.3)
>18.5-24.9	3,716 (33)	2,100 (31)	1,616 (38)
>25-29.9	4,998 (45)	3,105 (45)	1,893 (45)
>30	2,350 (21)	1,623 (24)	727 (17)
Unknown	361	237	124
Smoking, pack-years, median (IQR)	5 (0-34)	7 (0-37)	3 (0-26)
Unknown	327	224	103
Primary diagnosis, No. (%)			
Prostate	4,261 (37)	2,452 (35)	1,809 (41)
Breast (female)	2,276 (20)	1,435 (20)	841 (19)
Colon	872 (7.6)	598 (8.4)	274 (6.3)
Hematopoietic	855 (7.4)	565 (8.0)	290 (6.6)
Melanoma	773 (6.7)	423 (6.0)	350 (8.0)
Bladder	535 (4.7)	348 (4.9)	187 (4.3)
Lung	391 (3.4)	278 (3.9)	113 (2.6)
Endometrial	374 (3.3)	244 (3.4)	130 (3.0)
Renal	240 (2.1)	165 (2.3)	75 (1.7)
Head and neck	204 (1.8)	133 (1.9)	71 (1.6)
Ovarian	112 (1.0)	74 (1.0)	38 (0.9)
Thyroid	106 (0.9)	64 (0.9)	42 (1.0)
Upper GI	94 (0.8)	62 (0.9)	32 (0.7)
Pancreas	36 (0.3)	30 (0.4)	6 (0.1)
Male breast	14 (0.1)	9 (0.1)	5 (0.1)
Biliary	12 (0.1)	10 (0.1)	2 (<0.1)
Glioma	12 (0.1)	8 (0.1)	4 (<0.1)
Liver	9 (<0.1)	7 (<0.1)	2 (<0.1)
Other[b]	304 (2.6)	201 (2.8)	103 (2.4)
Cancer stage at diagnosis, No. (%)			
In situ	926 (8.1)	522 (7.3)	404 (9.2)
Localized	6,738 (59)	4,076 (57)	2,662 (61)
Regional	1,463 (13)	953 (13)	510 (12)
Distant	464 (4.0)	306 (4.3)	158 (3.6)
Unknown	1,889 (16)	1,249 (18)	640 (15)

(continued on following page)

TABLE 1. Characteristics of the Patients (continued)

Characteristic	Overall	Exercise Classification[a]	
		Nonexercisers	Exercisers
History of chronic conditions, No. (%)			
Arthritis	3,976 (36)	2,614 (38)	1,362 (32)
Unknown	289	187	102
Chronic bronchitis, No. (%)	449 (4.0)	317 (4.6)	132 (3.1)
Unknown	287	187	100
Colon-related comorbidity (ulcerative colitis, Crohn's disease, Gardner's syndrome, or familial polyposis), No. (%)	148 (1.3)	98 (1.4)	50 (1.2)
Unknown	313	202	111
Diabetes, No. (%)	640 (5.7)	460 (6.6)	180 (4.2)
Unknown	282	183	99
Diverticulitis/diverticulosis, No. (%)	830 (7.4)	530 (7.7)	300 (7.0)
Unknown	286	188	98
Emphysema, No. (%)	249 (2.2)	188 (2.7)	61 (1.4)
Unknown	283	185	98
Gallbladder stones or inflammation, No. (%)	1,203 (11)	819 (12)	384 (9.0)
Unknown	289	190	99
Coronary heart disease or history of heart attack, No. (%)	916 (8.2)	617 (8.9)	299 (7.0)
Unknown	288	186	102
Hypertension, No. (%)	3,636 (32)	2,409 (35)	1,227 (29)
Unknown	279	181	98
Liver-related comorbidity (hepatitis or cirrhosis), No. (%)	416 (3.7)	267 (3.9)	149 (3.5)
Unknown	294	189	105
Osteoporosis, No. (%)	422 (3.8)	308 (4.5)	114 (2.7)
Unknown	302	194	108
Stroke, No. (%)	205 (1.8)	144 (2.1)	61 (1.4)
Unknown	279	182	97

[a]Exercisers: moderate-intensity exercise ≥4 days per week, with each session, on average, ≥30 minutes in duration and/or strenuous-intensity exercise ≥2 days per week, with each session, on average, ≥20 minutes in duration; and nonexercisers: any exercise below the criteria for meeting national guidelines, including patients reporting 0 days of exercise per week.
[b]Other cancers include any other cancer site not listed.

selected given the close adherence with national and international exercise guidelines for cancer survivors.[20-23] To examine dose-response, exercise was collapsed into four categories: (1) no exercise (n = 3,111; 27%), (2) below exercise guidelines (n = 3,995; 35%), (3) meeting exercise guidelines (n = 2,515; 22%), and (4) exceeding exercise guidelines (n = 1,859; 16%).

Follow-Up, Ascertainment of Deaths, and End Points

PLCO trial participants were contacted annually to ascertain and confirm cancer diagnoses and deaths. This was supplemented by periodic linkage to the National Death Index to enhance completeness of end point ascertainment. Death certificates were obtained to confirm the death. Cause of death was defined on the basis of the National Center for Health Statistics guidance. The trial also used an end point adjudication process to assign the cause of death in a uniform and unbiased manner.[19,24] The last follow-up of end point ascertainment in the PLCO was conducted in 2018. The primary end point was ACM, defined as death from any cause after a cancer diagnosis. Secondary end points were cancer mortality and death from other causes.

Statistical Analysis

ACM was analyzed using Kaplan-Meier methods and Cox models. Cumulative incidence curves for cause-specific mortality were estimated using the Aalen-Johansen method. Estimates of median survival (95% CI) are computed using Kaplan-Meier methods. Cause-specific hazards were estimated using Cox regression models. For all time-to-event analyses, using methods for left-truncated data, cancer diagnosis was the origin time and patients entered the risk set 6 months after SQX completion. Delayed study entry is introduced by the requirement of the SQX postdiagnosis; any patients dying before completing the SQX are excluded by design. Additionally, the delayed entry is prolonged by the requirement that patients

survive at least 6 months after the SQX. Therefore, patients can only have an event 6 months after completing the SQX, and consequently entered the risk set at that time.[25]

For Cox models of both ACM and cause-specific mortality, univariable analyses were performed considering relevant patient and cancer characteristics. Variables significant at a threshold of $P \leq .2$ were included in a multivariable model. PLCO randomization group and time from diagnosis to SQX were included in all multivariable models. Hazard ratios (HR) and 95% CIs from Cox models are presented. The proportional hazards assumption was assessed on the basis of tests of weighted residuals.[26] The dose-response relationship between exercise and the hazard of mortality was assessed using a linear model of the HRs from the resulting models as a function of exercise dose, weighted by the number of participants at risk.[27] Additionally, to reduce potential bias associated with reverse causation, we conducted a sensitivity analysis excluding all patients dying within 2 years after completion of the SQX; the results were consistent with the primary analysis (results not presented). Analyses were performed in R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).[28]

RESULTS

Of the 11,480 patients providing complete exercise data, 4,374 (38%) patients were defined as exercisers and 7,106 (62%) were defined as nonexercisers. Across both groups, the estimated median time spent on moderate and strenuous exercise per week was 44 minutes (IQR, 8-100) and 19 minutes (IQR, 8-86), respectively. Exercisers were more likely to be male, nonsmokers, and had a lower prevalence of cardiovascular disease (CVD) history (coronary heart disease or history of heart attack) compared with nonexercisers (Table 1). Among the types of cancer diagnoses observed during follow-up, prostate cancer (n = 4,261; 37%) was the most common diagnosis, followed by breast cancer (n = 2,276; 20%). The median interval between cancer diagnosis and completion of the SQX was 4.5 years (IQR, 2.1-7.0 years). The median time between landmark study entry (6 months after completion of the SQX) and last follow-up was 11.6 years

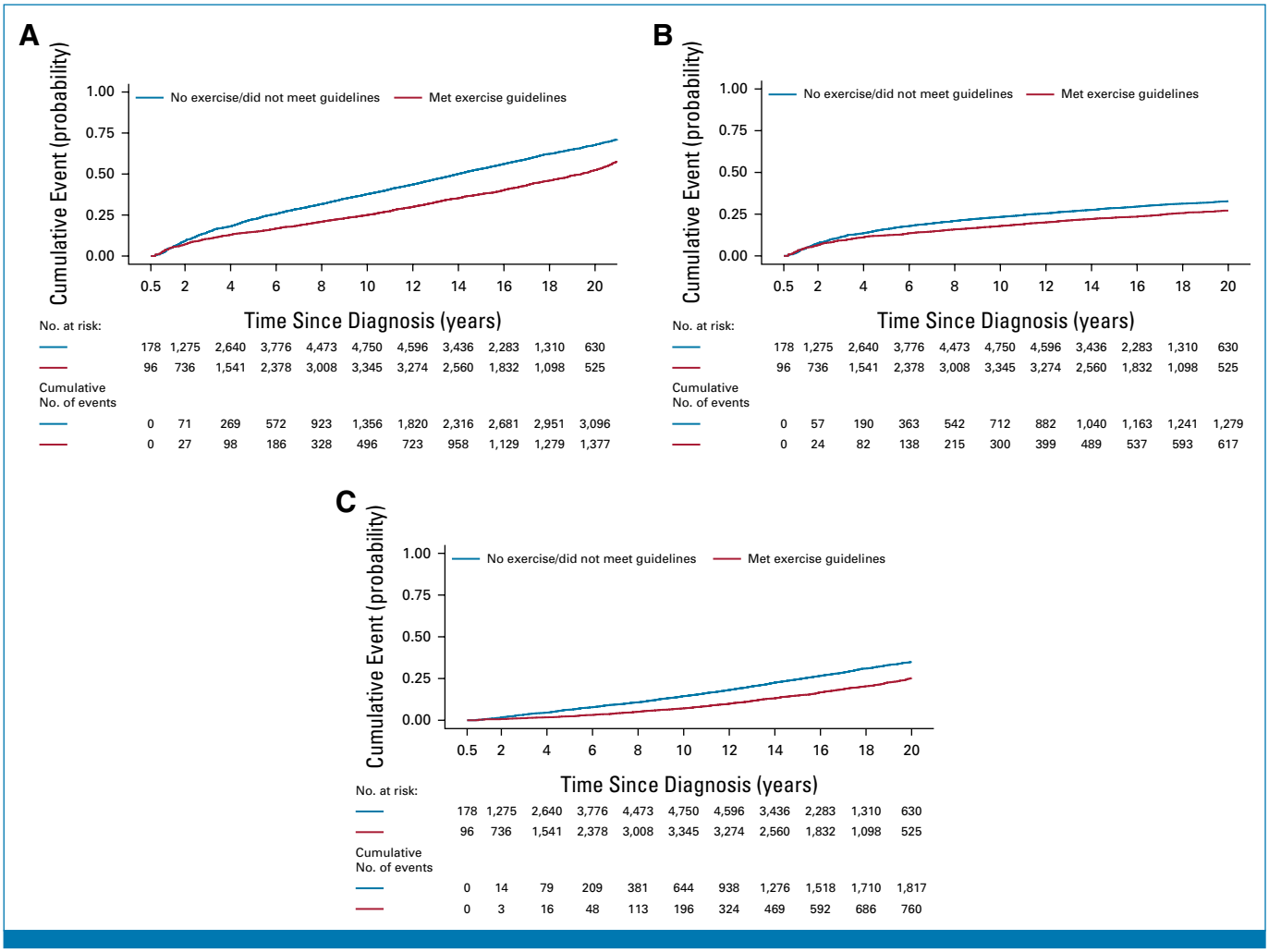

FIG 1. Cumulative incidence for (A) all-cause mortality, (B) cancer mortality, and (C) mortality from other causes by meeting exercise guidelines versus not meeting guidelines. The *x*-axis indicates years from diagnosis and begins at 0.5 years to reflect the landmark time.

(IQR, 11.4-12.2 years) among the 6,815 patients alive at the end of the study. During this period, 4,665 deaths were documented (1,940 due to cancer and 2,725 due to other causes; the number of deaths in each cancer site is presented in Table 2).

Pan-Cancer

During follow-up, 1,459 (33%) total deaths had occurred among the 4,374 patients classified as exercisers and 3,206 (45%) among the 7,106 classified as nonexercisers. Median overall survival from diagnosis was 19 years (95% CI, 19 to 20) for exercisers and 14 years (95% CI, 13 to 15) for nonexercisers. In multivariable analysis, exercisers had a 25% reduced risk of ACM compared with nonexercisers (HR, 0.75; 95% CI, 0.70 to 0.80; Fig 1A). The reduction in ACM in exercisers was apparent within 5 years, persisting for at least 20 years after diagnosis (Table 2). Exercise consistent with national guidelines was associated with a statistically significant reduction in cancer mortality (HR, 0.79; 95% CI, 0.72 to 0.88) and mortality from other causes (HR, 0.72; 95% CI, 0.66 to 0.78). The 5-year cumulative incidence of cancer mortality was 12% (95% CI, 10 to 16) for exercisers compared with 16% (95% CI, 14 to 18) for nonexercisers (95% CI, 0.72 to 0.88; Fig 1B). The 5-year cumulative incidence for death from other causes was 2.4% (95% CI, 1.5 to 3.8) for exercisers and 6.4% (95% CI, 5.3 to 7.7) for nonexercisers (95% CI, 0.66 to 0.78; Fig 1C). Exercise consistent with national guidelines was associated with a reduction in cancer mortality and mortality from other causes over the entire follow-up period (Table 2).

Pan-Cancer Dose Response

The inverse relationship between exercise and cause-specific mortality varied by dose (Appendix Table A2). For ACM, compared with no exercise, exercise below guidelines was associated with a 25% reduction (HR, 0.75; 95% CI, 0.70 to 0.80), meeting guidelines a 35% reduction (HR, 0.65; 95% CI, 0.59 to 0.71), and a 36% reduction for exceeding exercise guidelines (HR, 0.64; 95% CI, 0.58 to 0.71; $P < .001$; average change in HR for each increasing exercise dose: −0.12; 95% CI, −0.31 to 0.06; $P = .10$; Fig 2A). For cancer mortality, exercise below guidelines was associated with a 19% reduction (HR, 0.81; 95% CI, 0.72 to 0.90), meeting guidelines a 25% reduction (HR, 0.75; 95% CI, 0.66 to 0.86), and a 33% reduction for exceeding exercise guidelines (HR, 0.67; 95% CI, 0.58 to 0.78) compared with no exercise ($P < .001$; average change in HR for each increasing exercise dose: −0.11; 95% CI, −0.21 to 0.00; $P = .052$; Fig 2B). For death from other causes, compared with no exercise, exercise below guidelines was associated with a 29% reduction (HR, 0.71; 95% CI, 0.65 to 0.78), meeting guidelines a 42% reduction (HR, 0.58; 95% CI, 0.52 to 0.65), and a 37% reduction for exceeding exercise guidelines (HR, 0.63; 95% CI, 0.55 to 0.72; $P < .001$; average change in HR for each increasing exercise dose: −0.13; 95% CI, −0.38 to 0.11; $P = .14$; Fig 2C).

Mortality by Cancer Site

Exercise consistent with national guidelines was associated with a reduction in the hazard for ACM for patients with breast, endometrial, head and neck, hematopoietic, prostate, and renal cancer (Fig 3A; Table 3). The reduction in hazard of ACM ranged from 22% (HR, 0.78; 95% CI, 0.70 to 0.86) for prostate cancer to 59% (HR, 0.41; 95% CI, 0.24 to 0.72) for endometrial cancer for patients meeting exercise guidelines compared with patients not meeting exercise guidelines. Exercise consistent with national guidelines was associated with a reduction in cancer mortality for two sites: head and neck, and renal cancer (Fig 3B; Table 3). Compared with nonexercisers, exercisers had a significant reduction in death from other causes for breast, colon, endometrial, hematopoietic, and prostate cancer (Fig 3C; Table 3).

TABLE 2. Pan-Cancer Cumulative Incidence of ACM and Cause-Specific Mortality by Exercise Classification

	Cumulative Incidence, % (95% CI)			
Outcome by Exercise Status[a]	5 Years	10 Years	15 Years	20 Years
ACM				
Nonexercisers	22 (20 to 25)	38 (36 to 40)	53 (51 to 55)	68 (66 to 69)
Exercisers	15 (12 to 18)	25 (22 to 28)	38 (35 to 40)	52 (50 to 55)
Cancer mortality				
Nonexercisers	16 (14 to 18)	23 (21 to 26)	29 (27 to 31)	33 (31 to 35)
Exercisers	12 (9.6 to 16)	18 (15 to 21)	23 (20 to 26)	27 (24 to 30)
Other mortality				
Nonexercisers	6.4 (5.3 to 7.7)	14 (13 to 16)	25 (23 to 26)	35 (33 to 37)
Exercisers	2.4 (1.5 to 3.8)	7.1 (5.9 to 8.5)	15 (13 to 16)	25 (23 to 27)

Abbreviation: ACM, all-cause mortality.

[a]Exercisers: moderate-intensity exercise ≥4 days per week, with each session, on average, ≥30 minutes in duration and/or strenuous-intensity exercise ≥2 days per week, with each session, on average, ≥20 minutes in duration; and nonexercisers: any exercise below the criteria for meeting national guidelines, including patients reporting 0 days of exercise per week.

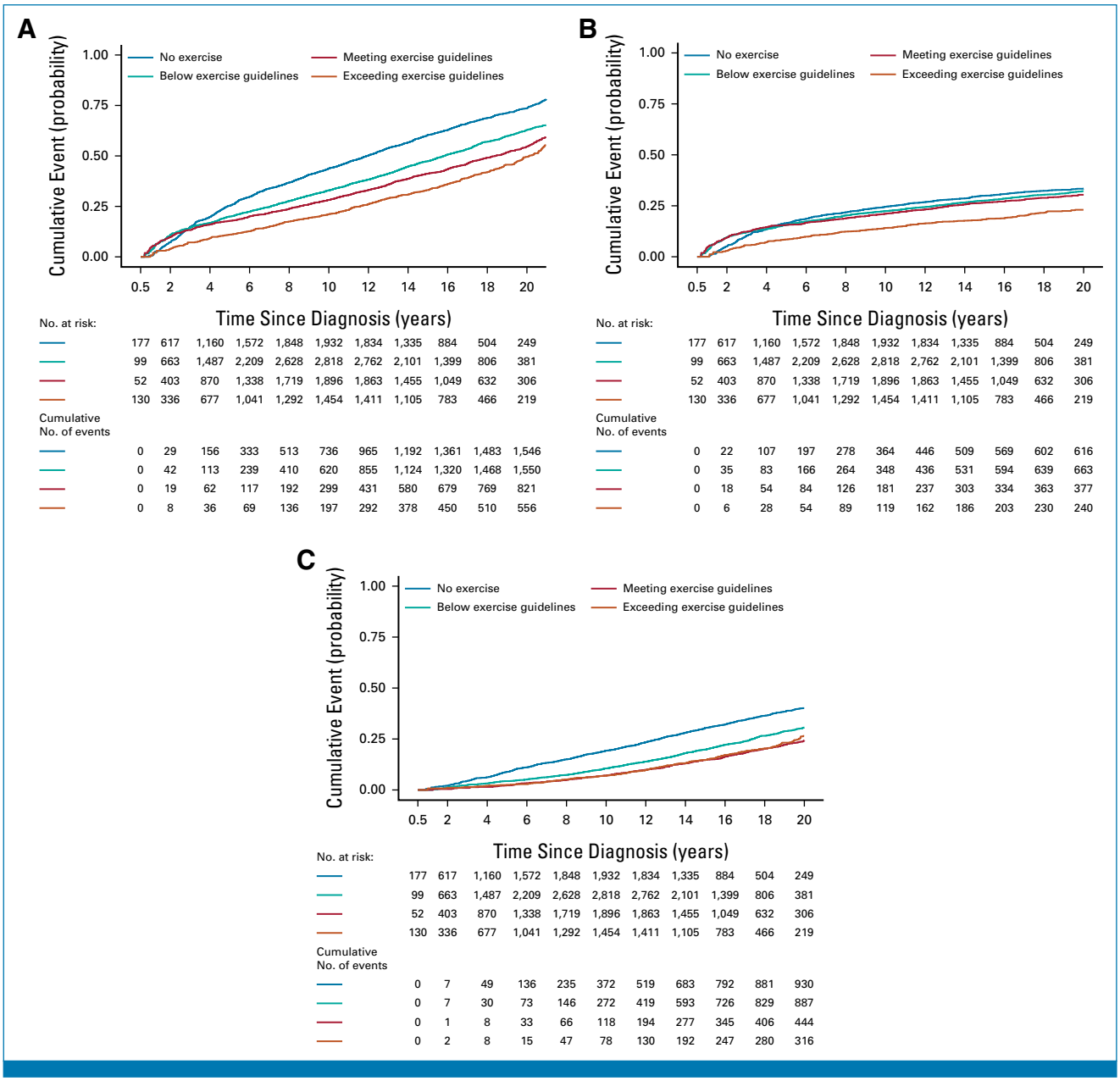

FIG 2. Cumulative incidence for (A) all-cause mortality, (B) cancer mortality, and (C) mortality from other causes by exercise dose. The *x*-axis indicates years from diagnosis and begins at 0.5 years to reflect the landmark time.

DISCUSSION

The findings of this study corroborate previous work investigating the relationship of postdiagnosis exercise and cause-specific mortality in cancer survivors. For example, a pooled analysis of six prospective pan-cancer studies (representing 22,511 survivors) found the highest level of exercise associated with a significant reduction in ACM compared with low exercise.[9] In the same review, pooled analysis of four pan-cancer prospective studies found high exercise also associated with a significant reduction in cancer mortality.[9] Dose-response analysis was not performed nor was analysis of noncancer deaths because of the small number of studies reporting such events. However, evidence from pooled analyses has important limitations. We leveraged the PLCO screening trial data to overcome these challenges: in addition to the large sample size, long follow-up, and resulting high event rate, uniform assessment and classification of exercise exposure together with rigorous ascertainment and adjudication of mortality attribution permits rigorous examination of the postdiagnosis exercise-mortality relationship in cancer survivors, thereby significantly extending the current evidence base.

A strength of the PLCO screening trial data set was adequate representation of patients across different cancer sites, permitting investigation of the clinically important question of whether exercise benefit on mortality differs as a function

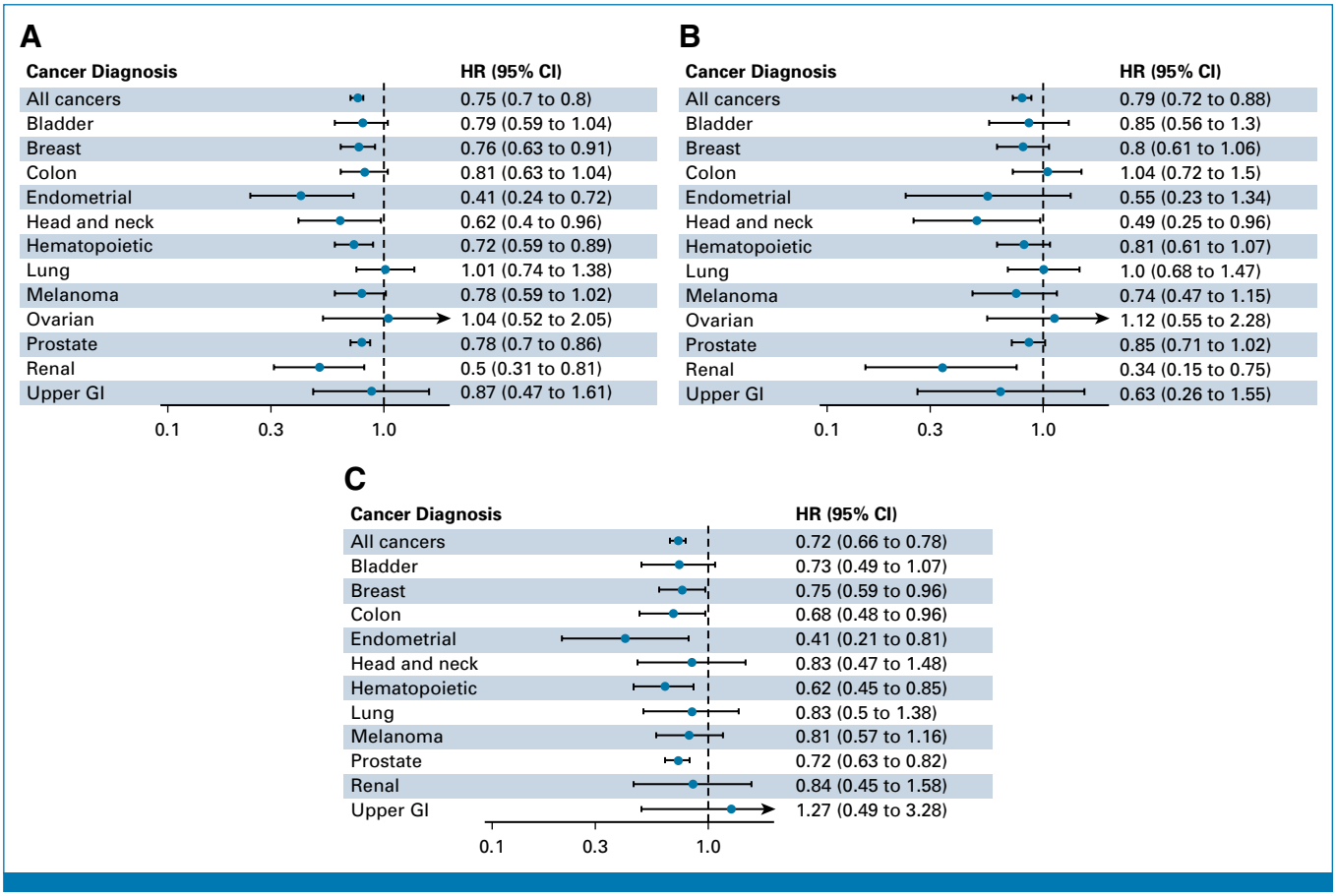

FIG 3. HRs for (A) all-cause mortality, (B) cancer mortality, and (C) mortality from other causes for all cancers and by cancer site. HR, hazard ratio.

of cancer site. The present findings indicate that exercise consistent with national guidelines associates with near-universal ACM benefit for most cancers included, although the cause-specific mortality events contributing to this benefit appeared cancer site–specific. For instance, in renal cancer, ACM benefit was driven by reductions in cancer mortality, whereas in bladder, colon, endometrial, and hematopoietic cancers, the potential reduction appeared driven by reduction in death from other causes. In breast, prostate, and melanoma cancers, ACM benefit was derived from reductions in both cancer mortality and other causes. It is important to interpret these findings within the context of the selected PLCO cohort, which was restricted to patients alive for a median time of 4.5 years after initial diagnosis. Thus, the generalizability of our findings is likely restricted to patients diagnosed with less-aggressive tumors at lower risk of disease recurrence and/or cancer mortality and, consequently, with sufficient longevity to be at higher risk of other causes of mortality (eg, CVD).

The observed variability in the postdiagnosis exercise-cancer mortality relationship across cancer sites is worth considering in this context. Most studies investigating this question have been conducted in breast cancer,[29-31] with fewer in prostate[32,33] and colorectal cancer.[34,35] Systematic reviews indicate postdiagnosis exercise (highest *v* lowest exercise) associates with significant reductions in cancer mortality risk, even after adjustment for important clinical covariates[9-11]—findings not replicated in our analysis, at least for these three cancers. Differences in sample attributable mortality risk might contribute to the discrepant findings, given our sample consisted of long-term survivors at high risk of noncancer mortality, thereby reducing the number cancer-specific events. Interestingly, we observed a significant univariable inverse relationship between exercise at recommended levels and cancer mortality for breast and prostate cancer, as well as for melanoma—all became nonsignificant in adjusted models, suggesting that the multivariable models accounted for observed confounding. Nonetheless, to our knowledge, our study is the first to show exercise at recommended levels lowers the risk of cancer death in head and neck cancer and renal cancer (when unadjusted for treatment), and the first to examine, and reveal no association, between exercise and cancer mortality in lung, upper GI, melanoma, ovarian, bladder, endometrial, and hematopoietic cancers. Overall, characterizing and understanding the variability in tumor response to exercise both across and within cancer sites will be a critical and exciting area of future work in exercise oncology.[36]

Limitations of our study require consideration. Self-reported assessment of exercise has well-known limitations, and therefore, some misclassification of exercise exposure is

TABLE 3. Multivariable HRs for Exercise and Cause-Specific Mortality

	All-Cause Mortality			Cancer-Specific Mortality			Noncancer Mortality		
Site	No.	No. of Events	Multivariable HR (95% CI)	No.	No. of Events	Multivariable HR (95% CI)	No.	No. of Events	Multivariable HR (95% CI)
All cancers	10,852	4,397	0.75 (0.70 to 0.80)	10,896	1,851	0.79 (0.72 to 0.88)	10,852	2,552	0.72 (0.66 to 0.78)
Bladder	520	241	0.79 (0.59 to 1.04)	524	104	0.85 (0.56 to 1.30)	519	137	0.73 (0.49 to 1.07)
Breast	2,159	607	0.76 (0.63 to 0.91)	2,199	250	0.80 (0.61 to 1.06)	2,159	365	0.75 (0.59 to 0.96)
Colon	809	351	0.81 (0.63 to 1.04)	827	146	1.04 (0.72 to 1.50)	817	210	0.68 (0.48 to 0.96)
Endometrial	361	95	0.41 (0.24 to 0.72)	365	31	0.55 (0.23 to 1.34)	361	65	0.41 (0.21 to 0.81)
Head and neck	196	117	0.62 (0.40 to 0.96)	196	51	0.49 (0.25 to 0.96)	196	66	0.83 (0.47 to 1.48)
Hematopoietic	818	458	0.72 (0.59 to 0.89)	818	241	0.81 (0.61 to 1.07)	826	217	0.62 (0.45 to 0.85)
Lung	361	245	1.01 (0.74 to 1.38)	362	147	1.00 (0.68 to 1.47)	369	101	0.83 (0.50 to 1.38)
Melanoma	744	241	0.78 (0.59 to 1.02)	745	90	0.74 (0.47 to 1.15)	741	151	0.81 (0.57 to 1.16)
Ovarian[a]	109	56	1.04 (0.52 to 2.05)	111	47	1.12 (0.55 to 2.28)	—	—	—
Prostate	3,980	1,590	0.78 (0.70 to 0.86)	4,055	556	0.85 (0.71 to 1.02)	4,035	1,052	0.72 (0.63 to 0.82)
Renal	234	125	0.50 (0.31 to 0.81)	234	56	0.34 (0.15 to 0.75)	234	69	0.84 (0.45 to 1.58)
Upper GI	92	59	0.87 (0.47 to 1.61)	92	28	0.63 (0.26 to 1.55)	92	31	1.27 (0.49 to 3.28)

NOTE. No. and No. of events shown are based on the multivariable models. Covariates included in each multivariable model are shown in Appendix Table A3.
Abbreviation: HR, hazard ratio.
[a]There were only nine noncancer deaths among patients with ovarian cancer; the noncancer mortality model could not be fit for this outcome.

expected. Generalizability of our findings are limited since our analyses were restricted to a selective sample of primarily non-Hispanic White, long-term survivors with a distribution of cancer sites not representative of general US survivor population,[37] which introduces selection bias. Furthermore, our sample consisted of survivors who were alive and willing to complete the SQX after initial cancer diagnosis and therefore perhaps more motivated to engage in heathy lifestyle behaviors.

Relatedly, it is not possible to delineate whether exercise simply reflects lower disease and/or treatment-related toxicities, as opposed to direct exercise-induced effects or better adherence to a healthier lifestyle (ie, residual confounding). We adjusted all analyses for available important clinical covariates and conducted a sensitivity analysis excluding all patients dying within 2 years of SQX completion; however, the contribution of unmeasured confounding, including diet and alcohol habits, cannot be disregarded, and only data from randomized controlled trials can definitively prove causality. Given the survey instrument used to evaluate exercise exposure and cross-sectional design, it is not known how long an individual had been exercising (or not) at the time of survey completion or whether exercise was continued after survey completion. Longitudinal studies, preferably using wearable devices to objectively assess exercise and physical activity, are required to address this important question. Because of the definitions and scope of exercise exposure used in this study, total physical activity (ie, occupational plus nonoccupational) or specific components of exercise such as intensity or duration were not investigated. These will be important analyses for future studies. Finally, information on primary cancer treatment was only available for PLCO cancers.

In summary, our findings show exercise is a holistic strategy that may complement contemporary management approaches to further reduce cancer mortality (in select sites) while simultaneously lowering risk of death from other competing causes, which combine to improve ACM. This benefit was observed within a few years after diagnosis and sustained for at least 20 years but was not dose-dependent. The cancer mortality impact of exercise differed by cancer site and requires further investigation.

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Pan-Cancer Analysis of Postdiagnosis Exercise and Mortality

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APPENDIX

TABLE A1. Characteristics for Patients Included in Analysis Versus Excluded From Analysis

Characteristic	Included in Analysis (N = 11,480)	Excluded From Analysis (N = 28,646)
Cancer type, No. (%)		
Biliary	12 (0.1)	204 (0.7)
Bladder	535 (4.7)	1,516 (5.3)
Breast	2,276 (20)	3,622 (13)
Colon	872 (7.6)	1,896 (6.6)
Endometrial	374 (3.3)	593 (2.1)
Glioma	12 (0.1)	383 (1.3)
Head and neck	204 (1.8)	661 (2.3)
Hematopoietic	855 (7.4)	3,213 (11)
Liver	9 (<0.1)	308 (1.1)
Lung	391 (3.4)	3,983 (14)
Male breast	14 (0.1)	31 (0.1)
Melanoma	773 (6.7)	1,685 (5.9)
Ovarian	112 (1.0)	508 (1.8)
Pancreatic	36 (0.3)	979 (3.4)
Prostate	4,261 (37)	5,905 (21)
Renal	240 (2.1)	733 (2.6)
Thyroid	106 (0.9)	225 (0.8)
Upper GI	94 (0.8)	749 (2.6)
Other cancer site	304 (2.6)	1,452 (5.1)
Diagnosis, years, age, median (IQR)	68 (64-72)	73 (68-78)
Survey completion, age, years, median (IQR)	73 (68-77)	71 (67-76)
Unknown	0	14,169
SQX survey timing, No. (%)		
No SQX available	0 (0)	14,169 (49)
Survey after cancer diagnosis	11,480 (100)	797 (2.8)
Survey before cancer diagnosis	0 (0)	13,680 (48)
Cancer stage, No. (%)		
In situ	926 (8.1)	1,813 (6.3)
Localized	6,738 (59)	10,973 (38)
Regional	1,463 (13)	4,113 (14)
Distant	464 (4.0)	5,185 (18)
Unknown	1,889 (16)	6,562 (23)
Sex, No. (%)		
Female	4,567 (40)	11,525 (40)
Race/ethnicity, No. (%)		
Non-Hispanic White	10,461 (93)	24,336 (88)
Other	807 (7.2)	3,248 (12)
Unknown	212	1,062
Smoking, pack-years, median (IQR)	5 (0-34)	14 (0-43)
Unknown	327	1,430

(continued on following page)

TABLE A1. Characteristics for Patients Included in Analysis Versus Excluded From Analysis (continued)

Characteristic	Included in Analysis (N = 11,480)	Excluded From Analysis (N = 28,646)
BMI (kg/m^2), No. (%)		
0-18.5	55 (0.5)	199 (0.7)
18.5-25	3,716 (33)	8,635 (32)
25-30	4,998 (45)	11,945 (44)
>30	2,350 (21)	6,381 (23)
Unknown	361	1,486
Intervention arm, No. (%)		
Control	5,450 (47)	14,463 (50)
Intervention	6,030 (53)	14,183 (50)
Randomization year, No. (%)		
1993	62 (0.5)	144 (0.5)
1994	1,653 (14)	3,692 (13)
1995	2,248 (20)	5,207 (18)
1996	2,389 (21)	5,657 (20)
1997	1,821 (16)	4,452 (16)
1998	1,285 (11)	3,521 (12)
1999	1,302 (11)	3,662 (13)
2000	648 (5.6)	1,984 (6.9)
2001	72 (0.6)	327 (1.1)
History of cancer, No. (%)	492 (4.4)	1,389 (5.0)
Unknown	289	1,237
History of chronic conditions, No. (%)		
Arthritis, No. (%)	3,976 (36)	10,170 (37)
Unknown	211	1,050
Chronic bronchitis, No. (%)	449 (4.0)	1,350 (4.9)
Unknown	287	1,248
Colon-related comorbidity, No. (%)	148 (1.3)	390 (1.4)
Unknown	313	1,349
Coronary heart disease or history of heart attack, No. (%)	916 (8.2)	2,813 (10)
Unknown	288	1,235
Diabetes, No. (%)	640 (5.7)	2,232 (8.1)
Unknown	282	1,237
Diverticulitis/diverticulosis, No. (%)	830 (7.4)	1,839 (6.7)
Unknown	286	1,284
Emphysema, No. (%)	249 (2.2)	936 (3.4)
Unknown	283	1,234
Gallbladder stones or inflammation, No. (%)	1,203 (11)	2,930 (11)
Unknown	289	1,269
Hypertension, No. (%)	3,636 (32)	9,514 (35)
Unknown	279	1,229
Liver-related comorbidity (hepatitis or cirrhosis), No. (%)	416 (3.7)	1,066 (3.9)
Unknown	294	1,273
Osteoporosis, No. (%)	422 (3.8)	1,166 (4.3)
Unknown	302	1,282
Stroke, No. (%)	205 (1.8)	670 (2.4)
Unknown	279	1,237

Abbreviation: SQX, supplemental questionnaire.

TABLE A2. Univariable and Multivariable HRs for Exercise Dose and Cause-Specific Mortality

	All-Cause Mortality		Cancer-Specific Mortality		Noncancer Mortality	
Exercise Classification[a]	Univariable HR (95% CI)	Multivariable HR (95% CI)	Univariable HR (95% CI)	Multivariable HR (95% CI)	Univariable HR (95% CI)	Multivariable HR (95% CI)
No exercise	Referent	Referent	Referent	Referent	Referent	Referent
Below exercise guidelines	0.68 (0.63 to 0.72)	0.75 (0.70 to 0.80)	0.75 (0.67 to 0.83)	0.81 (0.72 to 0.90)	0.63 (0.58 to 0.69)	0.71 (0.65 to 0.78)
Meeting exercise guidelines	0.54 (0.50 to 0.59)	0.65 (0.59 to 0.71)	0.65 (0.57 to 0.74)	0.75 (0.66 to 0.86)	0.47 (0.43 to 0.53)	0.58 (0.52 to 0.65)
Exceeding exercise guidelines	0.49 (0.44 to 0.53)	0.64 (0.58 to 0.71)	0.54 (0.47 to 0.63)	0.67 (0.58 to 0.78)	0.45 (0.40 to 0.51)	0.63 (0.55 to 0.72)

Abbreviation: HR, hazard ratio.

[a]No exercise (n = 3,111; 27%); below exercise guidelines (n = 3,995; 35%); meeting exercise guidelines (n = 2,515; 22%); exceeding exercise guidelines (n = 1,859; 16%).

TABLE A3. Covariates Included in Multivariable Models

Covariate	All Cancers	Bladder	Breast	Colon	Endometrial	Head and Neck	Hematopoietic	Lung	Melanoma	Ovarian[a]	Prostate	Renal	Upper GI
Cancer site	X	—	—	—	—	—	—	—	—	—	—	—	—
Time from diagnosis to SQX survey, years	X	X	X	X	X	X	X	X	X	X	X	X	X
PLCO randomization arm	X	X	X	X	X	X	X	X	X	X	X	X	X
SQX, age, years	X	ACM, NCM	X	ACM, NCM	ACM, NCM	ACM, NCM	X	ACM, NCM	X	X	X	ACM, NCM	ACM, NCM
PLCO randomization year	X	ACM, NCM	ACM, NCM	ACM, NCM	X	X	ACM, NCM	ACM, NCM	X	—	X	—	CSM, NCM
Sex	X	ACM, CSM	[b]	X	[b]	ACM, NCM	X	X	ACM, NCM	[b]	[b]	ACM, CSM	—
Race/ethnicity	X	—	—	NCM	ACM, CSM	NCM	ACM, NCM	ACM, NCM	—	—	—	—	CSM
Cancer stage	X	NCM	X	[b]	[b]	—	X	ACM[b]	ACM, CSM	ACM, CSM	X	ACM, CSM	[b]
Smoking, pack-years	X	X	X	X	ACM, NCM	X	X	X	X	—	X	ACM, NCM	—
BMI	X	—	ACM, NCM	ACM, NCM[b]	[b]	—	ACM, CSM	ACM, CSM	[b]	—	ACM	[b]	[b]
Treatment (only available for prostate, lung, colon, and ovarian)	—	—	—	ACM, CSM	—	—	—	ACM, CSM[b]	—	ACM	X	—	—
History of chronic conditions, No. (%)													
Arthritis	X	—	ACM, NCM	ACM, NCM	ACM, NCM	—	—	ACM, NCM	NCM	—	X	ACM, NCM	ACM, NCM
Chronic bronchitis	ACM, NCM	—	ACM, NCM	—	—	—	NCM	NCM	ACM, NCM	—	ACM, NCM	ACM, NCM	—
Colon-related comorbidity	—	—	—	—	—	[b]	—	X	—	—	—	ACM[b]	—
Coronary heart disease or history of heart attack	X	ACM, NCM	ACM, NCM	ACM, NCM	X	ACM, NCM	ACM, NCM	X	X	ACM	ACM, NCM	X	—
Diabetes	X	ACM, NCM	ACM, NCM	X	X	NCM	ACM, NCM	X	ACM, NCM	—	X	ACM, NCM	ACM, NCM
Diverticulitis/diverticulosis	ACM, NCM	ACM, NCM	ACM, NCM	NCM	ACM, NCM	—	—	—	ACM, CSM	ACM, CSM	ACM, NCM	CSM, NCM	[b]
Emphysema	X	ACM, NCM	X	CSM	—	ACM, NCM	ACM, NCM	ACM, CSM	NCM	—	ACM, NCM	—	—
Gallbladder stones or inflammation	X	—	X	NCM	X	—	—	—	—	ACM, CSM	X	CSM, NCM	—
Hypertension	ACM, NCM	ACM, NCM	X	X	ACM, NCM	ACM, NCM	ACM, NCM	NCM	ACM, NCM	ACM	ACM, NCM	X	—
Liver-related comorbidity (hepatitis or cirrhosis)	—	—	—	—	NCM[b]	—	—	ACM, NCM	—	[b]	—	ACM, NCM	NCM[b]
Osteoporosis	ACM, NCM	NCM	ACM, NCM	—	—	—	CSM	—	NCM	—	X	—	[b]
Stroke	X	—	ACM, CSM	X	ACM, NCM[b]	—	NCM	X	ACM, NCM	—	ACM, NCM	—	[b]

Abbreviations: ACM, all-cause mortality; CSM, cause-specific mortality; NCM, noncancer mortality; PLCO, Prostate, Lung, Colorectal, and Ovarian; SQX, supplemental questionnaire; X, adjusted for covariate in all three outcome models.

[a]There were only nine noncancer deaths among patients with ovarian cancer; the noncancer mortality model could not be fit for this cancer site.

[b]Univariable analyses did not converge; variable could not be considered for inclusion in one or more multivariable models for ACM, CSM, and NCM.

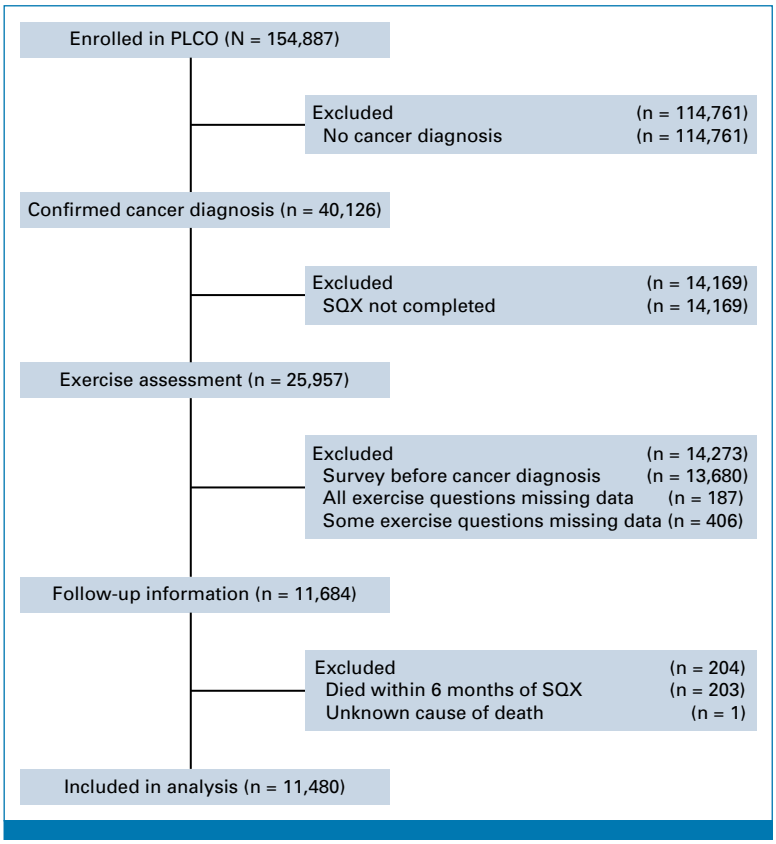

FIG A1. Flow diagram. PLCO, Prostate, Lung, Colorectal, and Ovarian; SQX, supplemental questionnaire.