Amount and Intensity of Leisure-Time Physical Activity and Lower Cancer Risk

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PURPOSE To determine whether recommended amounts of leisure-time physical activity (ie, 7.5-15 metabolic equivalent task [MET] hours/week) are associated with lower cancer risk, describe the shape of the dose-response relationship, and explore associations with moderate- and vigorous-intensity physical activity.

METHODS Data from 9 prospective cohorts with self-reported leisure-time physical activity and follow-up for cancer incidence were pooled. Multivariable Cox regression was used to estimate adjusted hazard ratios (HRs) and 95% CIs of the relationships between physical activity with incidence of 15 types of cancer. Dose-response relationships were modeled with restricted cubic spline functions that compared 7.5, 15.0, 22.5, and 30.0 MET hours/week to no leisure-time physical activity, and statistically significant associations were determined using tests for trend ($P < .05$) and 95% CIs (< 1.0).

RESULTS A total of 755,459 participants (median age, 62 years [range, 32-91 years]; 53% female) were followed for 10.1 years, and 50,620 incident cancers accrued. Engagement in recommended amounts of activity (7.5-15 MET hours/week) was associated with a statistically significant lower risk of 7 of the 15 cancer types studied, including colon (8%-14% lower risk in men), breast (6%-10% lower risk), endometrial (10%-18% lower risk), kidney (11%-17% lower risk), myeloma (14%-19% lower risk), liver (18%-27% lower risk), and non-Hodgkin lymphoma (11%-18% lower risk in women). The dose response was linear in shape for half of the associations and nonlinear for the others. Results for moderate- and vigorous-intensity leisure-time physical activity were mixed. Adjustment for body mass index eliminated the association with endometrial cancer but had limited effect on other cancer types.

CONCLUSION Health care providers, fitness professionals, and public health practitioners should encourage adults to adopt and maintain physical activity at recommended levels to lower risks of multiple cancers.

INTRODUCTION

In the United States, 1.7 million individuals are diagnosed with invasive cancer and > 600,000 people die as a result of malignant diseases annually,[1] which highlights the importance of cancer prevention. We have long known that physical activity is associated with a lower risk of colon and breast cancer,[2] but the 2018 US Physical Activity Guidelines Advisory Committee found strong evidence that physical activity is associated with a lower risk of several additional cancer sites, including endometrial, bladder, esophageal adenocarcinoma, kidney, and gastric.[3] Furthermore, our analysis of 1.44 million adults suggested that leisure-time physical activity is associated with a lower risk for as many as 13 cancer types.[4] Given this evidence, physical activity will play an increasingly important role in population-based cancer prevention efforts.

However, our understanding of the shape of the relation between physical activity and cancer risk and whether recommended amounts of physical activity (eg, 2.5-5 hours/week of moderate-intensity activity[5,6] or 7.5-15 metabolic equivalent task [MET] hours/week[5]) are associated with lower risk is still limited. Recent comprehensive reviews of physical activity and cancer[3,7] have been unable to determine whether engagement in recommended amounts of physical activity is associated with significantly lower cancer risk because of heterogeneity in activity measurements and analytic methods used in available studies. Similar issues complicate our understanding of whether the intensity of physical activity is relevant to cancer risk. An understanding of the amount and intensity of physical activity associated with reduced risk is essential for application of evidence-based recommendations for cancer prevention. Therefore, the goal of

this study was to quantify the leisure-time physical activity-cancer dose-response relationship. Specifically, we extend analyses from our pooled data to provide results applicable to clinical and public health practice by determining whether recommended amounts of leisure-time physical activity (7.5-15 MET hours/week) are associated with significantly lower cancer risk, describing the shapes of the physical activity-cancer dose-response relationships, and exploring whether the same amount of moderate- and vigorous-intensity leisure-time physical activity confers similar cancer risk reduction.

METHODS

Study Population

We examined 5 US cohorts, 3 European cohorts, and 1 Australian cohort.[8-16] Eight cohorts were included in our prior analysis,[4] and the Melbourne Collaborative Cohort Study[15] was added. Studies eligible for this analysis assessed leisure-time physical activity in sufficient detail to estimate energy cost (MET hours/week) and had necessary covariate data (Data Supplement, online only). Studies were approved by the institutional review board of host institutions, and participants provided informed or implied consent. For a detailed description of dose-response relationships, we focused on 15 cancers that we previously found to be associated with physical activity ($P < .05$) or associations with borderline significance ($P = .05$ or .06).[4] We did not examine lung cancer because of probable residual confounding by smoking.[4,7]

Measurement of Physical Activity

Leisure-time physical activities encompass discretionary exercise, sports, and recreational pursuits, typically of a moderate to vigorous intensity, and done to maintain fitness or health.[17] We focused only on leisure-time activities to minimize heterogeneity between studies and to enhance translation of our findings. A detailed description of the measures used is listed in the Data Supplement. Measurements of leisure-time physical activity have contributed valuable insight into the physical activity-mortality dose-response relationship[18] and revealed associations with cancer (eg, see Friberg et al[13], Howard et al[19]), and instruments like the ones we used have demonstrated validity.[20] We focused on the energy cost or total volume of leisure-time physical activity (MET hours/week) and the volume of both moderate-intensity (3-5.9 METs) and vigorous-intensity (≥ 6 METs) activity.

Covariate Assessment

We included covariates that are major predictors of cancer risk on the basis of previous studies,[4,21] although we acknowledge that this list is not exhaustive. Covariates were harmonized as follows: age, race (black, white, other), education (less than high school, high school graduate, post–high school training, some college, college degree or greater, missing), smoking status (never, former, current,

missing), personal history of cancer (yes, no/missing) or heart disease (yes, no/missing), marital status (married, divorced, widowed, unmarried, missing), body mass index (BMI; < 20, 20-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30-32.4, 32.5-34.9, 35.0-37.4, ≥ 37.5 kg/m^2, missing <15 or >60 kg/m^2), and alcohol consumption (0, 0.1-14.9, 15.0-29.9, and ≥ 30.0 g/d). Hormonal and reproductive factors were harmonized as follows: postmenopausal hormone therapy use (ever, never), oral contraceptives (ever, never), age at menarche (< 10, 10-11, 12-13, ≥ 14 years), age at menopause (premenopausal, 40-44, 45-49, 50-54, $\geq$ 55 years), and parity (0, 1, 2, ≥ 3 children).

Incident Cancer Ascertainment

We used the SEER site recode and the International Classification of Diseases for Oncology, Third Edition,[22] to classify each cancer (Data Supplement). Incident first primary malignancies were identified in the following ways: follow-up questionnaires and confirmed by medical record review of radiation-related cancers[16] or all cancers,[23,24] cancer and death registry linkages,[11-13,15,25] or both.[24,26] Follow-up time was calculated from the date of the physical activity assessment to the date of cancer diagnosis, death, or the end of follow-up within each study, whichever came first. Numbers of participants with cancer for each site by activity levels are listed in the Data Supplement.

Statistical Analysis

Cox proportional hazards regression models with stratification by study were used to calculate covariate-adjusted hazard ratios (HRs) and 95% CIs for physical activity and each cancer outcome. For endometrial cancer, women who reported a hysterectomy were excluded. Our primary analysis was based on restricted cubic splines to facilitate detailed description of the dose-response curves.[27,28] Using splines, we estimated HRs and 95% CIs for specific MET hours/week values and described the shape of the overall dose-response and tested for linear and nonlinear shapes of each association. Splines used 3 knots distributed across the range of physical activity,[28] and the range was capped at 35 MET hours/week (approximately 95th percentile) to minimize the influence of sparse data. We used 7.5-15 MET hours/week to estimate recommended activity levels (eg, moderate-intensity activity [3 METs] $\times$ 2.5 hours/week = 7.5 MET hours/week).[5] Statistical significance of the overall association and for nonlinearity of the risk curves was evaluated with likelihood ratio tests.[27,29] We evaluated the role of BMI by fitting models with and without BMI and tested for interactions by sex using cross-product terms. All studies contributed to the overall leisure-time physical activity results, while 5 studies contributed to the analysis of physical activity intensity.[9-11,15,16] Evaluation of moderate- and vigorous-intensity activity entailed the fitting of models with and without adjustment for each.

In sensitivity analyses, we examined results after excluding the first 2 years of follow-up and modeled associations

TABLE 1. Participant Characteristics by Level of Leisure-Time Physical Activity

Characteristic	Leisure-Time Physical Activity Level (MET hours/week), %				
	Ref[a]	Ref-7.4	7.5-14.9	15-29.9	≥ 30
No. of participants	104,841	157,713	200,518	179,631	112,756
Age, years	60.8	59.8	60.8	61.2	61.1
Sex					
Male	50	40	46	49	50
Female	50	60	54	51	50
Education					
College/graduate degree	28	34	38	38	39
Race					
White	94	95	95	95	95
Smoking					
Never	38	46	44	43	41
Former	42	40	43	45	47
Current	19	13	11	10	9
Alcohol, g/d					
0	28	27	23	21	23
> 0	69	69	75	76	75
Body mass index, kg/m²					
< 18.5	1	1	1	1	1
18.5-24.9	31	37	40	44	46
25-29.9	38	39	40	39	39
30-34.9	18	15	13	11	10
≥ 35	10	6	4	3	3
Age at menarche, years[b]					
< 10	4	2	3	3	4
10-11	27	21	25	26	30
12-13	48	53	51	51	48
14-15	17	19	18	17	15
≥ 16	3	3	3	3	2
Age at menopause, years[b]					
Premenopausal	21	30	23	26	29
< 40	12	9	10	10	12
40-44	11	9	105	10	11
45-49	20	18	19	18	18
50-54	28	26	29	28	23
≥ 55	6	6	7	6	6
Parity[b]					
0	14	12	12	13	13
1	12	10	10	10	10
2	29	31	31	31	29
3-4	34	36	36	36	37
≥ 5	10	10	9	9	9

TABLE 1. Participant Characteristics by Level of Leisure-Time Physical Activity (continued)

Characteristic	Leisure-Time Physical Activity Level (MET hours/week), %				
	Ref[a]	Ref-7.4	7.5-14.9	15-29.9	≥ 30
Postmenopausal hormones[b]					
Ever	47	50	51	51	49
Oral contraceptive use[b]					
Ever	51	56	53	53	51

Abbreviations: MET, metabolic equivalent task; Ref, reference.

[a]Ref = 0 MET hours/week for all cohorts, except SMC and COSM, where the lowest response option was assigned as the reference (< 0.5 hours/week [1.2 MET hours/week]).

[b]Females only.

using 5 physical activity categories (reference, < 7.5, 7.5-14.9, 15.0-29.9, and ≥ 30.0 MET hours/week), with cohort- and cancer site–specific results summarized using random-effects meta-analysis.[30] Analyses were performed using SAS 9.4 statistical software (SAS Institute, Cary, NC). Statistical tests were 2-sided using the 5% level of significance, which corresponds to 95% CIs for the HR not covering the value 1.

RESULTS

We studied 755,459 individuals (53% female) with leisure-time physical activity measures who had no history of cancer at the start of follow-up. Participant characteristics by leisure-time physical activity are listed in Table 1. There was broad consistency in reported amounts of leisure-time physical activity among cohorts, with 7 of the 9 cohorts having a median value between 7.6 and 8.0 MET hours/week (Data Supplement). Cancers with strong evidence of association per the US Physical Activity Guidelines Advisory Committee[3] were grouped separately to highlight results for these malignancies.

Associations for Overall Leisure-Time Physical Activity

Higher levels of physical activity were statistically significantly associated ($P_{overall}$ < .05) with lower risk for breast, colon, endometrial, and kidney cancer and esophageal adenocarcinoma (Fig 1A) and head and neck and liver cancer (Fig 1B). Associations for gastric cardia (Fig 1A) and myeloma (Fig 1B) were of borderline significance (P = .05). Evaluation of statistical interaction by sex revealed 2 interactions (both $P_{interaction}$ ≤ .01): The associations with colon cancer was evident in men (HR, 0.81; 95% CI, 0.74 to 0.89; 15 v 0 MET hours/week) but attenuated in women (HR, 0.94; 95% CI, 0.85 to 1.04) and for non-Hodgkin lymphoma in women (HR, 0.82; 95% CI, 0.74 to 0.94) but not in men (HR, 1.00; 95% CI, 0.88 to 1.14; Table 2). Adjustment for BMI resulted in complete attenuation of the endometrial cancer association and in an increase in the HR comparing 15-0 MET hours/week from 0.82 (95% CI, 0.74 to 0.92) to 1.02 (95% CI, 0.91 to 1.14; Data Supplement) but more modest attenuations of only 8% for

kidney (from 0.83 [95% CI, 0.74 to 0.94] to 0.90 [95% CI, 0.80 to 1.01]) and liver (from 0.73 [95% CI, 0.59 to 0.92] to 0.79 [95% CI, 0.64 to 0.99]) cancer. Associations with other sites were little changed.

Risk Reductions for Recommended Amounts of Physical Activity

Among cancers with strong prior evidence of association per the US Physical Activity Guidelines Advisory Committee,[3] engagement in 7.5-15 MET hours/week of leisure-time physical activity versus none was associated with a significantly reduced risk for breast, colon, endometrial, and kidney cancer as indicated by HRs and 95% CIs < 1 within this activity range (Fig 1A; Data Supplement). The strength of association within the recommended activity range varied from 6% to 10% lower for breast cancer (HR at 7.5 MET hours/week [$HR_{7.5}$], 0.94; HR at 15 MET hours/week [HR_{15}], 0.90) to 11%-17% lower risk for kidney cancer ($HR_{7.5}$, 0.89; HR_{15}, 0.83) compared with 0 MET hours/week. For other sites, 7.5-15 MET hours/week was associated with a significantly lower risk for myeloma (14%-19% lower risk), liver cancer (18%-27% lower risk; Fig 1B), and non-Hodgkin lymphoma in women (11%-18% lower risk; Table 2). Compared with doing none, engagement in recommended amounts of leisure-time physical activity was associated with a significantly lower risk for 7 cancer types.

Shape of Dose-Response Curves

Examination of the shape of the dose-response curves using statistical testing for nonlinearity and visual inspection revealed that half of the sites with significant overall associations were approximately linear. Specifically, linear associations—with graded reductions in risk with higher activity—were noted for breast, colon, and endometrial cancer and esophageal adenocarcinoma (Fig 1A) and head and neck cancer (Fig 1B). For these cancers, engagement in physical activity greater than the recommended levels was associated with additional risk reduction. In contrast, associations for kidney and gastric cancer (Fig 1A), liver cancer (Fig 1B), and non-Hodgkin lymphoma in women (Table 2) seemed to be curvilinear,
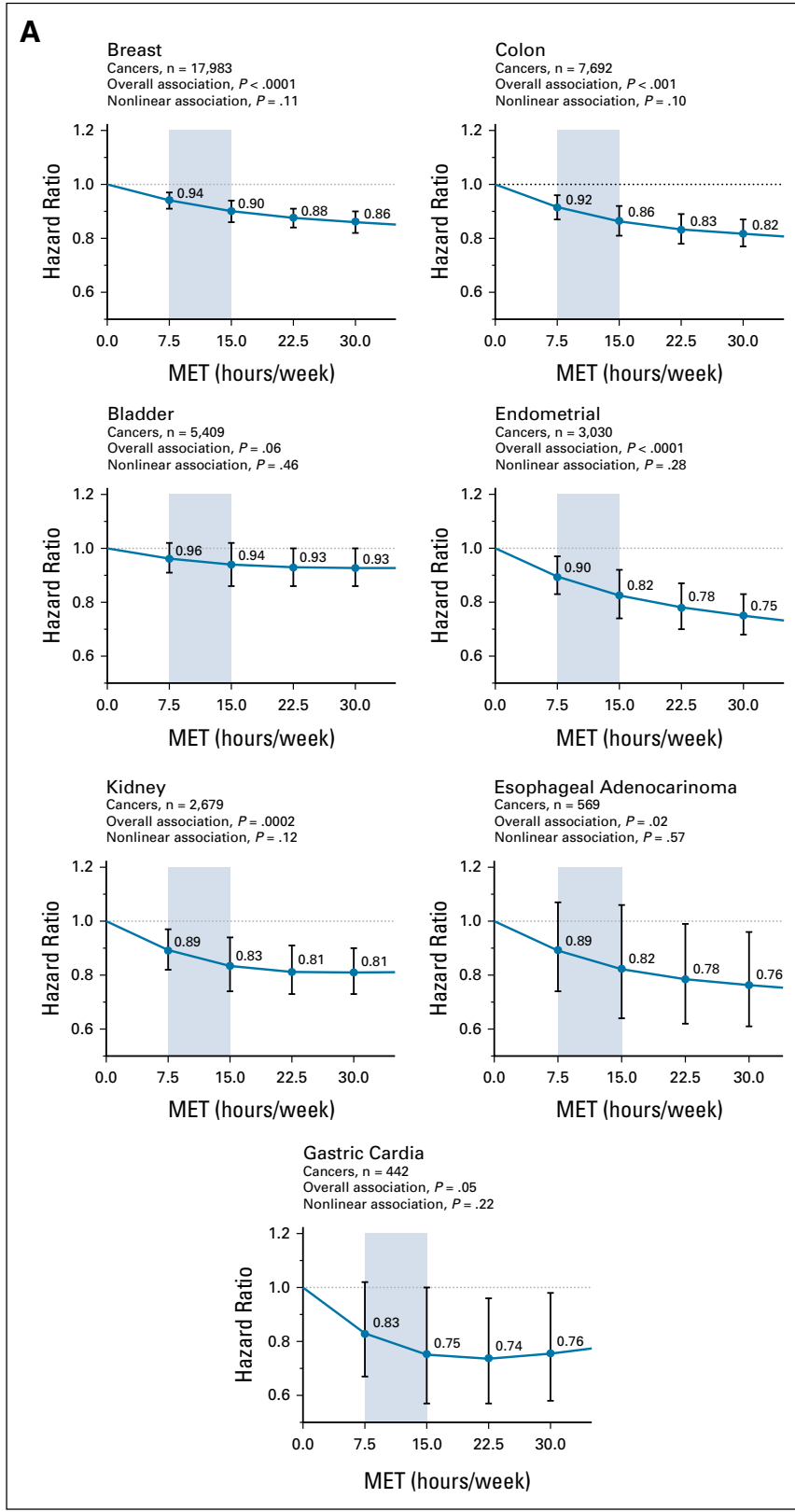
FIG 1. (A) Leisure-time physical activity (metabolic equivalent task [MET]–hours/week) and risk of cancer sites with strong evidence of association.
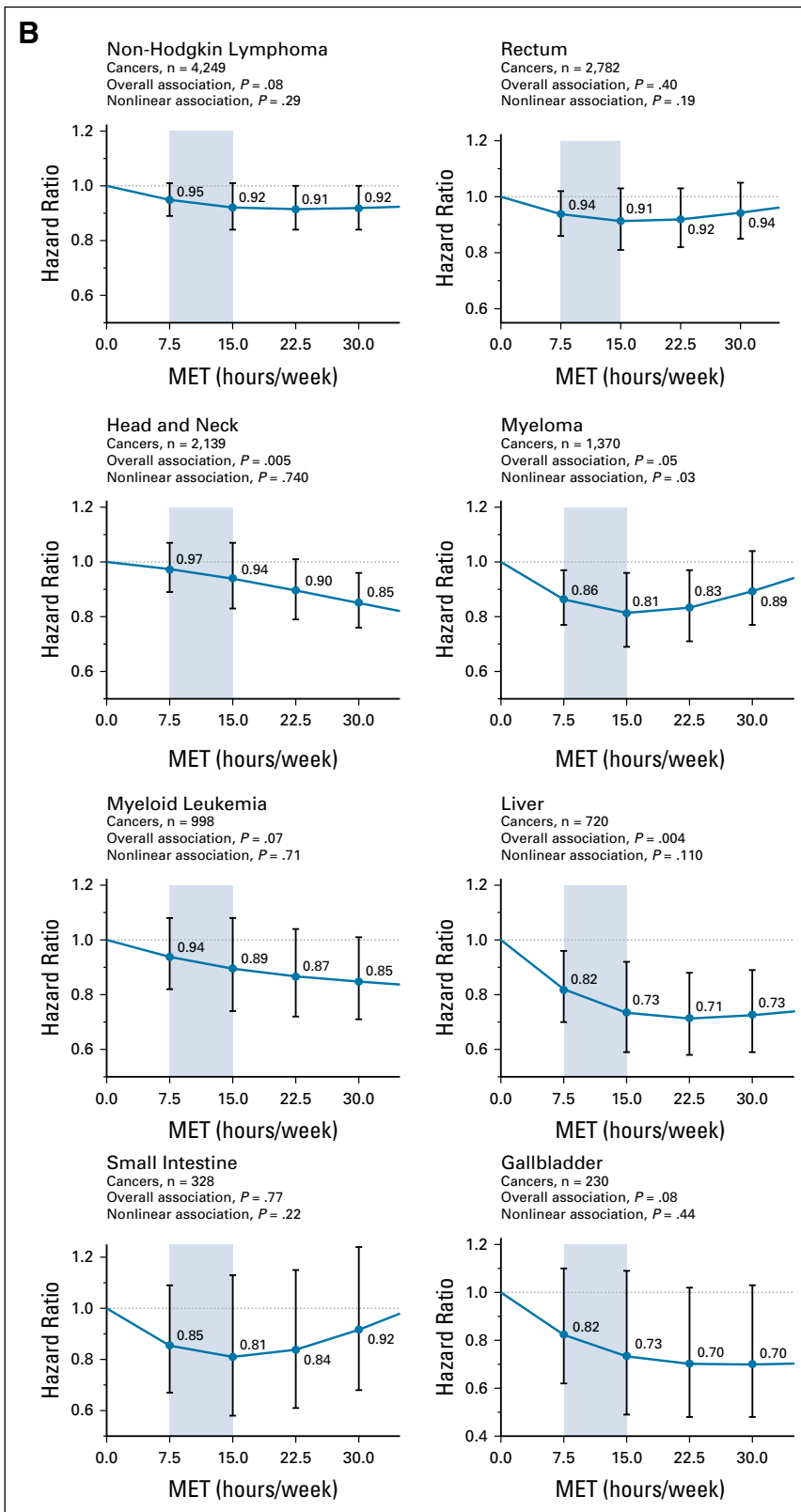
B

Non-Hodgkin Lymphoma
Cancers, n = 4,249
Overall association, *P* = .08
Nonlinear association, *P* = .29

Rectum
Cancers, n = 2,782
Overall association, *P* = .40
Nonlinear association, *P* = .19

Head and Neck
Cancers, n = 2,139
Overall association, *P* = .005
Nonlinear association, *P* = .740

Myeloma
Cancers, n = 1,370
Overall association, *P* = .05
Nonlinear association, *P* = .03

Myeloid Leukemia
Cancers, n = 998
Overall association, *P* = .07
Nonlinear association, *P* = .71

Liver
Cancers, n = 720
Overall association, *P* = .004
Nonlinear association, *P* = .110

Small Intestine
Cancers, n = 328
Overall association, *P* = .77
Nonlinear association, *P* = .22

Gallbladder
Cancers, n = 230
Overall association, *P* = .08
Nonlinear association, *P* = .44

FIG 1. (Continued). (B) Association between leisure-time physical activity (MET hours/week) and cancer sites with moderate or lower evidence of association. Analysis is adjusted for entry age, sex, race, education, smoking, and alcohol intake. For breast and endometrial cancer, we also adjusted for postmenopausal hormone treatment, age at menarche and menopause, parity, and oral contraceptive use. Restricted cubic splines were fit with 3 knots placed at the 5th, 50th, and 95th percentiles of physical activity. Shaded area indicates recommended amounts of physical activity. Cancer sites were judged as strong evidence of association by the 2018 US Physical Activity Guidelines Advisory Committee.[3]

TABLE 2. Associations Between Leisure-Time Physical Activity and Cancer, and Interactions by Sex

Cancer Site	No. of Cancers	Leisure-Time Physical Activity (MET hours/week), HR (95% CI)					$P_{overall}$	$P_{interaction}$
		0 (ref)	7.5	15	22.5	30		
Cancers with strong evidence[a]								
Colon								
Women	3,449	1	0.96 (0.89 to 1.03)	0.94 (0.85 to 1.04)	0.94 (0.85 to 1.04)	0.95 (0.86 to 1.04)	.37	< .01
Men	4,243	1	0.89 (0.83 to 0.95)	0.81 (0.74 to 0.89)	0.76 (0.70 to 0.83)	0.73 (0.67 to 0.79)	< .0001	
Bladder								
Women	1,029	1	1.10 (0.96 to 1.26)	1.11 (0.92 to 1.34)	1.04 (0.87 to 1.25)	0.93 (0.78 to 1.12)	.25	.56
Men	4,380	1	0.93 (0.87 to 1.00)	0.90 (0.82 to 0.99)	0.90 (0.83 to 0.99)	0.92 (0.85 to 1.00)	.12	
Kidney								
Women	905	1	0.79 (0.69 to 0.92)	0.71 (0.58 to 0.87)	0.71 (0.59 to 0.86)	0.76 (0.63 to 0.91)	.002	.44
Men	1,774	1	0.95 (0.86 to 1.05)	0.91 (0.79 to 1.05)	0.87 (0.76 to 1.00)	0.84 (0.74 to 0.96)	.01	
Esophageal adenocarcinoma								
Women	43	1	1.07 (0.55 to 2.09)	0.90 (0.37 to 2.23)	0.61 (0.26 to 1.44)	0.36 (0.14 to 0.96)	.02	.19
Men	526	1	0.88 (0.73 to 1.06)	0.81 (0.63 to 1.06)	0.80 (0.62 to 1.01)	0.80 (0.63 to 1.01)	.08	
Gastric (cardia)								
Women	60	1	1.39 (0.78 to 2.48)	1.45 (0.65 to 3.23)	1.16 (0.54 to 2.49)	0.80 (0.37 to 1.74)	.41	.85
Men	382	1	0.77 (0.61 to 0.96)	0.68 (0.50 to 0.92)	0.69 (0.52 to 0.91)	0.75 (0.57 to 0.99)	.04	
Cancers with moderate or lower evidence[b]								
Non-Hodgkin lymphoma								
Women	1,918	1	0.89 (0.80 to 0.98)	0.82 (0.72 to 0.94)	0.80 (0.70 to 0.91)	0.79 (0.70 to 0.90)	.001	.01
Men	2,331	1	1.00 (0.91 to 1.09)	1.00 (0.88 to 1.14)	1.02 (0.90 to 1.14)	1.03 (0.92 to 1.15)	.57	
Rectum								
Women	1,043	1	0.87 (0.76 to 1.00)	0.82 (0.68 to 0.99)	0.83 (0.69 to 0.99)	0.87 (0.73 to 1.03)	.21	.48
Men	1,739	1	0.99 (0.89 to 1.10)	0.98 (0.85 to 1.14)	0.98 (0.86 to 1.13)	0.99 (0.87 to 1.13)	.96	
Head and neck								
Women	584	1	1.04 (0.87 to 1.24)	1.02 (0.79 to 1.30)	0.94 (0.74 to 1.19)	0.85 (0.67 to 1.07)	.10	.80
Men	1,555	1	0.95 (0.85 to 1.06)	0.91 (0.78 to 1.06)	0.88 (0.77 to 1.02)	0.86 (0.75 to 0.98)	.03	
Myeloma								
Women	557	1	0.80 (0.66 to 0.96)	0.74 (0.58 to 0.96)	0.80 (0.62 to 1.02)	0.92 (0.73 to 1.16)	.05	.64
Men	813	1	0.91 (0.78 to 1.06)	0.87 (0.70 to 1.08)	0.86 (0.71 to 1.06)	0.88 (0.72 to 1.06)	.24	
Myeloid leukemia								
Women	379	1	0.85 (0.68 to 1.06)	0.77 (0.57 to 1.05)	0.75 (0.56 to 1.01)	0.75 (0.56 to 1.01)	.07	.32
Men	619	1	0.99 (0.83 to 1.18)	0.97 (0.76 to 1.24)	0.94 (0.75 to 1.18)	0.90 (0.72 to 1.13)	.34	
Liver								
Women	206	1	0.93 (0.69 to 1.26)	0.88 (0.58 to 1.34)	0.84 (0.56 to 1.24)	0.80 (0.54 to 1.19)	.28	.70
Men	514	1	0.78 (0.65 to 0.95)	0.69 (0.53 to 0.89)	0.67 (0.53 to 0.86)	0.70 (0.55 to 0.89)	.01	
Small intestine								
Women	150	1	0.76 (0.53 to 1.09)	0.70 (0.43 to 1.15)	0.75 (0.47 to 1.20)	0.89 (0.57 to 1.39)	.89	.88
Men	178	1	0.94 (0.68 to 1.32)	0.92 (0.58 to 1.46)	0.93 (0.60 to 1.43)	0.94 (0.62 to 1.43)	.83	

TABLE 2. Associations Between Leisure-Time Physical Activity and Cancer, and Interactions by Sex (continued)

Cancer Site	No. of Cancers	0 (ref)	7.5	15	22.5	30	$P_{overall}$	$P_{interaction}$
Gallbladder								
Women	150	1	0.72 (0.50 to 1.04)	0.64 (0.39 to 1.06)	0.68 (0.43 to 1.10)	0.81 (0.51 to 1.29)	.50	.29
Men	80	1	1.04 (0.64 to 1.70)	0.93 (0.48 to 1.83)	0.73 (0.39 to 1.38)	0.53 (0.27 to 1.05)	.05	

NOTE. Adjusted for entry age, race, education, smoking, and alcohol intake. Restricted cubic splines fit with 3 knots placed at the 5th, 50th, and 95th percentiles of physical activity were used to estimate the HRs and 95% CIs.

Abbreviations: HR, hazard ratio; MET, metabolic equivalent task; ref, reference.

[a]Cancer sites judged as strong evidence of association by the 2018 US Physical Activity Guidelines Advisory Committee.[3]

[b]Cancer sites judged as moderate or lower evidence of association by the 2018 US Physical Activity Guidelines Advisory Committee.[3]

with a plateau in risk reduction at higher levels of activity. For these cancers, engagement in more physical activity was associated with little, if any, additional risk reduction. Myeloma had a significant nonlinear association with lower risks in the recommended activity range but not at higher levels.

Moderate- and Vigorous-Intensity Physical Activity

In a subset of 5 cohorts that represented less than half of our total sample size (n = 309,881), we explored mutually adjusted associations for moderate- and vigorous-intensity physical activity among the 9 cancer types we found to be significantly associated with overall leisure-time physical activity. Although 95% CIs were often wide, we observed significant overall associations with breast and kidney cancer for moderate-intensity activity, while vigorous-intensity activity was significantly associated with endometrial cancer (Fig 2). Associations for colon cancer were of borderline significance for moderate-intensity ($P = .06$) and vigorous-intensity ($P = .10$) activity. There was evidence of nonlinear u-shaped associations with vigorous-intensity activity for colon and endometrial cancer such that the protective associations observed at intermediate activity levels were eroded at higher levels of activity (ie, 30 v 0 MET hours/week). For the other cancer sites, differences between moderate-intensity and vigorous-intensity physical activity were limited, and the 95% CIs were wide.

Sensitivity Analyses

Comparison of spline with meta-analytic results showed broadly similar findings for the overall shape and strength of association (Data Supplement). Exclusion of the first 2 years of follow-up revealed no substantive changes to our dose-response findings (Data Supplement).

DISCUSSION

This analysis of the dose-response relationship between leisure-time physical activity and cancer provides new insight into the amount of physical activity needed for a reduced risk of many cancer types—critical evidence for more precise cancer prevention messaging in the clinical and public health settings. In this pooled study of 750,000

adults, engagement in recommended amounts of leisure-time physical activity (7.5-15 MET hours/week), an equivalent of 2.5 to 5.0 hours/week of moderate-intensity activity (eg, brisk walking), was associated with significantly lower risk for breast, colon (men only), endometrial, kidney, myeloma, and liver cancer and non-Hodgkin lymphoma (women only). The strength of associations for recommended amounts of physical activity versus none ranged from a 6% to 10% lower risk for breast cancer to an 18% to 27% lower risk for liver cancer. The shape of the dose-response curves varied by cancer type. Both moderate- and vigorous-intensity activity seemed to be associated with lower risk for colon, breast, and kidney cancer, but the sample size for other cancer types was too limited to draw firm conclusions. Adjustment for BMI had a minimal impact on our results, except for endometrial cancer.

In the past decade, our knowledge of the number of cancers linked to physical activity has expanded substantially, but whether engagement in recommended amounts of leisure-time physical activity may lower risk for these cancers has remained unclear. In preparation for the second edition of the US Physical Activity Guidelines, an advisory committee conducted a comprehensive evaluation of > 40 systematic reviews and meta-analyses but concluded that "it was not possible to determine the exact levels of physical activity that provide a given level of effect"[3(pF4-56)] because of methodological diversity in the investigations examined. Using harmonized leisure-time physical activity data from 9 cohorts, we found that engagement in recommended amounts of physical activity was associated with significantly lower risk for 7 cancer types and that additional benefits beyond 15 MET hours/week varied by cancer type. Our findings provide robust quantitative evidence that supports the new US Physical Activity Guidelines[5] for cancer prevention as well as recommendations that have been promoted by the American Cancer Society,[6] World Cancer Research Fund International,[31] the International Agency for Research on Cancer,[32,33] and the American College of Sports Medicine.[7]

Our detailed examination of the physical activity-cancer dose-response relationship revealed 2 unique observations.
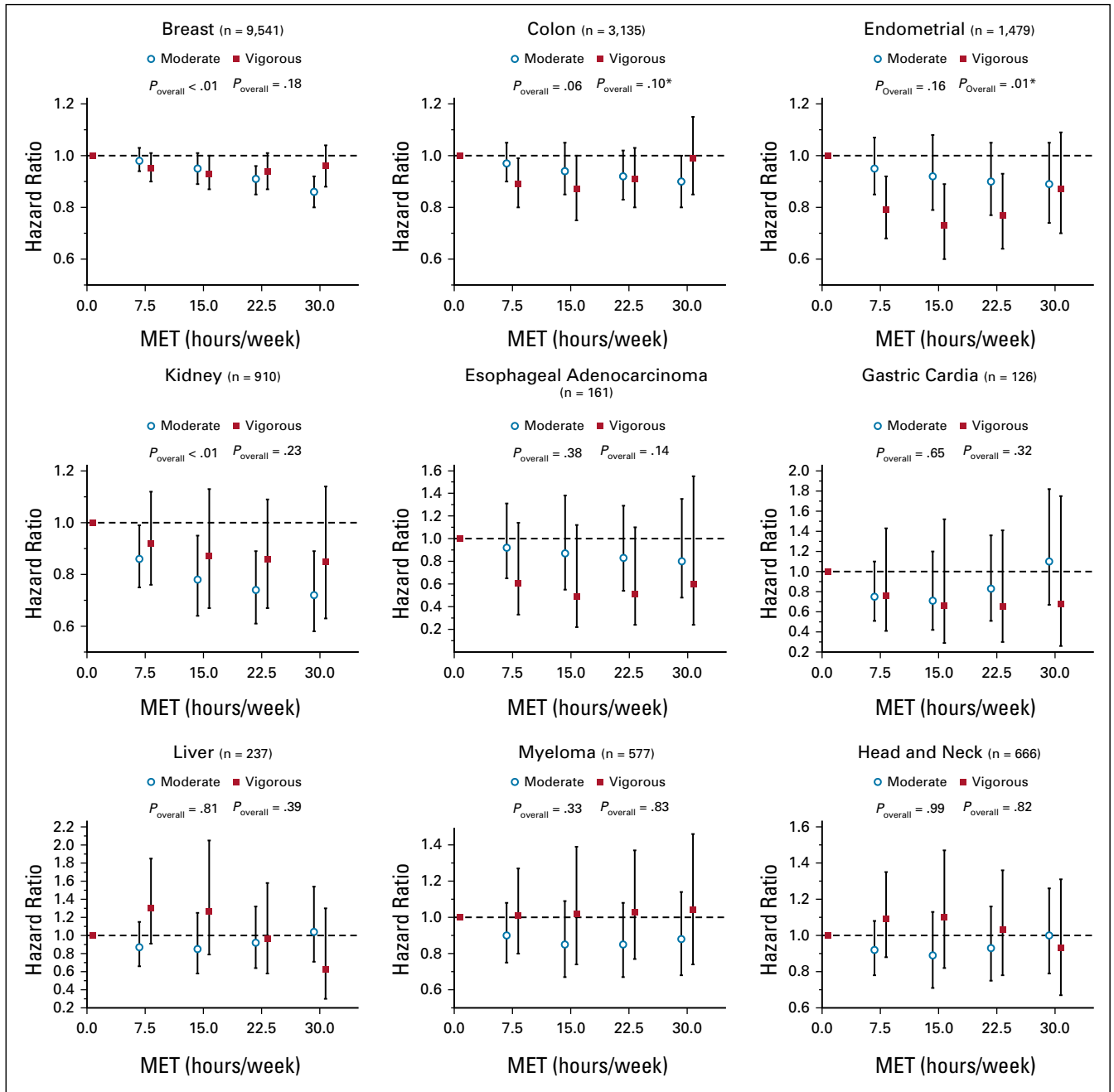
FIG 2. Mutually adjusted associations (hazard ratios with 95% CIs) between moderate- and vigorous-intensity activity and cancers with statistically significant associations with overall leisure-time physical activity. Analysis is adjusted for standard covariates and moderate- and vigorous-intensity activity as necessary. (*) $P < .05$, nonlinear association. n = number of participants with a given type of cancer.

First, in contrast to the archetypal curvilinear dose-response observed between physical activity and all-cause and cardiovascular mortality,[18,34] approximately half of the cancers associated with physical activity were found to have linear dose-response curves (ie, colon, breast, endometrial and head and neck cancer, esophageal adenocarcinoma), with the lowest risk at levels well above the recommended minimum level of activity. This finding may explain in part previous observations that higher levels of activity were needed to achieve significantly lower risk of colon and breast cancer.[35] Given these linear associations, substantially lower relative risk estimates may have only been observable at higher activity levels in previous studies, particularly given smaller participant numbers and more limited statistical power in individual studies. Of note, for several cancers with a curvilinear association in our data (eg, kidney, gastric, and liver cancer), most of the risk reduction observed was associated with recommended amounts of physical activity.

Second, we observed nearly a 3-fold difference in the strength of associations for engaging in 7.5-15 MET hours/week when comparing results for breast cancer (6%-10% lower risk) with liver cancer (18%-27% lower risk). This large difference in the shape and strength of association for the same dose of physical activity may reflect important differences in the underlying biologic mechanisms for distinct cancer types. For example, the primary mechanisms proposed to explain associations with breast cancer are circulating factors (eg, sex steroid hormones, insulin, inflammatory biomarkers) that may exert less-direct effects on breast tumorigenesis in response to exercise.[36] In contrast, in addition to these systemic effects, exercise exerts a direct effect on glucose, glycogen, and lipid metabolism in the liver[37] and may reduce risk of or reverse nonalcoholic fatty liver disease, an emergent risk factor for liver cancer.[38-40] Together, these findings suggest that there are fundamentally different physical activity dose-response relationships for all-cause and cardiovascular mortality and some cancers and substantial variation in the underlying biologic mechanisms that link physical activity to different types of cancer. Additional research is needed to better understand these differences.

Limitations of this report should be considered. First, even with > 750,000 participants, our patient numbers were limited for some types of cancer and our participants were primarily white. Second, our analyses of moderate- versus vigorous-intensity were also limited by the number of cohorts with detailed physical activity measures. Third, we relied on self-reported physical activity measures. Although there is adequate evidence for validity of leisure-time physical activity questionnaires in comparison with objective and physiologic criterion measures,[41,42] we anticipate measurement error and probable attenuation of associations observed. Future research using self-report could be strengthened by incorporating quantitative bias analyses to explore attenuation of risk estimates as a result of measurement error. Fourth, by design, we examined only leisure-time physical activity at one point in time and did not evaluate associations with total activity levels or different domains of behavior. Finally, this was an observational study that cannot demonstrate causality, and we cannot rule out effects of unmeasured or residual confounding.

Our study also had a number of strengths. A unique strength was our focus on a single domain of physical activity (leisure-time), and pooling of original MET hours/week data for 9 prospective cohorts from the United States, Europe, and Australia. This feature overcomes many of the limitations inherent in available meta-analyses related to wide variation in the types of activity examined, differences in summary measures assessed, and dissimilarities in how activity was classified in individual studies (eg, tertiles, quintiles).[3] The pooling of original data also allowed us to quantify dose-response relationships using restricted cubic splines, which afforded greater statistical power and avoided arbitrary categorization of activity levels.[28] Our results provide the best available description of the dose-response for leisure-time physical activity and cancer risks of which we are aware.

In this pooled analysis of prospective studies, we found that engagement in recommended amounts of leisure-time physical activity (7.5-15 MET hours/week) was associated with lower risk for 7 cancers (colon, breast, endometrial, kidney, myeloma, liver, non-Hodgkin lymphoma). Additional benefits for engaging in still higher levels of physical activity were cancer type dependent owing to heterogeneity in the dose-response curves observed. These findings provide direct quantitative support for the levels of activity recommended for cancer prevention and provide actionable evidence for ongoing and future cancer prevention efforts.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Amount and Intensity of Leisure-Time Physical Activity and Lower Cancer Risk

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