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Regular recreational physical activity and risk of hematologic malignancies: results from the prospective VITamins And lifestyle (VITAL) study†

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Background: Conflicting evidence exists on the relationship between physical activity (PA) and incident hematologic malignancies. Herein, we used a large cohort study to examine this association.
Patients and methods: Sixty-five thousand three hundred twenty-two volunteers aged 50–76 years were recruited from 2000 to 2002. Incident hematologic malignancies ($n = 666$) were identified through 2009 by linkage to the Surveillance, Epidemiology, and End Results cancer registry. Hazard ratios (HRs) for hematologic malignancies associated with PA averaged over 10 years before baseline were estimated with Cox proportional hazards models, adjusting for factors associated with hematologic cancers or PA.
Results: There was a decreased risk of hematologic malignancies associated with PA (HR = 0.66 [95% confidence interval, 95% CI 0.51–0.86] for the highest tertile of all PA, *P*-trend = 0.005, and HR = 0.60 [95% CI 0.44–0.82] for the highest tertile of moderate/high-intensity PA, *P*-trend = 0.002). These associations were strongest for myeloid neoplasms (HR = 0.48 [95% CI 0.29–0.79] for the highest tertile of all PA, *P*-trend = 0.013, and HR = 0.40 [95% CI 0.21–0.77] for the highest tertile of moderate/high-intensity PA, *P*-trend = 0.016). There were also significant associations between PA and chronic lymphocytic leukemia/small lymphocytic lymphoma or other mature B-cell lymphomas except plasma cell disorders.
Conclusions: Our study offers the strongest epidemiological evidence, to date, to suggest an association between regular PA and dose-dependent risk reduction for most hematologic malignancies, particularly myeloid neoplasms.

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Key words: cancer risk, epidemiology, hematologic malignancies, physical activity, prospective cohort study, VITamins And Lifestyle study

introduction

Regular physical activity (PA) provides numerous cardiovascular, metabolic, and mental/cognitive health benefits [1]. Increasing evidence from epidemiological studies also links PA to a reduced risk of major human cancers, particularly those of the colon and breast, with weaker evidence suggesting a beneficial effect for cancers of the lung, endometrium, ovary, and prostate [2–5]. On the other hand, available data have been considered insufficient to definitively assess an association of PA with the risk of cancers of the hematopoietic system [3, 5, 6].

In fact, several case–control [7–13] and cohort studies [14–22] have examined the relationship between PA and individual subtypes of hematologic malignancies, but these previous studies yielded inconsistent results. For example, while some case–control studies indicated a decreased risk of nonHodgkin lymphoma (NHL) with PA [9, 10], other case–control and cohort studies found no significant association [7, 8, 13–16, 19, 21, 22]. Similarly, while one case–control study suggested that vigorous PA may reduce the risk of acute or chronic leukemia [12], other studies failed to identify such an association [7, 14–16]. For multiple myeloma, studies similarly suggested either a decreased risk [17], a possible decrease in risk for women but not men [22], or no association [18]. Given these conflicting findings, we examined the association of regular recreational PA with incident hematologic malignancies overall and by subtypes in the prospective VITamins And Lifestyle (VITAL) study [23]. Unlike most of the past cohort studies that collected information on PA at baseline or over a short period of time before baseline, the VITAL study collected information on long-term (10 year) recreational activity, a time period sufficiently long to cover the induction period of cancer.

methods

study cohort

The VITAL study [23] was approved by the Institutional Review Board at Fred Hutchinson Cancer Research Center. From 2000 to 2002, we mailed questionnaires to 364 418 men and women aged 50–76 years living in the area of Washington State covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry; of these, 79 300 were returned and 77 719 were deemed eligible. To avoid the treatment of an earlier cancer as a cause of blood cancer, we excluded 11 487 participants with a prior history of any cancer other than nonmelanoma skin cancer reported at baseline ($n = 11\,273$) and those with missing cancer information at baseline ($n = 214$). We additionally excluded 904 participants with missing information regarding PA and six cases with postbaseline blood cancer on death certificate only without a diagnosis date, leaving 65 322 individuals for the study.

data collection

A 24-page self-administered, sex-specific questionnaire at baseline covered medication and supplement use, health history and risk factors, and diet. The PA questionnaire asked about recreational PA over the past 10 years and was divided into sections on walking, mild exercise, and moderate/strenuous exercise. Respondents were instructed to only report activities done regularly, defined as ≥1 time/week for ≥1 year in the previous 10 years, and to not report gardening, housework, or work on the job. For each type of activity, participants were asked to report the years in the last 10 that they did each activity, the days per week, and the minutes per day. For walking, usual pace was also asked, and for moderate or strenuous activities, participants were asked to select the 1 or 2 most common activities from a list of 10 activities. To calculate average episodes of activity over the past 10 years, we computed average episodes per week (years in the past 10 × frequency per week/10) for each activity and summed over all activities. We also assigned a corresponding metabolic equivalent (MET) intensity to each activity based on the Compendium of Physical Activities [24]. We calculated MET-hours (kilocalorie expenditure per kilogram of body weight) per week as a measure of activity independent of body size [25] and computed usual MET-hours per week for each activity averaged over the previous 10 years as follows: [Frequency of activity per week × minutes per session × years in the past 10 × MET for that activity]/[(60 min/h) × 10 years]. We then summed the MET-hours for all activities to quantify total 10-year average MET-hours per week. In addition, we calculated episodes per week and MET-hours per week of moderate- and high-intensity activities combined (activities with MET ≥4) [26].

case ascertainment

Incident cases of hematologic (ICD-O-3 morphology codes 9590/3–9989/3) and other malignancies were identified through 31 December 2009 by annual linkage to the western Washington SEER cancer registry [23]. Cases were categorized using the 2008 World Health Organization (WHO) classification system [27].

follow-up for censoring

The end date of follow-up was the earliest date of the following: diagnosis of hematologic malignancy (1.02%), withdrawal from study (0.03%), emigration from the SEER region (6.7%), cancer diagnosis other than hematologic malignancy or nonmelanoma skin cancer (10.7%), death (3.6%), or last linkage to the SEER registry (31 December 2009; 77.8%). Moves out of the SEER region were identified via linkage to the US Post Office National Change of Address file, follow-up letters, and phone calls. Deaths were ascertained via linkage to the Washington State death file.

statistical analysis

Sex- and multivariable-adjusted Cox proportional hazards models using robust standard errors [28] were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the associations between PA and the risk of hematologic malignancies. Age was the time metric in regression models, with participants entering at the age of completing the baseline questionnaire and exiting at their age at the end of follow-up. We selected a priori potential confounders including known and suspected risk factors for hematologic malignancies and factors associated with PA for adjustment in multivariable regression models (see footnote to Table 3 for the complete list of covariates). *P*-values for trend were computed by using the categorized 10-year average variable as an ordinal variable in the model. In cancer subtype analyses, cases of the other tumor morphologies were censored at the time of cancer diagnosis. All reported *P*-values are

two-sided, and a *P*-value <0.05 was considered statistically significant. All analyses were carried out using STATA 11 (StataCorp, College Station, TX).

results

Overall, 65 322 men and women, aged 61.5 ± 7.4 (mean ± standard deviation) years at baseline, were included in this study. After a mean follow-up of 7.3 ± 2.1 years, 666 (1.02%) developed a hematologic malignancy (Table 1). Participants who developed a hematologic malignancy were older at baseline (65.2 ± 7.2 versus 61.4 ± 7.3 years, $P < 0.0001$), were more likely male ($P < 0.001$), and more often had ≥2 first-degree relatives with a family history of leukemia or lymphoma ($P = 0.002$; Table 2). Cases also rated their health more often in the lower 3 of 5 categories (all $P < 0.03$) and more often self-reported a history of anemia in the year before baseline ($P = 0.003$) than noncases.

The associations between PA and incidence of hematologic malignancies are given in Table 3. In age- and sex-adjusted analysis, both any PA and any moderate/high-intensity activity were associated with a decreased risk of hematologic malignancies (HR = 0.74 [95% CI 0.61–0.90] and HR = 0.73 [95% CI 0.59–0.90], respectively). After adjustment, there was a decreased risk of hematologic malignancies associated with any PA (HR = 0.75 [95% CI 0.61–0.94]) and with any moderate/high-intensity activity (HR = 0.72 [95% CI 0.57–0.92]). The reduction in risk was greatest among those who exercised most frequently, both for all activities (>4.8 episodes/week: HR = 0.66 [95% CI 0.51–0.86], *P*-trend = 0.005) and for moderate/high-intensity activities only (>3.5 episodes/week: HR = 0.60 [95% CI 0.44–0.82], *P*-trend = 0.002). Results were similar but slightly less significant when metabolic activity was evaluated (>13.625 MET/week: HR = 0.71 [95% CI 0.54–0.92], *P*-trend = 0.029) and for moderate/high-intensity activities only (>11.2972 MET/week: HR = 0.65 [95% CI 0.48–0.89], *P*-trend = 0.0025).

To address the possibility of reverse causation, i.e. the possibility that study participants were physically less active as a result of a yet undiagnosed hematologic malignancy, we repeated these analyses after exclusion of the 146 incident cases that occurred within 2 years of baseline. After multivariate adjustment, the reduction in the risk of incident hematologic malignancies among the physically most active participants in this study subset was relatively similar to that of the entire study cohort (comparing the highest tertile to none for all episodes of activities/week: HR = 0.64 [95% CI 0.45–0.92]; for moderate/high-intensity activities/week: HR = 0.70 [95% CI 0.52–0.95]; MET-hours of all activities/week: HR = 0.77 [95% CI 0.56–1.03], MET-hours of moderate/high-intensity activities/week: HR = 0.67 [95% CI 0.46–0.97]; data not shown).

When we stratified malignancies by the WHO disease classification (Table 4), we found that the association between episodes of PA and a decreased risk of hematologic malignancies was most pronounced for the subset of cases with myeloid neoplasms (>4.8 episodes of all activities/week: HR = 0.48 [95% CI 0.29–0.79], *P*-trend = 0.013; >3.5 episodes of moderate/high-intensity activities/week: HR = 0.40 [95% CI 0.21–0.77], *P*-trend = 0.016). There were also significant associations between episodes of moderate/high-intensity PA and incident mature B-cell lymphomas other than chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or plasma cell disorders (>3.5 episodes/week: HR = 0.59 [95% CI 0.36–0.97], *P*-trend = 0.035) and between episodes of all activities and incident CLL/SLL (>4.8 episodes/week: HR = 0.52 [95% CI 0.26–1.03], *P*-trend = 0.023). In contrast, there was no association between PA and risk of plasma cell disorders.

When we stratified the entire cohort by gender, we found that the association between PA and total incident hematologic malignancies was seen in both females and males and appeared, perhaps, slightly more pronounced in females than males (e.g. >4.8 episodes/week of all activities: HR = 0.59 [95% CI 0.38–0.92] for females versus HR = 0.69 [95% CI 0.50–0.97] for males; >3.5 episodes/week of moderate/high-intensity activities: HR = 0.44 [95% CI 0.25–0.77] for females versus HR = 0.67 [0.46–0.98] for males; data not shown). Finally, when stratifying our analyses by body mass index (BMI), we found that the association between PA and total incident hematologic malignancies was seen in participants who were overweight/obese (BMI ≥25: 431 cases, 40 503 noncases) as well as in those who were not (BMI <25: 206 cases, 21 131 noncases): >4.8 episodes/week of all activities: HR = 0.70 [95% CI 0.51–0.97] for BMI ≥25 versus HR = 0.75 [95% CI 0.47–1.20] for BMI <25; >3.5 episodes/week of moderate/high-intensity activities: HR = 0.67 [95% CI 0.46–0.99] for BMI ≥25 versus HR = 0.65 [95% CI 0.39–1.08] for BMI <25; data not shown).

Table 1. Classification of incident hematologic malignancies

Disease	Cases *N* (%)
Myeloid neoplasms	167 (25.1)
Myelodysplastic syndromes	68 (10.2)
Acute myeloid leukemia	41 (6.2)
Myeloproliferative neoplasms	58 (8.7)
Mature B-cell neoplasms	441 (66.2)
Chronic lymphocytic leukemia	104 (15.6)
Plasma cell disorders	80 (12.0)
Other mature B-cell neoplasm entities	257 (38.6)
Hodgkin lymphoma	22 (3.3)
Mature NK/T-cell neoplasms	22 (3.3)
Others[a]	14 (2.1)
Total	666 (100)

[a]Includes cases of malignant lymphoma, not otherwise specified (NOS); leukemia, NOS; acute biphenotypic leukemia; and precursor B-cell lymphoblastic leukemia.

discussion

In our large prospective cohort study, we found that PA was significantly inversely related to the development of hematologic malignancies in a dose-dependent manner. Although our subset analyses were somewhat limited by the relative small number of incident cases, our findings indicate that this association is not uniform across all hematopoietic cancer entities. Rather, our data suggest that this inverse

Table 2. Associations between baseline characteristics and risk of hematologic malignancies

Characteristic	Cases ($N = 666$)	Noncases ($N = 64\,656$)	Age- and sex-adjusted HR (95% CI), P-value
Demographic factors			
Age at baseline, *n* (%)			N/A
<55 years	64 (9.6%)	16 282 (25.2%)	
55 to <60 years	126 (18.9%)	15 328 (23.7%)	
60 to <65 years	114 (17.1%)	11 775 (18.2%)	
65 to <70 years	138 (20.7%)	10 159 (15.7%)	
≥70 years	224 (33.6%)	11 112 (17.2%)	
Gender, *n* (%)			
Female	268 (40.2%)	32 912 (50.9%)	1.00 (Reference)
Male	398 (59.8%)	31 744 (49.1%)	1.63 (1.39–1.90), <0.001
Race/ethnicity, *n* (%)			
White	616 (92.5%)	59 183 (91.5%)	1.00 (Reference)
Hispanic	9 (1.4%)	574 (0.9%)	1.75 (0.91–3.39), 0.096
Others	32 (4.8%)	3835 (5.9%)	0.84 (0.59–1.20), 0.329
Missing information	9 (1.4%)	1064 (1.7%)	
Education, *n* (%)			
High school graduate or less	145 (21.8%)	12 303 (19.0%)	1.00 (Reference)
Some college	229 (34.4%)	24 338 (37.6%)	0.94 (0.76–1.16), 0.585
College or advanced degree	283 (42.5%)	26 970 (41.7%)	1.03 (0.84–1.27), 0.749
Missing information	9 (1.4%)	1045 (1.6%)	
Lifestyle			
Smoking status (cigarettes)			
Never smoker, *n* (%)	303 (45.5%)	30 995 (47.8%)	1.00 (Reference)
Current or former smoker, *n* (%)	356 (53.5%)	33 253 (51.4%)	0.98 (0.84–1.14), 0.788
Pack-years, mean (SD)[a]	27.4 (23.6)	25.6 (23.2)	1.00 (1.00–1.00), 0.957
Missing information, *n* (%)	7 (1.1%)	408 (0.6%)	
Medical history			
Body mass index at baseline, mean (SD)	27.4 (4.8)	27.4 (5.2)	1.01 (0.99–1.03), 0.219
Self-reported health, *n* (%)			
Excellent	78 (11.7%)	10 220 (15.8%)	1.00 (Reference)
Very good	254 (38.1%)	25 459 (39.4%)	1.23 (0.96–1.59), 0.106
Good	241 (36.2%)	21 558 (33.3%)	1.34 (1.04–1.72), 0.026
Fair	78 (11.7%)	6242 (9.7%)	1.52 (1.11–2.08), 0.009
Poor	15 (2.3%)	1028 (1.6%)	2.09 (1.21–3.63), 0.009
Missing information	0 (0%)	149 (0.2%)	
History of fatigue/lack of energy, *n* (%)			
No	546 (82.0%)	53 104 (82.1%)	1.00 (Reference)
Yes	120 (18.0%)	11 540 (17.9%)	1.14 (0.93–1.39), 0.196
Missing information	0 (0%)	12 (0.02%)	
Daily fruit servings, *n* (%)			
First tertile	213 (32.0%)	19 613 (30.3%)	1.00 (Reference)
Second tertile	186 (27.9%)	19 629 (30.4%)	0.84 (0.69–1.02), 0.077
Third tertile	214 (32.1%)	19 710 (30.5%)	1.01 (0.83–1.22), 0.940
Missing information	53 (8.0%)	5704 (8.8%)	
Daily vegetable servings,[b] *n* (%)			
First tertile	207 (31.1%)	19 621 (30.4%)	1.00 (Reference)
Second tertile	216 (32.4%)	19 620 (30.4%)	1.03 (0.85–1.25), 0.756
Third tertile	190 (28.5%)	19 711 (30.5%)	0.97 (0.79–1.18), 0.736
Missing information	53 (8.0%)	5704 (8.8%)	
Self-reported anemia in year before baseline, *n* (%)			
No	643 (96.6%)	63 221 (97.8%)	1.00 (Reference)
Yes	23 (3.5%)	1423 (2.2%)	1.90 (1.25–2.89), 0.003
Missing information	0 (0%)	12 (0.02%)	
Family history of leukemia/lymphoma, *n* (%)			
None	604 (90.7%)	60 432 (93.5%)	1.00 (Reference)
1 first-degree relative	40 (6.0%)	3293 (5.1%)	1.19 (0.87–1.64), 0.275
≥2 first-degree relatives	5 (0.8%)	147 (0.2%)	3.08 (1.27–7.48), 0.002
Missing information	17 (2.6%)	784 (1.2%)	

[a]Among smokers and former smokers.

[b]Excluding potatoes.

CI, confidence interval; HR, hazard ratio; N/A, not applicable; SD, standard deviation.

Table 3. Associations between average 10-year recreational physical activity levels and risk of hematologic malignancies

Average over 10 years before baseline	Cases ($N = 666$) n (%)	Noncases ($N = 64\,656$) n (%)	Age- and sex-adjusted HR (95% CI), P-value	Multivariable-adjusted HR (95% CI)[a], P-value
Recreational physical activity				
None	123 (18.5)	9552 (14.8)	1.00 (Reference)	1.00 (Reference)
Any	543 (81.5)	55 104 (85.2)	0.74 (0.61–0.90), 0.002	0.75 (0.61–0.94), 0.011
Moderate/high-intensity[b]	298 (70.8)	31 653 (76.8)	0.73 (0.59–0.90), 0.004	0.72 (0.57–0.92), 0.008
Episodes of all activities per week				
First tertile (0.2–1.8)	168 (25.2)	18 409 (28.5)	0.74 (0.59–0.93), 0.012	0.78 (0.61–1.01), 0.056
Second tertile (1.85–4.8)	205 (30.8)	18 721 (29.0)	0.82 (0.65–1.02), 0.075	0.80 (0.62–1.02), 0.076
Third tertile (>4.8)	170 (25.5)	18 974 (27.8)	0.66 (0.52–0.83), <0.001	0.66 (0.51–0.86), 0.002
P-trend			0.004	0.005
Episodes of moderate/high-intensity activities per week[b]				
First tertile (0.15–1.1)	98 (23.3)	10 395 (25.2)	0.78 (0.60–1.02), 0.065	0.76 (0.57–1.02), 0.068
Second tertile (1.125–3.4)	112 (26.6)	10 519 (25.5)	0.82 (0.64–1.07), 0.140	0.78 (0.58–1.04), 0.089
Third tertile (>3.5)	88 (20.9)	10 740 (26.1)	0.60 (0.46–0.79), <0.001	0.60 (0.44–0.82), 0.001
P-trend			0.001	0.002
MET-hours of all activities per week				
First tertile (0.175–4.3745)	163 (24.5)	18 298 (28.3)	0.72 (0.57–0.91), 0.006	0.77 (0.59–0.98), 0.038
Second tertile (4.375–13.624)	197 (29.6)	18 437 (28.5)	0.80 (0.64–1.00), 0.047	0.78 (0.61–1.00), 0.053
Third tertile (>13.625)	183 (27.5)	18 369 (28.4)	0.70 (0.56–0.88), 0.002	0.71 (0.54–0.92), 0.010
P-trend			0.023	0.029
MET-hours of moderate/high-intensity activities per week[b]				
First tertile (0.197–3.5)	106 (25.2)	10 546 (25.6)	0.82 (0.63–1.06), 0.135	0.80 (0.60–1.06), 0.118
Second tertile (3.504–11.29167)	96 (22.8)	10 553 (25.6)	0.70 (0.54–0.92), 0.009	0.69 (0.51–0.93), 0.015
Third tertile (>11.2972)	96 (22.8)	10 554 (25.6)	0.68 (0.52–0.89), 0.005	0.65 (0.48–0.89), 0.007
P-trend			0.003	0.005

[a]Models adjusted for age, sex, race/ethnicity (white, Hispanic, and others), education (high school graduate or less, some college, college, or advanced degree), smoking (pack-years), BMI at baseline, history of fatigue/lack of energy, self-reported health (excellent, very good, good, fair, and poor), daily fruit consumption, daily vegetable consumption (excluding potatoes), self-reported history of anemia in year before baseline, and number of first-degree relatives with a history of leukemia or lymphoma (none, 1, and ≥2).

[b]For this analysis, participants with only low-intensity physical activities were excluded (leaving 421 cases and 41 205 noncases).

CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent.

association was strongest for the category of myeloid neoplasms, which included cases acute myeloid leukemia (AML), myelodysplastic syndromes, and myeloproliferative neoplasms. By contrast, our findings revealed a less consistent association between PA and risk of CLL/SLL and other mature B-cell NHLs, and no relationship between regular PA and incident plasma cell disorders in our study. Our gender-stratified analyses indicated that the association between regular PA and a reduced risk of incident hematologic malignancies held for both men and women, with perhaps a trend toward stronger association in women.

Comparisons between data from our study and previous reports are limited by differences in study design, study participants, measurement of PA, and disease types analyzed. For example, in a population-based case–control study from Canada, Kasim et al. [12] observed a 25% risk reduction for adult leukemia in the highest tertile of strenuous PA. Similar to our study, these authors noted that more vigorous/frequent activity was associated with a lower risk of malignancy. However, their cases not only included AMLs, but also acute lymphoblastic leukemias, chronic myeloid leukemias, CLL/SLLs, and hairy cell leukemias—entities for which (with the exception of CLL/SLL) we had insufficient numbers of incident cases for adequate analysis. In the subset of AMLs, risk reduction appeared relatively modest at best (odds ratio = 0.82 [95% CI 0.46–1.47] for the highest tertile of strenuous PA, $P = 0.74$ for trend). Other case–control studies similarly included the cases of myeloid and lymphoid leukemia but, unlike the study by Kasim et al. found no association with PA [7, 14]. Thus, ours may be the first study to suggest a significant risk reduction of myeloid neoplasms with regular PA.

Previous results of the role PA on incident lymphomas have been inconsistent across several case–control and cohort studies. Specifically, while some case–control studies indicated a decreased risk with PA [9, 10], other case–control studies [7, 8, 13] and some cohort studies [14–16, 19, 21] failed to identify such an association. Of note, however, in a recent report on the American Cancer Society (ACS) Cancer Prevention Study II cohort on 146 850 participants, Teras et al. [22] observed a borderline-significant trend ($P = 0.05$) toward reduction in the risk of NHL among women, with those reporting the highest levels of recreational PA having an approximately 30% reduced risk (HR = 0.69 [95% CI 0.54–0.88]), but no association in men (HR = 1.02 [95% 0.82–1.26]). We found a reduced risk of mature B-cell lymphomas other than CLL/SLL or plasma cell disorders associated with

Table 4. Multivariable-adjusted hazard ratios of 10-year average physical activity and risk of individual hematologic malignancies

Average over 10 years before baseline	Myeloid neoplasms ($N = 167$)		CLL/SLL ($N = 104$)		Plasma cell disorders ($N = 80$)		Mature B-cell neoplasms other than CLL/SLL or plasma cell disorders ($N = 257$)	
	N (%)	HR (95% CI)[a], *P*-value	*N* (%)	HR (95% CI)[a], *P*-value	*N* (%)	HR (95% CI)[a], *P*-value	*N* (%)	HR (95% CI)[a], *P*-value
Recreational physical activity								
None	38 (22.8)	1.00 (Reference)	20 (19.2)	1.00 (Reference)	9 (11.3)	1.00 (Reference)	46 (17.9)	1.00 (Reference)
Any	129 (77.3)	0.59 (0.40–0.88), 0.010	84 (80.8)	0.74 (0.43–1.27), 0.276	71 (88.8)	1.23 (0.58–2.57), 0.590	211 (82.1)	0.74 (0.52–1.07), 0.110
Moderate/high-intensity	63 (62.3)	0.53 (0.34–0.85), 0.008	45 (69.2)	0.65 (0.35–1.22), 0.185	46 (83.6)	1.37 (0.65–2.92), 0.410	119 (72.1)	0.72 (0.49–1.07), 0.108
Episodes of all activities per week								
First tertile (0.2–1.8)	43 (25.8)	0.62 (0.39–0.99), 0.047	32 (30.8)	0.95 (0.52–1.73), 0.870	18 (22.5)	1.08 (0.46–2.50), 0.862	41 (24.9)	0.74 (0.49–1.12), 0.156
Second tertile (1.85–4.8)	49 (29.3)	0.65 (0.41–1.05), 0.077	28 (26.9)	0.70 (0.37–1.30), 0.257	37 (46.3)	1.78 (0.82–3.85), 0.143	44 (26.7)	0.71 (0.47–1.07), 0.100
Third tertile (>4.8)	37 (22.2)	0.48 (0.29–0.79), 0.004	24 (23.1)	0.52 (0.26–1.03), 0.061	16 (20.0)	0.74 (0.30–1.79), 0.504	34 (20.6)	0.80 (0.53–1.22), 0.302
P-trend		0.013		0.023		0.636		0.460
Episodes of moderate/high-intensity activities per week[b]								
First tertile (0.15–1.1)	21 (20.8)	0.50 (0.28–0.92), 0.025	12 (18.5)	0.62 (0.28–1.34), 0.223	17 (30.9)	1.66 (0.71–3.85), 0.240	42 (22.1)	0.81 (0.51–1.29), 0.372
Second tertile (1.125–3.4)	26 (25.7)	0.69 (0.40–1.19), 0.182	17 (26.2)	0.70 (0.33–1.50), 0.356	17 (30.9)	1.33 (0.56–3.15), 0.517	62 (32.6)	0.74 (0.46–1.18), 0.207
Third tertile (>3.5)	16 (15.8)	0.40 (0.21–0.77), 0.006	16 (24.6)	0.65 (0.30–1.42), 0.285	12 (21.8)	1.03 (0.43–2.46), 0.956	55 (29.0)	0.59 (0.36–0.97), 0.037
P-trend		0.016		0.366		0.694		0.035

[a]Models adjusted for age, sex, race/ethnicity, education, smoking, body mass index at baseline, fatigue/lack of energy, self-reported health, daily fruit consumption, daily vegetable consumption (excluding potatoes), self-reported history of anemia in year before baseline, and family history of leukemia/lymphoma.

[b]For this analysis, participants with only low-intensity physical activities were excluded (leaving 101 cases of myeloid neoplasms, 65 cases of CLL/SLL, 55 cases of plasma cell disorders, and 165 cases of other mature B-cell neoplasms).

CI, confidence interval; HR, hazard ratio.

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moderate/high-intensity activities and a reduced risk of CLL/SLL associated with all PA activities. Together with the ACS results, this may suggest a modest benefit of PA for mature B-cell lymphomas other than plasma cell disorders, although additional studies will be required to test this idea further.

The mechanisms by which PA may influence the risk of human cancers are not well understood. The proposed mechanisms involve changes in metabolic and sex-hormone levels, altered immune function, up-regulation of antioxidants and/or reduced free radical generation, enhancement of apoptosis, decreased inflammation, reduction in fat stores, and direct effects on tumorigenesis [3, 5, 6, 29–33]. PA may also cause alterations in gene expression favoring tumor suppression over oncogenesis, as indicated in recent studies on prostate cancer [34, 35]. PA has effects on the hematopoietic system, which might underlie the association with a reduced risk of hematologic cancers as observed in our study. In particular, besides regulation of apoptosis, PA has been linked to enhanced function of the innate immune system in experimental animals [36, 37] as well as increased resistance to oxidative stress [38–40] and, perhaps, increased DNA repair [41] in humans. Of note, it has been suggested that PA may reduce the risk of hematologic malignancies by reducing adiposity, thereby reducing the production of pro-inflammatory and proliferative cytokines and altering the bone marrow microenvironment [42, 43]. However, BMI was not associated with incident hematologic malignancies in our study and was controlled for in the PA analyses.

This study has several strengths, including its prospective design, the large cohort size, case ascertainment through the SEER cancer registry, and the use of the most recent WHO disease classification system to categorize the subtypes of hematologic malignancies. Another advantage is the availability of baseline information on personal lifestyle and medical history, which allowed adjustment for major potential confounding factors. As an important characteristic, the VITAL study assessed PA over the 10 years before baseline, a time period sufficiently long to be etiologically relevant for the development of cancer. Most past cohort studies on the association between PA and hematologic malignancies have only assessed PA at baseline or over a short period of time before baseline, which may partially explain our stronger associations compared with many previous studies. Some support for increased accuracy of associations with PA by using a long-term measure comes from a stronger correlation between our 10-year PA measure with BMI than the correlation other studies have found between current PA and BMI [44]. On the other hand, some limitations need to be acknowledged. While we ascertained episodes of recreational PA per week as well as the amount of time spent on low-, moderate-, and high-intensity PA, the VITAL study did not collect information on nonrecreational PA (e.g. from occupational or household activities) or how activity varied over the 10-year period we inquired about. Moreover, PA was self-reported and, therefore, subject to measurement error. However, the measurement properties of our questionnaire were very good, based on its validation study against a detailed personal interview on 10-year recreational activity, with age- and sex-adjusted correlations of average MET-hours per week from all activities between the questionnaire and validation interview being 0.65 for men and 0.71 for women, respectively [44]. Nevertheless, the measurement error, which would be nondifferential in a prospective study, would have likely led to attenuation of results.

Of some concern is the possibility of reverse causation, i.e. disease/symptoms could lead to reduced PA rather than the reverse. As an example, anemia or systemic symptoms, such as fatigue or malaise, may precede the diagnosis of a hematologic malignancy and lead to reduced participation in recreational PA. However, we collected and averaged data over 10 years before study enrollment, a time period considerably longer than the typical patient is symptomatic before diagnosis with a hematologic malignancy. For instance, recent investigations in patients with lymphoma, including those with oftentimes-indolent disease such as CLL/SLL, suggest that the median time from symptoms to diagnosis ranges from 2 to 4 months [45–47], while patients with acute leukemia are typically diagnosed within the weeks of symptom onset [48]. Even with multiple myeloma, a disease that may present with musculoskeletal symptoms that limit exercise capabilities, the vast majority of patients are diagnosed within the 1 year of the onset of symptoms [49]. Nevertheless, we additionally excluded cases arising in the first 2 years of follow-up. In this analysis, the HR remained significant and comparable with the initial data, further supporting the notion that reverse causation is very unlikely to account for the inverse association between regular PA and incident hematologic malignancies seen in our study.

In conclusion, our study offers the strongest epidemiological evidence, to date, to suggest an association of PA with a dose-dependent reduction in incidence of certain hematologic malignancies, with a >50% risk reduction for the development of neoplasms of myeloid origin for individuals within the top tertile of all or moderate/high-intensity activities. Our data also suggest a trend toward the reduced risk for CLL/SLL and other mature B-cell NHLs, although further studies in larger cohorts of participants will be required to assess this association further. Together, our findings may thus suggest additional important health benefits attributable to regular PA.

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disclosure

The authors have declared no conflicts of interests.

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