MAYO CLINIC

ORIGINAL ARTICLE

April 2020
Volume 4
Number 2

MAYO CLINIC
PROCEEDINGS
Innovations, Quality & Outcomes

Leisure-Time Physical Activity and Cancer Risk Among Older Adults: A Cohort Study

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Abstract

Objective: To examine the association between leisure-time physical activity (LTPA) and long-term cancer risk in a nationwide cohort of older adults.

Participants and Methods: The cohort comprised participants of a national survey conducted between July 2005 and December 2006, constituting a random sample of Israeli community-dwelling adults aged 65 years or older. Based on self-reported LTPA habits, participants were classified as sufficiently active, insufficiently active, or inactive according to published guidelines. Cancer diagnosis was assessed via the Israeli National Cancer Registry through September 2015. Inverse probability weighted hazard ratios for incident cancer, based on propensity score, were estimated for LTPA categories.

Results: Analysis included 1542 participants with no history of cancer at baseline (median [25th-75th percentile] age, 73 years [69-78 years]; 826 [53.6%] women). Inactive participants (n=641 [41.6%]) were more likely to be female, of lower socioeconomic status, and with higher body mass index and poorer perceived health compared with their insufficiently active (n=443 [28.7%]) and sufficiently active (n=458 [29.7%]) counterparts. In the propensity score–weighted synthetic sample, the distribution of measured baseline covariates was similar across LTPA categories. Over a median follow-up of 9 years, 254 new cancer cases (16.5%) were diagnosed. Leisure-time physical activity was inversely associated with incident cancer, with adjusted hazard ratios (95% CIs) of 0.66 (0.46-0.93) in insufficiently active and 0.59 (0.42-0.82) in sufficiently active participants compared with inactive individuals (P value for trend = .002).

Conclusion: Among older adults, engaging in LTPA, even at lower levels than officially recommended, may have a beneficial effect on primary prevention of cancer.

 ■ Mayo Clin Proc Inn Qual Out 2020;4(2):115-125

Regular engagement in leisure-time physical activity (LTPA) is considered to have a protective effect against cancer among the general population.[1] In light of the aging of the population, there is a growing interest in whether this protective effect of LTPA equally applies to older age groups, characterized by decreased levels of physical activity[2] and increased cancer incidence.[3] Few previous cohort studies have focused specifically on adults aged 65 years or older,[4-8] while others have reported an overall risk for both middle-aged and old adults[9-16] or considered the older age groups separately in their analyses,[17-19] including several

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meta-analyses.[20-24] Findings of these studies support an inverse association between LTPA and cancer of the lung,[11,12,21] colon and rectum,[13] endometrium,[23] and breast[5,6,15,24] (although lack of association with breast cancer was also reported[14]), whereas no evidence was observed for ovarian,[9] prostate,[20] or pancreatic[10,17,22] cancers (Supplemental Table 1, available online at http://www.mcpiqojournal.org). Although consistent with findings from the general population,[1] for older adults, some uncertainties still remain regarding the nature of this association. Studies of older adults are particularly vulnerable to reverse causation[25] because older individuals who are healthy enough to exercise may experience a reduced health risk irrespective of their physical activity level.[26] Hence, attributes of aging, such as poor self-rated health, functional limitations, cognitive impairment, and decreased psychological functioning,[27] may serve as important confounders because they are strongly associated with both physical activity engagement[28-30] and health outcomes,[31] including cancer.[32-34] Socioeconomic status (SES) constitutes another important confounder in this context because it is related to both exercise[30] and cancer.[35] Nevertheless, many previous investigations among older adults have not addressed these potential key confounders in their analyses. For example, only a few studies have incorporated measures of mental health,[7,8] self-rated health,[7,19] functional limitations, or any additional SES aspects beyond education,[15] which may result in substantial residual confounding.[36] Additionally, a substantial proportion of the studies among older adults examined cancer mortality rather than incidence,[7,8,16,18,19] which constitutes an inadequate measure for cancer risk assessment.[37] Therefore, in the current investigation we utilized a nation-wide cohort of community-dwelling adults (median age of 73 years) with a wealth of information on potential confounders and a complete long-term follow-up of cancer incidence to assess whether LTPA is predictive of a reduced cancer risk.

PARTICIPANTS AND METHODS

Study Design and Setting

The cohort comprised all participants interviewed in the first National Health and Nutrition Survey of the Elderly in Israel ("Mabat Zahav"), carried out between 2005 and 2006 by the Israel Center for Disease Control and the Nutrition Department of the Israel Ministry of Health.[38] The survey population constituted a random sample of Israeli citizens aged 65 years or older, with the sampling framework provided by the 2 major health maintenance organizations in Israel (Clalit Health Services and Maccabi Health Services), representing approximately 86% of all elderly individuals in Israel. The final sample included 1852 community-dwelling participants residing in Israel for at least 1 year. Data were obtained via a personal interview in the interviewee's place of residence (own home or retirement home) using a structured questionnaire. Among the participants interviewed, 53 were excluded because of severe cognitive impairment (n=46) or incomplete questionnaires (n=7), yielding 1799 participants (for whom survey data are available online at the Ministry of Health government website[39]). For the current analysis, individuals with a history of cancer at baseline (n=257) were additionally excluded, leaving 1542 participants. All aspects of the study were approved by the institutional ethics committees.

Assessment of Physical Activity

Leisure-time physical activity was self-reported during the baseline interview, based on a standard questionnaire (Supplemental Material, The Physical Activity Questionnaire, available online at http://www.mcpiqojournal.org), as previously described in detail.[40] In 2 sets of questions, participants were asked about their physical activity habits during leisure time. One set of questions referred to vigorous-intensity activity and another set addressed any type of moderate physical activity that lasted at least 10 minutes. Participants reported the frequency (times per week) and average time they devoted to each specific activity, as follows: walking outdoors or on a treadmill, jogging, swimming, bike riding or stationary cycling, light exercise (such as yoga, the Feldenkrais method, the Alexander technique, light gymnastics), body shaping, and strength training; an "other activity" option was also offered. Based on reported total weekly time of LTPA and intensity, participants were classified into 3 LTPA categories according to the official American College of Sports Medicine guidelines[41]: sufficiently active, insufficiently active, or inactive. Individuals who performed

Mayo Clin Proc Inn Qual Out ■ April 2020;4(2):115-125 ■ https://doi.org/10.1016/j.mayocpiqo.2019.11.005
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moderate physical activity for at least 150 min/wk or a vigorous-intensity activity for at least 75 min/wk or a combination of the two were classified as sufficiently active; those who engaged in LTPA but in a lesser amount than these definitions were classified as insufficiently active; and those who reported no activity or activity less than once a week were classified as inactive.

Cancer Diagnosis Ascertainment

Members of the cohort were linked to the Israel National Cancer Registry via their national identification numbers. The National Cancer Registry records all incident cases of malignant neoplasms (excluding basal and squamous cell skin cancers), carcinoma in situ and high-grade intraepithelial neoplasia, and benign neoplasms of the brain and central nervous system.[42] The registry covers the entire Israeli population (approximately 8.5 million as of 2016), with 97% estimated completeness of ascertainment for solid tumors.[43] Data on date of diagnosis and the diagnostic code, assigned according to the *International Classification of Diseases for Oncology, Third Edition*, regarding primary cancers only (ie, not metastases), were obtained, and thereby incident as well as previous cases of all-site cancer (codes C00.0-C80.9) were identified. Individuals with previous cancer diagnosis were excluded from the analysis. Participants who did not have a diagnosis of cancer by the end of follow-up were right-censored at the date of death or last cancer update date (September 2015). Data on all-cause mortality (available until the end of cancer follow-up) were obtained by linking the cohort (also via national identification numbers) to the nationwide database of causes of death, managed by the Ministry of Health.

Additional Covariates

Comprehensive information on sociodemographic status, health conditions, disabilities, mental health, cognitive function, anthropometric measures, and nutritional status was obtained at the baseline interview.[38] All questionnaires are described in detail in the Ministry of Health website (English version available).[39]

Statistical Analyses

A propensity score was constructed using a multinomial logistic regression, through which the probability of being classified into a specific LTPA category (inactive, insufficiently active, or sufficiently active), conditional on measured baseline covariates, was estimated. Baseline covariates included age, sex, multimorbidity index (calculated as the number of preexisting chronic diseases, including stroke, kidney disease, chronic respiratory diseases, diabetes, hypercholesterolemia, osteoporosis, and hypertension, and analyzed categorically [0 = no morbidity; 1-3 = moderate morbidity; and 4 or more = severe morbidity]), smoking status, pack-years ([age at interview − age of smoking beginning] × [number of cigarettes per day/20]), perceived general health, perceived health 1 year before interview, cardiovascular disease, hypertension, functional status (measured via activities of daily living score[44]), mental health (assessed via General Health Questionnaire score[45]), cognitive status (evaluated through the Mini-Mental State Examination score[46]), alcohol consumption, dietary fiber intake, total calorie intake (the latter 3 obtained via the multiple-pass 24-hour dietary recall questionnaire[47]), body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), ethnicity, marital status, employment, education, personal income, and household income. Missing values existed for BMI (10%), personal income (10%), household income (22%) and General Health Questionnaire score (37%) and were handled using a missing indicator. Inverse probability weights were calculated using the propensity score[48] by weighting each participant in each LTPA category inverse to their probability of being classified into that specific LTPA category. In this manner, we created a pseudopopulation in which the distribution of measured baseline covariates is independent of LTPA category, thus accounting for differences between the individuals in LTPA categories that could influence the outcome. Because of the instability that can be induced by extreme weights, stabilized weights were used to preserve the original sample size.[49] Truncation was additionally applied by resetting observations with weights below the 1st percentile and above the 99th percentile to

TABLE 1. Selected Characteristics of Study Cohort Before and After Inverse Probability of Treatment Weighting[a,b]

Characteristic	Observed cohort				Weighted cohort[c]			
	Physical activity category				Physical activity category			
	Inactive (n=641)	Insufficiently active (n=443)	Sufficiently active (n=458)	*P* value	Inactive (n=636)	Insufficiently active (n=438)	Sufficiently active (n=433)	*P* value
Age (y)	74.8±6.6	74.7±6.0	73.7±5.9	.01	74.6±6.7	74.9±5.8	74.7±6.2	.91
Female sex	387 (60.4)	249 (56.2)	190 (41.5)	<.01	349 (54.9)	230 (52.5)	214 (49.4)	.35
Perceived poor health	364 (56.8)	193 (43.6)	112 (24.5)	<.01	294 (46.2)	193 (44.1)	184 (42.5)	.61
Cardiovascular disease	246 (38.4)	148 (33.4)	144 (31.4)	.04	226 (35.5)	151 (34.6)	159 (36.7)	.84
Hypertension	259 (40.4)	188 (42.4)	210 (45.9)	.27	274 (43.1)	183 (41.8)	191 (44.1)	.86
Health trajectories[d]				<.01				.75
Better	46 (7.2)	49 (11.1)	40 (8.7)		54 (8.5)	39 (8.9)	37 (8.5)	
Similar	262 (40.9)	218 (49.2)	288 (62.9)		307 (48.3)	218 (49.7)	229 (53.0)	
Worse	333 (52.0)	176 (39.7)	130 (28.4)		275 (43.3)	181 (41.4)	167 (38.5)	
Comorbidities				<.01				.82
0	66 (10.3)	61 (13.8)	66 (14.4)		82 (13.0)	59 (13.5)	65 (14.9)	
1-3	476 (74.3)	317 (71.6)	359 (78.4)		474 (74.5)	323 (73.8)	324 (74.8)	
≥4	99 (15.4)	65 (14.7)	33 (7.2)		80 (12.6)	56 (12.7)	44 (10.2)	
MMSE score	30.6±4.7	30.6±3.3	30.9±2.8	.29	30.6±3.7	30.5±3.8	30.4±3.2	.63
Functional limitations[e]				<.01				.13
None	419 (65.4)	372 (84.0)	427 (93.2)		496 (78.0)	353 (80.7)	366 (84.5)	
Moderate	182 (28.4)	58 (13.1)	29 (6.3)		118 (18.6)	68 (15.4)	63 (14.6)	
Severe	40 (6.2)	13 (2.9)	2 (0.4)		22 (3.5)	17 (3.9)	4 (1.0)	
GHQ score	2.2±2.2	1.8±2.2	2.1±2.6	.07	2.1±2.2	2.1±2.3	1.9±2.2	.60
Smoking status				.03				.99
Current smoker	88 (13.7)	41 (9.3)	42 (9.2)		73 (11.4)	51 (11.6)	51 (11.9)	
Former smoker	200 (31.2)	146 (33.0)	170 (37.1)		222 (34.9)	151 (34.5)	156 (36.0)	
Never smoker	353 (55.1)	256 (57.8)	246 (53.7)		342 (53.7)	236 (53.8)	226 (52.1)	
Pack-years	23.1±41.2	15.0±28.4	18.1±36.6		17.9±31.5	15.0±29.8	19.3±41.2	.67
BMI (kg/m^2)	30.3±5.3	29.2±4.6	28.0±4.0	<.01	29.1±4.8	29.4±4.9	29.2±4.5	.64
Total calorie intake (kcal/d)	1371±585	1461±530	1549±625	<.01	1468±647	1446±510	1451±588	.89
Dietary fiber intake (g/d)	15.1±8.4	17.5±8.6	19.5±9.2	<.01	17.1±9.0	18.3±8.8	17.8±8.1	.38
Alcohol consumption (g/d)	0.8±3.9	1.4±5.9	2.0±6.1	<.01	1.2±4.5	1.7±6.8	1.5±4.8	.42
Married	370 (58.1)	268 (60.9)	330 (73.2)	<.01	392 (62.1)	273 (63.0)	285 (66.3)	.48
Arab ethnicity	203 (31.7)	30 (6.8)	49 (10.7)	<.01	115 (18.1)	76 (17.3)	62 (14.3)	.45
Employed[f]	550 (85.8)	333 (75.2)	320 (69.9)	<.01	500 (78.6)	339 (77.4)	325 (75.1)	.51
Education (y)	8.4±5.6	11.2±4.7	12.4±4.6	<.01	11.1±5.5	10.5±5.0	11.8±4.7	.04
Living arrangement				<.01				.81
Living alone	160 (25.0)	102 (23.0)	98 (21.4)		152 (23.8)	104 (23.7)	99 (22.9)	
Living with a spouse	365 (56.9)	271 (61.2)	328 (71.6)		392 (61.5)	273 (62.4)	283 (65.3)	
Living with a kin/ companion/ caregiver/other	116 (18.1)	70 (15.8)	32 (7.0)		93 (14.6)	61 (13.9)	51 (11.8)	
Personal income				<.01				.62
Low	475 (83.0)	282 (71.0)	247 (59.7)		424 (74.3)	277 (70.4)	274 (70.1)	
Intermediate	84 (14.7)	90 (22.7)	129 (31.2)		122 (21.3)	95 (24.2)	92 (23.5)	
High	13 (2.3)	25 (6.3)	38 (9.2)		25 (4.4)	21 (5.4)	25 (6.4)	

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Mayo Clin Proc Inn Qual Out ■ April 2020;4(2):115-125 ■ https://doi.org/10.1016/j.mayocpiqo.2019.11.005
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TABLE 1. Continued

Characteristic	Observed cohort				Weighted cohort[c]			
	Physical activity category				Physical activity category			
	Inactive (n=641)	Insufficiently active (n=443)	Sufficiently active (n=458)	*P* value	Inactive (n=636)	Insufficiently active (n=438)	Sufficiently active (n=433)	*P* value
Household income				<.01				.47
Low	331 (69.4)	180 (52.2)	161 (42.4)		285 (58.1)	182 (53.1)	185 (53.8)	
Intermediate	108 (22.6)	104 (30.1)	136 (35.8)		145 (29.5)	106 (30.9)	100 (29.1)	
High	38 (8.0)	61 (17.7)	83 (21.8)		61 (12.4)	55 (16.0)	59 (17.1)	

[a]ADL = activities of daily living; BMI = body mass index; GHQ = General Health Questionnaire; MMSE = Mini-Mental State Examination.
[b]Data are presented as mean ± SD or No. (percentage) of participants.
[c]Weighted by inverse probability of treatment, as described in the Statistical Analyses section.
[d]Perceived health at the time of the interview in comparison to preceding year.
[e]Evaluated via ADL score, as described in the Statistical Analyses section.
[f]Including salaried/unsalaried/volunteer.

the values of the 1st and 99th percentiles, respectively.[48,50] Weighted Cox proportional hazards regression models[51] with age as the time scale were constructed to estimate the hazard ratios (HRs) and 95% CIs for all-site cancer incidence in LTPA categories. Hazard ratios were further estimated individually for cancer of the breast, lung, colon, and prostate, as well as for all other cancers combined. Additional cancer sites were not analyzed individually because of power considerations. Linear trend across LTPA categories was tested by treating LTPA categories as a continuous variable in the regression model. The heterogeneity in the association with different cancer sites was formally tested.[52] We repeated the main analysis by using a conventionally adjusted Cox model adjusted for age, sex, number of comorbidities, activities of daily living score, Mini-Mental State Examination score, smoking status, BMI, dietary fiber intake, total calorie intake, ethnicity, marital status, education, and household income included as covariates in the model. Multivariable adjustment was not performed for the site-specific cancers because of power limitations. To reduce the likelihood of reverse causality, we repeated the primary analysis after excluding participants with cancer diagnosed during the first 2 years of follow-up. Cumulative cancer incidence rates across LTPA categories were determined using the Fine-Gray subdistribution hazard regression model,[53] with death treated as a competing event. We used the Fine-Gray models because standard survival indicators are known to produce biased estimates in the presence of competing risks,[54] particularly among populations of older individuals in which a substantial number of participants die during a long follow-up.[55] To assess whether the observed association differs across major subgroups in the cohort, the HRs were estimated according to sex, age category (young-old vs middle- and oldest-old), ethnicity (Jews vs Arabs), obesity (BMI <30 kg/m^2 vs ≥ 30 kg/m^2), and smoking status (never smoker vs previous smoker vs current smoker). In a sensitivity analysis, the weighted Cox model was further adjusted for sex, smoking, obesity, and education. In addition, we calculated the total time (minutes) of LTPA summing all the activities reported. We then applied spline methodology, using a penalized spline term to assess the relationship between total time of LTPA and cancer incidence in a Cox regression model. The proportional hazards assumption was tested using the Schoenfeld residuals, with no violations found in any of the models. Analyses were performed using R software, version 3.4.1 (R Development Core Team).

RESULTS

At baseline, the median (25th-75th percentile) age of the 1542 participants included in the analysis was 73 (69-78) years, and 826 (53.6%) were women. Overall, 669 participants (43.4%) perceived their health as poor, and 324 (21.0%) had some level of functional impairment. A total of 641 participants (41.6%) did not engage in any type of LTPA, 443 (28.7%)

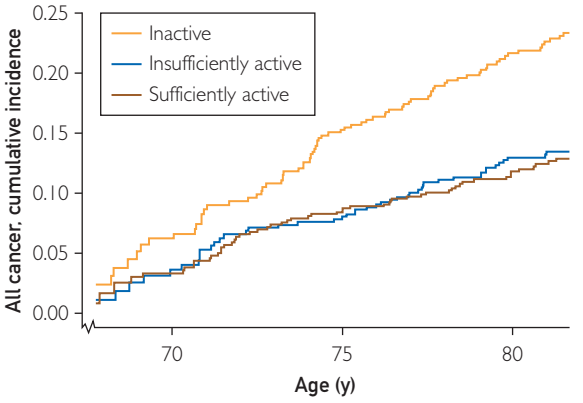

FIGURE 1. Propensity score–adjusted cumulative incidence curves for cancer according to physical activity category. The cumulative incidence was calculated as a function of age with minimum age of 65 years and truncated at age 81 years (cohort's median age at diagnosis/death/censoring). Death was treated as a competing event in the Fine and Gray model. Model was adjusted for the propensity score for being insufficiently active and sufficiently active (derived from a multinomial regression model as described in the Statistical Analyses section).

engaged in LTPA below official American College of Sports Medicine guidelines, and 458 (29.7%) met the guidelines. Among the 901 active individuals (insufficiently and sufficiently), the median (25th-75th percentile) total weekly time of LTPA was 80 minutes (40-160 minutes). Major differences were seen in baseline characteristics across LTPA categories. Compared with active participants, inactive individuals were more likely to perceive their health as poor and had more functional limitations, higher BMI, and lower SES. Stabilized weighting using the inverse propensity score resulted in a balance in baseline characteristics between the groups (Table 1). The median (25th-75th percentile) follow-up until cancer diagnosis, death, or censoring was 9 years (6-10 years). During this period, 254 new cancer cases (16.5%) were identified, of which 71 were diagnosed in the first 2 years of follow-up. The most common cancers in the cohort were breast (33 [13.0%]), lung (30 [11.8%]), colon (25 [9.8%]), and prostate (23 [9.1%]) (Supplemental Figure 1, available online at http://www.mcpiqojournal.org). In addition, a total of 370 participants died during follow-up with no preceding cancer diagnosis.

The overall cancer incidence rates per 1000 person-years in the weighted cohort were 28.3 (95% CI, 23.8-33.8), 18.7 (95% CI, 14.4-23.8), and 16.8 (95% CI, 12.6-21.6) among inactive, insufficiently active, and sufficiently active participants, respectively (P value for trend = .002). The cumulative incidence rates of cancer during follow-up across LTPA categories, with death treated as a competing event, are presented in Figure 1. The cancer rate among inactive individuals was significantly higher than among insufficiently active and sufficiently active participants (P=.006).

In an unadjusted Cox model, the HRs for all cancer were 0.76 (95% CI, 0.56-1.04) in insufficiently active and 0.84 (95% CI, 0.63-1.12) in sufficiently active participants compared with inactive individuals. In the propensity score–weighted model, a stronger association was seen: 0.66 (95% CI, 0.46-0.93) and 0.59 (95% CI, 0.42-0.82), respectively (Table 2). Including sex, smoking, BMI, and education as additional covariates in the weighted model did not attenuate the HRs (0.64 [95% CI, 0.45-0.91] and 0.57 [95% CI, 0.40-0.80], respectively [data not shown]). Excluding cases diagnosed during the first 2 years of follow-up slightly strengthened the association. A conventionally adjusted Cox model yielded similar results in both analyses (Table 2). In site-specific analysis (P value for heterogeneity = .81), although limited due to the small number of events for each site, an inverse association with LTPA was seen for most cancer outcomes, yet with CIs exceeding unity (Supplemental Table 2, available online at http://www.mcpiqojournal.org). Effect estimates for breast and colon cancers were most pronounced, with the insufficiently active participants experiencing the most favorable outcome. In an exploratory subgroup analysis, albeit limited in statistical power (all P values for interaction $\geq$.10), there were some suggestive patterns regarding the LTPA-cancer association (Supplemental Figure 2, available online at http://www.mcpiqojournal.org). Although similar benefit from LTPA was seen among insufficiently active and sufficiently active women, a clear dose-response relationship was evident among men. A greater benefit was also seen among older individuals (≥75 years) and current smokers, particularly with sufficient levels of LTPA. In addition, the LTPA-cancer

Mayo Clin Proc Inn Qual Out ■ April 2020;4(2):115-125 ■ https://doi.org/10.1016/j.mayocpiqo.2019.11.005
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association varied by ethnic group, with a weaker effect estimated among Arabs.

Applying spline methodology, a nonlinear relationship between the total time of LTPA (minutes per week) and cancer incidence was seen; as the total weekly minutes increased, the risk of all cancers decreased exponentially (Figure 2). The protective effect of LTPA was evident up to 220 to 240 minutes per week (approximately 80th percentile among the 901 active individuals), beyond which no association was seen.

DISCUSSION

Our findings in this study suggest that community-dwelling adults aged 65 years or older who engaged in any regular LTPA (weekly or more often), even at lower levels than recommended by official guidelines, were at lower risk of incident cancer than counterparts who did not engage in any LTPA. This association was robust to multiple sensitivity analyses. In site-specific analysis, although limited due to small number of events, an inverse association was observed for most cancer sites.

The association we observed is similar to findings from previous cohort studies among older adults, yet somewhat stronger in magnitude than most previously seen associations. For example, among adults aged 65 years or older, adjusted HRs for all cancer mortality in previous investigations were no stronger than 0.70,[7,8,16,18] with one exception.[19] In the present analysis of cancer incidence (rather than cancer death), we observed propensity score–weighted HRs of 0.66 (95% CI, 0.46-0.93) among the insufficiently active and 0.59 (95% CI, 0.42-0.82) among the sufficiently active participants compared with inactive individuals. Importantly, results derived from cancer mortality analysis combine the complex influence of LTPA on both cancer incidence and case fatality rate,[37] so they cannot be directly compared with our incidence analysis results. The differences between HRs observed in the present study and previous investigations may also be related to the different age ranges of the cohorts studied. Most previous cohort studies on cancer incidence considered adults in their 50s as older adults, whereas in the present cohort, the median age was 73 years at study entry. Unlike pancreatic cancer, for which the inverse

TABLE 2. Hazard Ratios (95% CIs) for All-Site Cancer and Cancer Associated With Leisure-Time Physical Activity

Physical activity category	Entire cohort (N=1542)					Excluding participants diagnosed during the first 2 years of follow-up (n=1471)				
	No. of participants	No. of events	Unadjusted[a]	Inverse probability of treatment weighted[b]	Multiple adjustment[c]	No. of participants	No. of events	Unadjusted[a]	Inverse probability of treatment weighted[b]	Multiple adjustment[c]
	All-site *(total number of events=254)*					All-site *(total number of events=183)*				
Inactive	641	112	1	1	1	615	86	1	1	1
Insufficiently active	443	66	0.76 (0.56-1.04)	0.66 (0.46-0.93)	0.62 (0.45-0.86)	422	45	0.67 (0.47-0.96)	0.56 (0.37-0.85)	0.55 (0.38-0.81)
Sufficiently active	458	76	0.84 (0.63-1.12)	0.59 (0.42-0.82)	0.66 (0.47-0.90)	434	52	0.76 (0.54-1.07)	0.52 (0.35-0.76)	0.58 (0.40-0.86)
P value for trend[d]	-	-	.20	.002	.009	-	-	.08	<.001	.005

[a]Age at diagnosis was used as the time scale.
[b]Cox proportional hazards regression model based on the propensity score for physical activity category.
[c]Multivariable adjusted Cox model adjusted for age, sex, number of comorbidities, activities of daily living score, Mini-Mental State Examination score, smoking status, body mass index, dietary fiber intake, total calorie intake, ethnicity, marital status, education, and household income.
[d]*P* values for trend were derived from a model including leisure-time physical activity categories modeled as a continuous variable.

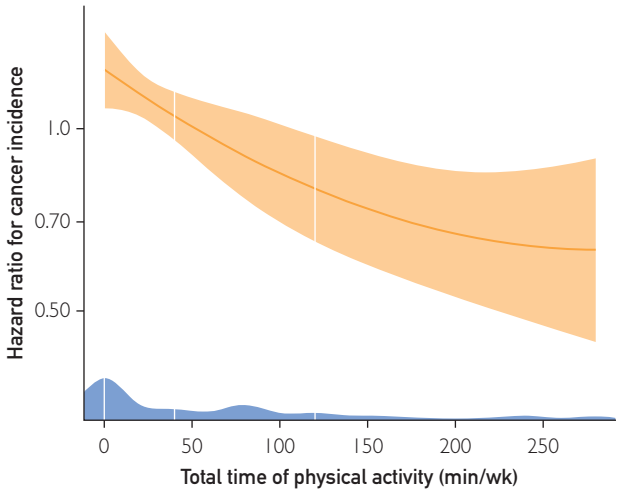

FIGURE 2. Spline-based hazard ratios (95% CIs) for cancer incidence associated with the total amount of leisure-time physical activity (minutes per week). The curve is based on a spline-based Cox model, adjusted for baseline covariates including age, sex, cardiovascular disease, multimorbidity index, smoking status, pack-years, perceived general health, perceived health 1 year before interview, hypertension, activities of daily living score, General Health Questionnaire score, Mini-Mental State Examination score, alcohol consumption, dietary fiber intake, total calorie intake, body mass index, ethnicity, marital status, living arrangement, employment, education, personal income, and household income. Total amount of physical activity was calculated as the sum of all leisure activities reported at the baseline interview, based on duration and frequency of each activity. The histogram at the bottom shows the relative overall distribution of total physical activity time. The highest 5% of total times have been trimmed for visualization purposes.

association with LTPA was weaker among older adults,[17,22] increasing evidence suggests stronger associations among older vs younger adults for overall cancer mortality[18,19] and breast cancer incidence.[56]

The inverse association between LTPA and cancer incidence in our study also applied to insufficiently active individuals. In terms of cumulative risk, although incidence curves of inactive and sufficiently active participants have clearly diverged, no clear divergence was seen between the insufficiently active and sufficiently active groups (Figure 1). Recent evidence suggests a protective effect of LTPA against mortality among older adults even at levels below current recommendations. This effect was observed both when LTPA was self-reported[57] and when it was measured objectively.[58] Yet, interestingly, in the exploratory subgroup analysis in our study, sufficient levels of LTPA had the potential for most prevention benefit among several subgroups, including men, middle- and oldest-olds (≥75 years), and current smokers. In relation to ethnicity, although a robust inverse association between LTPA and cancer was evident among Jews, it was less apparent among Arabs. The mechanism behind this finding is not completely clear; yet, there remain differences in recreational activity habits,[59] as well as in cancer incidence rates,[60] between Arabs and Jews in Israel.

Several biological pathways, both hormonal and nonhormonal, were suggested to play a role in the protective effect of exercise on malignancy development. Hormonal systems include sex steroids, insulin and insulinlike growth factors, and adipokines; nonhormonal mechanisms include inflammation, immune function, oxidative stress, and—for colon and breast cancer—reduced gastrointestinal transit time.[61] In the context of aging, it has been implied that habitual physical exercise may help prevent or possibly reverse many aspects of age-related declines in the normal functioning of the immune system.[62] "Inflammaging," the chronic low-grade inflammation that characterizes the aging process,[63] was found to constitute a tumor-promoting environment in older age.[64] Recent evidence suggests that training programs among sedentary elders may reduce inflammation[65] and enhance antigen presentation.[66] Aerobic exercise training was further reported to reduce inflammaging and the incidence of several types of cancer in a naturally aging mouse model.[67] Hence, the ameliorating effects of exercise on the aging immune system may serve as a key mechanism in its role in cancer prevention in older age.[63]

The present investigation has several merits. Only a few studies have specifically explored the association between LTPA engagement and cancer among individuals aged 65 years or older while accounting for myriad potential confounders related to aging.[7,8] The wealth of aging-related information constitutes the primary strength of this study. This factor enabled us to construct a balanced cohort of older individuals who differed with respect to regular engagement in LTPA but were similar with respect to multiple measured characteristics.[48] Our analytic approach constitutes another strength, enabling us to control for a multitude of confounders despite the relatively small

Mayo Clin Proc Inn Qual Out ■ April 2020;4(2):115-125 ■ https://doi.org/10.1016/j.mayocpiqo.2019.11.005
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number of events that occurred. Thus, the approach to confounder adjustment and the rich data set used in our study might overcome some of the limitations faced by previous studies. Also, unlike previous investigations, time to cancer incidence rather than mortality served as the outcome. Furthermore, data on cancer diagnosis were ascertained through a national registry with high completeness of case ascertainment and accuracy.[43]

Several weaknesses should be acknowledged. The main limitation of our study is our reliance on self-reported LTPA. Although found to be reasonably valid among older populations,[68,69] self-reported physical activity may lead to an erroneous estimation of activity levels, which may result in exposure misclassification across activity groups. It cannot be ruled out that the similar risk observed in the sufficiently and insufficiently active groups reflects this misclassification. However, considering the discrete, structured nature of LTPAs that make them comparatively easy to recall,[70] we assume that our approach to exposure measurement would have satisfactorily captured the habitual LTPAs of the study participants and was particularly useful to distinguish between active and inactive individuals.[71] Another limitation that should be recognized is the fairly small number of cases in the major cancer sites in our cohort. Although a site-specific analysis was included, the number of cases was too low to examine these associations with a satisfactory statistical precision. Power considerations also limited the subgroup analysis. Lack of information on nonleisure activities, such as household, occupational, and transportation physical activity, constitutes another limitation of our study, and thus, only a subset of the total physical activity in this population has been captured in this study. Yet, it should be noted that our questionnaire was able to capture other types of moderate physical activity (such as a habitual 10-minute walk to the grocery store) under the category of "any type." Finally, our cohort consists of community-dwelling adults, excluding individuals with cancer history and those with severe cognitive decline. Hence, the results may not be generalizable to these subgroups.

Obviously, randomized controlled trials would be helpful to assess whether a causal relationship exists between engagement in LTPA in older age and cancer risk reduction.[72] However, because randomized controlled trials are not feasible for the long term, carefully designed observational studies will continue to serve as the primary tool for assessing the LTPA-cancer relationship.[73] Because studies of older adults are particularly vulnerable to reverse causation,[25] residual confounding may be even more of a concern than in observational studies of younger populations. Only settings and data sets with extensive and high-quality data on potential confounders can properly address this question. Because cancer prevention intervention among older adults is an area of great interest,[74] although currently underutilized and not well understood,[3] further research is clearly needed. In future investigations, accelerometer-based assessments should be more commonly incorporated to study the relationship between LTPA and cancer incidence among older adults.[75]

CONCLUSION

In this cohort of older adults with a median age of 73 years and abundant information on potential confounders, habitual engagement in LTPA—even at lower levels than officially recommended—was associated with a reduced cancer risk. Results of this investigation highlight the potential role of physical activity in primary prevention of cancer among older individuals.

ACKNOWLEDGMENTS

We thank Dr Yael Netz and Ms Aviva Zeev from the Zinman College of Physical Education and Sport Sciences at the Wingate Institute for assistance with the calculation and classification of physical activity levels.

This work was performed in partial fulfillment of the requirements for the PhD degree (G.C.) from Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BMI** = body mass index; **HR** = hazard ratio; **LTPA** = leisure-time physical activity; **SES** = socioeconomic status

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Grant Support: This work was supported in part by grant 3-12787 from the Chief Scientist Office, Israel Ministry of Health (principal investigator, Y.G.) and research grant awards from the Bircher-Benner Foundation, Sackler Faculty of Medicine (principal investigator, Y.G.), the Stanley Steyer Institute for Cancer Epidemiology and Research (principal investigator, Y.G.), and the Lilian and Marcel Pollak Chair in Biological Anthropology, Sackler Faculty of Medicine, Tel Aviv University, Israel (principal investigator, Y.G.).

Potential Competing Interests: The authors report no competing interests.

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REFERENCES

1. Moore SC, Lee IM, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med*. 2016;176(6):816-825.
2. Watson KB, Carlson SA, Gunn JP, et al. Physical inactivity among adults aged 50 years and older—United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2016;65(36):954-958.
3. Miller SM, Bowen DJ, Lyle J, et al. Primary prevention, aging, and cancer: overview and future perspectives. *Cancer*. 2008;113(12, suppl):3484-3492.
4. Greenlee H, Strizich G, Lovasi GS, et al. Concordance with prevention guidelines and subsequent cancer, cardiovascular disease, and mortality: a longitudinal study of older adults. *Am J Epidemiol*. 2017;186(10):1168-1179.
5. Cerhan JR, Chiu BC, Wallace RB, et al. Physical activity, physical function, and the risk of breast cancer in a prospective study among elderly women. *J Gerontol A Biol Sci Med Sci*. 1998;53(4):M251-M256.
6. Wyrwich KW, Wolinsky FD. Physical activity, disability, and the risk of hospitalization for breast cancer among older women. *J Gerontol A Biol Sci Med Sci*. 2000;55(7):M418-M421.
7. Ueshima K, Ishikawa-Takata K, Yorifuji T, et al. Physical activity and mortality risk in the Japanese elderly: a cohort study. *Am J Prev Med*. 2010;38(4):410-418.
8. Wu C-Y, Hu H-Y, Chou Y-C, Huang N, Chou Y-J, Li C-P. The association of physical activity with all-cause, cardiovascular, and cancer mortalities among older adults. *Prev Med*. 2015;72:23-29.
9. Xiao Q, Yang HP, Wentzensen N, Hollenbeck A, Matthews CE. Physical activity in different periods of life, sedentary behavior, and the risk of ovarian cancer in the NIH-AARP diet and health study. *Cancer Epidemiol Biomarkers Prev*. 2013;22(11):2000-2008.
10. Sinner PJ, Schmitz KH, Anderson KE, Folsom AR. Lack of association of physical activity and obesity with incident pancreatic cancer in elderly women. *Cancer Epidemiol Biomarkers Prev*. 2005;14(6):1571-1573.
11. Wang A, Qin F, Hedlin H, et al. Physical activity and sedentary behavior in relation to lung cancer incidence and mortality in older women: the Women's Health Initiative. *Int J Cancer*. 2016;139(10):2178-2192.
12. Sinner P, Folsom AR, Harnack L, Eberly LE, Schmitz KH. The association of physical activity with lung cancer incidence in a cohort of older women: the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev*. 2006;15(12):2359-2363.
13. Chao A, Connell CJ, Jacobs EJ, et al. Amount, type, and timing of recreational physical activity in relation to colon and rectal cancer in older adults: the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev*. 2004;13(12):2187-2195.
14. Moore DB, Folsom AR, Mink PJ, Hong CP, Anderson KE, Kushi LH. Physical activity and incidence of postmenopausal breast cancer. *Epidemiology*. 2000;11(3):292-296.
15. McTiernan A, Kooperberg C, White E, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. *JAMA*. 2003;290(10):1331-1336.
16. Patel AV, Hildebrand JS, Leach CR, et al. Walking in relation to mortality in a large prospective cohort of older U.S. adults. *Am J Prev Med*. 2018;54(1):10-19.
17. Noor NM, Banim PJ, Luben RN, Khaw KT, Hart AR. Investigating physical activity in the etiology of pancreatic cancer: the age at which this is measured is important and is independent of body mass index. *Pancreas*. 2016;45(3):388-393.
18. Koolhaas CM, Dhana K, Schoufour JD, et al. Physical activity and cause-specific mortality: the Rotterdam Study. *Int J Epidemiol*. 2018;47(5):1705-1713.
19. Mok A, Khaw K-T, Luben R, Wareham N, Brage S. Physical activity trajectories and mortality: population based cohort study. *BMJ*. 2019;365:l2323.
20. Benke IN, Leitzmann MF, Behrens G, Schmid D. Physical activity in relation to risk of prostate cancer: a systematic review and meta-analysis. *Ann Oncol*. 2018;29(5):1154-1179.
21. Brenner DR, Yannitsos DH, Farris MS, Johansson M, Friedenreich CM. Leisure-time physical activity and lung cancer risk: a systematic review and meta-analysis. *Lung Cancer*. 2016;95:17-27.
22. Farris MS, Mosli MH, McFadden AA, Friedenreich CM, Brenner DR. The association between leisure time physical activity and pancreatic cancer risk in adults: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2015;24(10):1462-1473.
23. Schmid D, Behrens G, Keimling M, Jochem C, Ricci C, Leitzmann M. A systematic review and meta-analysis of physical activity and endometrial cancer risk. *Eur J Epidemiol*. 2015;30(5):397-412.
24. Neilson HK, Farris MS, Stone CR, Vaska MM, Brenner DR, Friedenreich CM. Moderate-vigorous recreational physical activity and breast cancer risk, stratified by menopause status: a systematic review and meta-analysis. *Menopause*. 2017;24(3):322-344.
25. Wade KH, Richmond RC, Davey Smith G. Physical activity and longevity: how to move closer to causal inference [editorial]. *Br J Sports Med*. 2018;52(14):890-891.
26. Kujala UM. Is physical activity a cause of longevity? it is not as straightforward as some would believe: a critical analysis. *Br J Sports Med*. 2018;52(14):914-918.
27. Meng X, D'Arcy C. Successful aging in Canada: prevalence and predictors from a population-based sample of older adults. *Gerontology*. 2014;60(1):65-72.
28. Chad KE, Reeder BA, Harrison EL, et al. Profile of physical activity levels in community-dwelling older adults. *Med Sci Sports Exercise*. 2005;37(10):1774-1784.
29. Notthoff N, Reisch P, Gerstorf D. Individual characteristics and physical activity in older adults: a systematic review. *Gerontology*. 2017;63(5):443-459.
30. Picorelli AMA, Pereira LSM, Pereira DS, Felício D, Sherrington C. Adherence to exercise programs for older people is influenced by program characteristics and personal factors: a systematic review. *J Physiother*. 2014;60(3):151-156.

31. Maier H, Smith J. Psychological predictors of mortality in old age. *J Gerontol B Psychol Sci Soc Sci*. 1999;54(1):P44-P54.
32. Gross AL, Gallo JJ, Eaton WW. Depression and cancer risk: 24 years of follow-up of the Baltimore Epidemiologic Catchment Area sample. *Cancer Causes Control*. 2010;21(2):191-199.
33. Jia Y, Li F, Liu YF, Zhao JP, Leng MM, Chen L. Depression and cancer risk: a systematic review and meta-analysis. *Public Health*. 2017;149:138-148.
34. Jackson SE, Williams K, Beeken RJ, Steptoe A. Changes in health and wellbeing in the years leading up to a cancer diagnosis: a prospective cohort study. *Cancer Prev Res (Phila)*. 2019;12(2):79-88.
35. Akinyemiju T, Ogunsina K, Okwali M, Sakhuja S, Braithwaite D. Lifecourse socioeconomic status and cancer-related risk factors: analysis of the WHO Study on Global Ageing and Adult Health (SAGE). *Int J Cancer*. 2017;140(4):777-787.
36. Braveman PA, Cubbin C, Egerter S, et al. Socioeconomic status in health research: one size does not fit all. *JAMA*. 2005;294(22):2879-2888.
37. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348(17):1625-1638.
38. Goshen A, Goldbourt U, Shohat T, Shimony T, Keinan-Boker L, Gerber Y. Diet quality in relation to healthy ageing: the Israeli Longitudinal Study on Aging (ILSA)—a study protocol. *BMJ Open*. 2019;9(4):e024673.
39. ICDC. Mabat Zahav National Health and Nutrition Survey Age 65 and over 2005-2006. https://www.health.gov.il/PublicationsFiles/Mabat_2005-2006-a.pdf. Published 2011. Accessed March 3, 2020.
40. Netz Y, Goldsmith R, Shimony T, Ben-Moshe Y, Zeev A. Adherence to physical activity recommendations in older adults: an Israeli national survey. *J Aging Phys Act*. 2011;19(1):30-47.
41. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 10th ed. Philadelphia, PA: Wolters Kluwer; 2018.
42. State of Israel Ministry of Health. Israel National Cancer Registry. https://www.health.gov.il/English/MinistryUnits/HealthDivision/Icdc/Icr/Pages/default.aspx. Accessed March 13, 2020.
43. Fishler Y, Keinan-Boker L, Ben-Adiva E, Zatlawi M, Davidov O, Edri H. The Israel National Cancer Registry: Completeness and Timeliness of Data. Results of a National Survey. https://www.Health.Gov.Il/publicationsfiles/icdc_365_en_summary.pdf. Published 2017. Accessed March 13, 2020.
44. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged: the Index of ADL; a standardized measure of biological and psychosocial function. *JAMA*. 1963;185:914-919.
45. Goldberg DP, Gater R, Sartorius N, et al. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychol Med*. 1997;27(1):191-197.
46. Folstein MF, Folstein SE, McHugh PR. Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
47. Johnson RK, Driscoll P, Goran MI. Comparison of multiple-pass 24-hour recall estimates of energy intake with total energy expenditure determined by the doubly labeled water method in young children. *J Am Diet Assoc*. 1996;96(11):1140-1144.
48. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med*. 2014;33(7):1242-1258.
49. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value Health*. 2010;13(2):273-277.
50. Hernán MA, Robins JM. *Causal Inference: What If*. Boca Raton, FL: Chapman & Hall/CRC Press; 2020.
51. Cox DR. Regression models and life-tables. *J R Stat Soc B*. 1972;34(2):187-220.
52. Abramson JH. WINPEPI (PEPI-for-Windows): computer programs for epidemiologists. *Epidemiol Perspect Innov*. 2004;1(1):6.
53. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.
54. Wolbers M, Koller MT, Witteman JCM, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology*. 2009;20(4):555-561.
55. Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing risk of death: an important consideration in studies of older adults. *J Am Geriatr Soc*. 2010;58(4):783-787.
56. Monninkhof EM, Elias SG, Vlems FA, et al. Physical activity and breast cancer: a systematic review. *Epidemiology*. 2007;18(1):137-157.
57. Hupin D, Roche F, Gremeaux V, et al. Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged ≥60 years: a systematic review and meta-analysis. *Br J Sports Med*. 2015;49(19):1262-1267.
58. Jefferis BJ, Parsons TJ, Sartini C, et al. Objectively measured physical activity, sedentary behaviour and all-cause mortality in older men: does volume of activity matter more than pattern of accumulation? *Br J Sports Med*. 2019;53(16):1013-1020.
59. Israel Center for Disease Control, Ministry of Health, and Israel Ministry of Culture and Sports. Physical Activity Survey Among Israelis Aged 21 and Above [in Hebrew]. Publication 349. https://www.health.gov.il/publicationsfiles/activities21_01122012.pdf. Published 2012. Accessed March 13, 2020.
60. Muhsen K, Green MS, Soskolne V, Neumark Y. Inequalities in non-communicable diseases between the major population groups in Israel: achievements and challenges. *Lancet*. 2017;389(10088):2531-2541.
61. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. *Eur J Cancer*. 2010;46(14):2593-2604.
62. Simpson RJ, Guy K. Coupling aging immunity with a sedentary lifestyle: has the damage already been done?—a mini-review. *Gerontology*. 2010;56(5):449-458.
63. Bigley AB, Spielmann G, LaVoy EC, Simpson RJ. Can exercise-related improvements in immunity influence cancer prevention and prognosis in the elderly? *Maturitas*. 2013;76(1):51-56.
64. Anisimov VN. Biology of aging and cancer. *Cancer Control*. 2007;14(1):23-31.
65. Timmerman KL, Flynn MG, Coen PM, Markofski MM, Pence BD. Exercise training-induced lowering of inflammatory (CD14+CD16+) monocytes: a role in the anti-inflammatory influence of exercise? *J Leukoc Biol*. 2008;84(5):1271-1278.
66. Shimizu K, Suzuki N, Imai T, et al. Monocyte and T-cell responses to exercise training in elderly subjects. *J Strength Cond Res*. 2011;25(9):2565-2572.
67. Nilsson MI, Bourgeois JM, Nederveen JP, et al. Lifelong aerobic exercise protects against inflammaging and cancer. *PLoS One*. 2019;14(1):e0210863.
68. Lewis LS, Hernon J, Clark A, Saxton JM. Validation of the IPAQ against different accelerometer cut-points in older cancer survivors and adults at risk of cancer. *J Aging Phys Act*. 2018;26(1):34-40.
69. Orsini N, Bellocco R, Bottai M, et al. Validity of self-reported total physical activity questionnaire among older women. *Eur J Epidemiol*. 2008;23(10):661-667.
70. Matthews CE, Moore SC, George SM, Sampson J, Bowles HR. Improving self-reports of active and sedentary behaviors in large epidemiologic studies. *Exerc Sport Sci Rev*. 2012;40(3):118-126.
71. Siebeling L, Wiebers S, Beem L, Puhan MA, Ter Riet G. Validity and reproducibility of a physical activity questionnaire for older adults: questionnaire versus accelerometer for assessing physical activity in older adults. *Clin Epidemiol*. 2012;4:171-180.
72. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. *Lancet Oncol*. 2017;18(8):e457-e471.
73. Giovannucci E. An integrative approach for deciphering the causal associations of physical activity and cancer risk: the role of adiposity. *J Nat Cancer Inst*. 2018;110(9):935-941.
74. Brown JC, Winters-Stone K, Lee A, Schmitz KH. Cancer, physical activity, and exercise. *Compr Physiol*. 2012;2(4):2775-2809.
75. Sternfeld B, Gabriel KP, Jiang SF, et al. Risk estimates for diabetes and hypertension with different physical activity methods. *Med Sci Sports Exerc*. 2019;51(12):2498-2505.