Original Investigation

Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults

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IMPORTANCE Leisure-time physical activity has been associated with lower risk of heart-disease and all-cause mortality, but its association with risk of cancer is not well understood.

OBJECTIVE To determine the association of leisure-time physical activity with incidence of common types of cancer and whether associations vary by body size and/or smoking.

DESIGN, SETTING, AND PARTICIPANTS We pooled data from 12 prospective US and European cohorts with self-reported physical activity (baseline, 1987-2004). We used multivariable Cox regression to estimate hazard ratios (HRs) and 95% confidence intervals for associations of leisure-time physical activity with incidence of 26 types of cancer. Leisure-time physical activity levels were modeled as cohort-specific percentiles on a continuous basis and cohort-specific results were synthesized by random-effects meta-analysis. Hazard ratios for high vs low levels of activity are based on a comparison of risk at the 90th vs 10th percentiles of activity. The data analysis was performed from January 1, 2014, to June 1, 2015.

EXPOSURES Leisure-time physical activity of a moderate to vigorous intensity.

MAIN OUTCOMES AND MEASURES Incident cancer during follow-up.

RESULTS A total of 1.44 million participants (median [range] age, 59 [19-98] years; 57% female) and 186 932 cancers were included. High vs low levels of leisure-time physical activity were associated with lower risks of 13 cancers: esophageal adenocarcinoma (HR, 0.58; 95% CI, 0.37-0.89), liver (HR, 0.73; 95% CI, 0.55-0.98), lung (HR, 0.74; 95% CI, 0.71-0.77), kidney (HR, 0.77; 95% CI, 0.70-0.85), gastric cardia (HR, 0.78; 95% CI, 0.64-0.95), endometrial (HR, 0.79; 95% CI, 0.68-0.92), myeloid leukemia (HR, 0.80; 95% CI, 0.70-0.92), myeloma (HR, 0.83; 95% CI, 0.72-0.95), colon (HR, 0.84; 95% CI, 0.77-0.91), head and neck (HR, 0.85; 95% CI, 0.78-0.93), rectal (HR, 0.87; 95% CI, 0.80-0.95), bladder (HR, 0.87; 95% CI, 0.82-0.92), and breast (HR, 0.90; 95% CI, 0.87-0.93). Body mass index adjustment modestly attenuated associations for several cancers, but 10 of 13 inverse associations remained statistically significant after this adjustment. Leisure-time physical activity was associated with higher risks of malignant melanoma (HR, 1.27; 95% CI, 1.16-1.40) and prostate cancer (HR, 1.05; 95% CI, 1.03-1.08). Associations were generally similar between overweight/obese and normal-weight individuals. Smoking status modified the association for lung cancer but not other smoking-related cancers.

CONCLUSIONS AND RELEVANCE Leisure-time physical activity was associated with lower risks of many cancer types. Health care professionals counseling inactive adults should emphasize that most of these associations were evident regardless of body size or smoking history, supporting broad generalizability of findings.

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Physical activity is known to reduce risks of heart disease and all-cause mortality,[1] as well as risks of colon, breast, and endometrial cancers.[2] Less is known, however, about whether physical activity reduces risk of other cancers, which, together, constitute 75% of incident cancers in the United States[3] and 61% of cancers worldwide.[4] Physical inactivity is highly prevalent, with an estimated 51% of people in the United States[5] and 31% of people worldwide not attaining recommended physical activity levels.[6] Any decrease in risk of cancer associated with physical activity may therefore be relevant to public health and cancer prevention efforts.

To date, hundreds of prospective studies have examined associations between physical activity and cancer risk,[2] but, owing to small case numbers, results have been inconclusive for most cancer types. Meta-analyses, to a degree, mitigate the sample size issue by pooling the published studies.[2(pp198-209)] However, pooled studies have typically been heterogeneous in study design (eg, case-control vs prospective cohort), physical activity types examined (eg, leisure-time vs occupational activity), and in the contrasts examined (tertiles vs quintiles). Such heterogeneity can attenuate risk estimates, thereby masking true underlying associations.

In the present study, we examined leisure-time physical activity in relation to risk of 26 different cancer types in a pooled analysis of 12 prospective cohort studies and 1.44 million participants. We address several methodologic limitations in prior research by attaining case numbers comparable to or exceeding that of the current literature for most cancer types (see eTable 1 in the Supplement), by restricting analyses to a specific study design (prospective cohort) and type of physical activity (leisure time), and by examining the same consistent and large contrast (90th vs 10th percentile) across studies. Our objectives were to determine the cancers associated with leisure-time physical activity, and whether associations varied by excess bodyweight and smoking, among other factors of prior interest. Our hypothesis was that higher levels of leisure-time physical activity would be associated with lower risk of the 26 cancer types.

Key Points

Question What is the association of leisure-time physical activity with incidence of 26 types of cancer, and do the associations vary by body size and/or smoking?

Findings In this study of pooled data from 12 US and European cohorts, high vs low levels of leisure-time physical activity were associated with lower risks of 13 of 26 cancers. Most of these associations were evident regardless of body size or smoking history.

Meaning Promotion of physical activity may be important for population-wide cancer prevention and control efforts.

Methods

Study Population

The Physical Activity Collaboration of the National Cancer Institute's Cohort Consortium was formed to estimate physical activity and disease associations using pooled prospective data and a standardized analytical approach. In a prior pooled analysis, we evaluated dose-response associations between leisure-time physical activity and mortality.[1]

Prospective studies in the National Cancer Institute Cohort Consortium were eligible for inclusion in the present study if they assessed leisure-time physical activity and had appropriate covariate data. For cohorts with key data missing at baseline but collected later (5 cohorts), baseline was redefined as the later date. Twenty of 23 cohorts (87%) met the inclusion criteria and 12 (52%) agreed to participate, including 8 from the United States and 4 from Europe (**Table 1**).[7-18] Each study received approval from its respective institutional review board.

Leisure-Time Physical Activity Assessment

Leisure-time physical activities are activities done at an individual's discretion that improve or maintain fitness or health. Our analysis includes leisure-time activities of moderate intensity, defined as an intensity of 3 or more metabolic equivalents (METs), or vigorous intensity, defined as 6 or more METs; these are the intensity levels recommended by physical activity guidelines.[19(pvii)]

Seven of the 12 cohorts[9-11,14,15,18] (29% of the overall sample) assessed time per week in moderate and vigorous leisure-time physical activities, enabling calculation of MET-hours per week. These cohorts assessed physical activity by asking about discrete activities such as walking, running, or swimming,[9,11] or, alternately, by inquiring about overall weekly participation in moderate- to vigorous-intensity activities.[10,14,15,18] The median activity level was 8 MET-h/wk (interquartile range, 4-22 MET-h/wk) overall, and in 6 of 7 cohorts (eTable 2 in the Supplement). This is equivalent to 150 minutes of moderate-intensity activity (eg, walking) per week, and comparable to the median activity level for the US population.[5] Of the remaining cohorts, 4 evaluated only vigorous-intensity leisure-time physical activity,[8,13,16,17] and 1 evaluated frequency of moderate- to vigorous-intensity activities, but not time spent.[12] Ten of 12 cohorts used questionnaires previously validated against objective criterion measures (eMethods in the Supplement).

Leisure-time physical activity levels were harmonized by converting them to cohort-specific percentiles, with values from 0 (low activity) to 100 (high activity). If physical activity was based on categorical responses, the percentile at the category midpoint was assigned. For example, if 20% of participants indicated the lowest level of activity, they were assigned the 10th percentile.

Cancer Ascertainment

Incident first primary cancers were identified by follow-up questionnaires and review of medical records,[7-9] cancer registry linkage,[10-12,18] or both.[13-17] Overall, 99% of cancer cases were confirmed by medical records or pathology reports. Cancer type was defined using the Surveillance, Epidemiology, and End Results site recode and the *International Classification of Diseases for Oncology, Third Edition*[20] (eTable 3 in the Supplement). Participants were observed from baseline to date of cancer diagnosis, death, or end of follow-up, whichever came first. Cancer types were selected for analysis if there were at least

Table 1. Selected Participant Characteristics According to Cohort Study

Cohort[a]	Participants	Men	Women	Study Entry	Follow-Up, Median (Maximum), y	Age, Median (Range), y	BMI, Median (IQR)	Ever Smokers, %
AARP	507 826	308 073	199 753	1995-1997	11 (11)	62 (50-71)	27 (24-29)	61
BCDDP	37 228	0	37 228	1987-1989	9 (11)	60 (39-93)	25 (22-27)	42
COSM	40 919	40 919	0	1998	10 (10)	60 (45-80)	26 (24-28)	63
CPSII	154 425	73 083	81 342	1992-1993	14 (17)	63 (40-91)	26 (23-28)	55
EPIC	410 165	126 664	283 501	1991-2001	12 (18)	52 (19-98)	26 (22-28)	49
IWHS	37 584	0	37 584	1986	20 (20)	61 (52-70)	26 (23-29)	34
PHS	27 890	27 890	0	1982-2001	21 (28)	54 (40-87)	25 (23-27)	47
PLCO	60 200	30 970	29 230	1993-2003	9 (13)	62 (52-77)	27 (24-30)	53
SMC	33 006	0	33 006	1998	10 (10)	60 (47-83)	25 (22-27)	46
USRT	57 967	12 357	45 610	1994-1998	9 (12)	45 (31-88)	26 (22-28)	44
WHS	39 414	0	39 414	1993-1996	17 (18)	52 (39-90)	26 (22-28)	49
WLH	30 000	0	30 000	2003-2004	7 (7)	51 (40-62)	25 (22-27)	51
Total	1 436 624	619 956	816 668	1982-2004	11 (28)	59 (19-98)	26 (23-29)	54

[a] Abbreviations: AARP, National Institutes of Health–AARP Diet and Health Study; BCDDP, Breast Cancer Detection and Demonstration Project; COSM, Cohort of Swedish Men; CPS II, Cancer Prevention Study II; EPIC, European Prospective Investigation Into Cancer and Nutrition; IQR, interquartile range; IWHS, Iowa Women's Health Study; PHS, Physician's Health Study I and II; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SMC, Swedish Mammography Cohort; USRT, US Radiologic Technologists Cohort; WHS, Women's Health Study; WLH, Women's Lifestyle and Health Study.

300 cases across studies. For each cancer, only cohorts with at least 15 cases were included for analysis (eTable 4 in the Supplement).

Statistical Analysis

Cox proportional hazards models were used to estimate HRs and 95% confidence intervals (CIs) for the association between leisure-time physical activity and cancer. The linearity of physical activity and cancer associations was evaluated with cubic splines and likelihood ratio tests. Associations were predominantly linear (eFigure 1 in the Supplement); therefore, physical activity was modeled on a continuous linear basis for subsequent analyses. Hazard ratios for higher vs lower physical activity levels are estimated by comparing hazards at the 90th and 10th percentiles of cohort-specific distributions, respectively. Hazard ratios comparing higher vs lower activity levels were computed as $e^{90\beta\text{-}10\beta}$, where β is the log HR from the model for the continuous physical activity percentile. DerSimonian and Laird[21] random-effects meta-analysis methods were used to summarize cohort- and cancer site-specific results. $P < .05$ was considered statistically significant. To account for an increased type I error rate due to testing of multiple outcomes, we also calculated the false-discovery rate[22] for primary findings. Statistical heterogeneity between studies was evaluated by Cochran Q.[23] Analyses were performed in SAS, version 9.4.

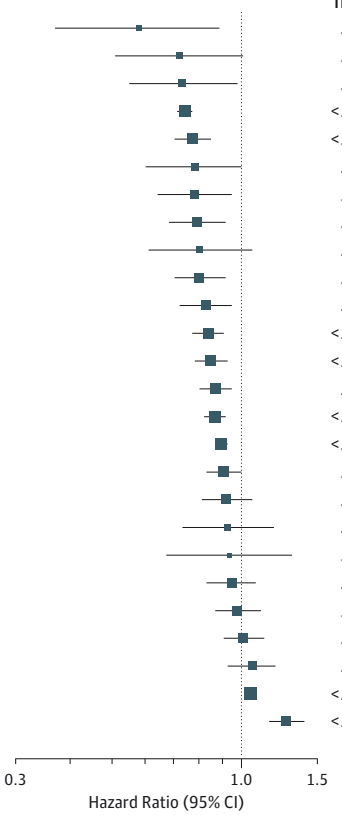
Models included age, sex, smoking, alcohol, race/ethnicity, education, and, for female-only cancers, hormone therapy, oral contraceptive use, age at menarche, age at menopause, and parity. For ovarian and endometrial cancers, women who reported a history of oophorectomy and hysterectomy at baseline, respectively, were excluded from analysis. Covariates were selected on the basis of known associations with cancer and are similar to those used in a study by Park et al[24] of multiple cancer end points. Multiple-imputation procedures[25(pp104-117)] were used to accommodate missing data within each cohort, with the overall proportions of missing data as follows: smoking status (2.3%), alcohol intake (1.3%), race/ethnicity (1.7%), education (2.9%), hormone therapy (2.2%), oral contraceptive use (0.8%), age at menarche (1.1%), age at menopause (1.2%), and parity (1.9%). We also evaluated the role of body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) in physical activity–cancer associations by running all models with and without adjustment for BMI.

We evaluated multiplicative effect modification by BMI (<25, ≥25), smoking status (current, former, never smokers), geographic region (United States, Europe), postmenopausal hormone therapy (women only: ever-user, never-user), sex, race (white, black), and follow-up (<5 years, ≥5 years) using the Wald test for homogeneity. Interactions were declared if $P < .01$.

We conducted selected cancer subgroup analyses using additional detailed data from the National Institutes of Health (NIH)-AARP Diet and Health Study (eMethods in the Supplement). Specifically, we examined associations for estrogen receptor (ER)-positive and -negative breast cancers and for nonadvanced and advanced prostate cancers. These specific cancers and subtypes were selected on the basis of prior data suggesting subtype specificity of associations.[26,27] We also examined malignant melanoma associations stratified by ground-level solar UV radiation of participant residence, as determined by linkage to the solar UV radiation data set from the National Aeronautics and Space Administration (eMethods in the Supplement). We evaluated diet as a potential confounder by adding covariates for intake of kilocalories, multivitamins, individual vitamin supplements, fruit, vegetables, and red meat. These diet covariates are the same as in Park et al.[24]

Figure 1. Summary Multivariable Hazard Ratios for a Higher (90th Percentile) vs Lower (10th Percentile) Level of Leisure-Time Physical Activity by Cancer Type

Cancer	Studies, No.	Cases, No.	HR (95% CI)	*P* Value Trend	*P* Value Heterogeneity[a]
Esophageal adenocarcinoma	5	899	0.58 (0.37-0.89)	.01	.01
Gallbladder	6	382	0.72 (0.51-1.01)	.06	.29
Liver	10	1384	0.73 (0.55-0.98)	.04	.02
Lung	12	19 133	0.74 (0.71-0.77)	<.001	.47
Kidney	11	4548	0.77 (0.70-0.85)	<.001	.40
Small intestine	7	503	0.78 (0.60-1.00)	.05	.85
Gastric cardia	6	790	0.78 (0.64-0.95)	.02	.99
Endometrial	9	5346	0.79 (0.68-0.92)	.003	.001
Esophageal squamous	6	442	0.80 (0.61-1.06)	.12	.78
Myeloid leukemia	10	1692	0.80 (0.70-0.92)	.002	.78
Myeloma	9	2161	0.83 (0.72-0.95)	.008	.36
Colon	12	14 160	0.84 (0.77-0.91)	<.001	.01
Head and neck	11	3985	0.85 (0.78-0.93)	<.001	.45
Rectum	12	5531	0.87 (0.80-0.95)	.001	.38
Bladder	12	9073	0.87 (0.82-0.92)	<.001	.84
Breast	10	35 178	0.90 (0.87-0.93)	<.001	.30
Non-Hodgkin lymphoma	11	6953	0.91 (0.83-1.00)	.05	.18
Thyroid	11	1829	0.92 (0.81-1.06)	.26	.48
Gastric noncardia	7	1428	0.93 (0.73-1.19)	.56	.09
Soft tissue	10	851	0.94 (0.67-1.31)	.70	.03
Pancreas	10	4186	0.95 (0.83-1.08)	.40	.14
Lymphocytic leukemia	10	2160	0.98 (0.87-1.11)	.73	.99
Ovary	9	2880	1.01 (0.91-1.13)	.81	.98
Brain	10	2110	1.06 (0.93-1.20)	.41	.43
Prostate	7	46 890	1.05 (1.03-1.08)	<.001	.90
Malignant melanoma	12	12 438	1.27 (1.16-1.40)	<.001	.02



Multivariable models were adjusted for age, sex, smoking status (never, former, current), alcohol consumption (0, 0.1-14.9, 15.0-29.9, and ≥30.0 g/d), education (did not complete high school, completed high school, post–high-school training, some college, completed college), and race/ethnicity (white, black, other). Models for endometrial, breast, and ovarian cancers are additionally adjusted for postmenopausal hormone therapy use (ever, never), oral contraceptive use (ever, never), age at menarche (<10, 10-11, 12-13, ≥14 years), age at menopause (premenopausal, 40-44, 45-49, 50-54, ≥55 years), and parity (0, 1, 2, ≥3 children). The Surveillance, Epidemiology, and End Results site recode and the *International Classification of Diseases for Oncology, Third Edition,* code corresponding to each cancer type are shown in eTable 3 in the Supplement. Data markers indicate hazard ratio, and error bars, 95% confidence intervals. Size of the data markers corresponds to the relative weight assigned in the pooled analysis using random-effects meta-analysis.

[a] Indicates the *P* value for heterogeneity across participating studies.

Results

In our pooled data set, 1.44 million of 1.65 million participants had complete leisure-time physical activity data and no history of cancer at baseline. Among participants, 57% were women, the median age at baseline was 59 years (range, 19-98 years), and the median BMI was 26 (interquartile range, 23-29) (Table 1). Higher activity levels were associated with younger age, more education, lower BMI, and lower likelihood of being a current smoker (eTable 5 in the Supplement). During a median 11 years (interquartile range, 9-12 years) of follow-up, 186 932 incident cancers were identified.

A higher level of leisure-time physical activity was associated with lower risk for 13 of the 26 types of cancer (**Figure 1**, eFigure 2 in the Supplement). Compared with a lower level of leisure-time physical activity (10th percentile), higher level of activity (at the 90th percentile) had strong inverse associations (greater than 20% reduction in risk) for 7 cancers: esophageal adenocarcinoma (HR, 0.58 [95% CI, 0.37-0.89]), cancers of the liver (HR, 0.73 [95% CI, 0.55-0.98]), lung (HR, 0.74 [95% CI, 0.71-0.77]), kidney (HR, 0.77 [95% CI, 0.70-0.85]), gastric cardia (HR, 0.78 [95% CI, 0.64-0.95]), and endometrium (HR, 0.79 [95% CI, 0.68-0.92]), and myeloid leukemia (HR, 0.80 [95% CI, 0.70-0.92]). Moderate inverse associations (10%-20% reduction in risk) were observed for myeloma (HR, 0.83 [95% CI, 0.72-0.95]), colon cancer (HR, 0.84 [95% CI, 0.77-0.91]), head and neck cancer (HR, 0.85 [95% CI, 0.78-0.93]), rectal cancer (HR, 0.87 [95% CI, 0.80-0.95]), bladder cancer (HR, 0.87 [95% CI, 0.82-0.92]), and breast cancer (HR, 0.90 [95% CI, 0.87-0.93]). Suggestive inverse associations were also noted for gallbladder cancer (HR, 0.72 [95% CI, 0.51-1.01]), small intestine cancer (HR, 0.78 [95% CI, 0.60-1.00]), and non-Hodgkin lymphoma (HR, 0.91 [95% CI, 0.83-1.00]). Higher levels of physical activity were associated with an increased risk of prostate cancer (HR, 1.05 [95% CI, 1.03-1.08]) and malig-

Table 2. Comparison of Multivariable Hazard Ratios (HRs)[a] for a Higher (90th Percentile) vs Lower (10th Percentile) Level of Leisure-Time Physical Activity by Cancer Type, Without and With Adjustment for Body Mass Index (BMI)[b]

Cancer[c]	HR (95% CI)		Difference in HR, %
	Not BMI Adjusted	BMI Adjusted	
Esophageal adenocarcinoma	0.58 (0.37-0.89)	0.62 (0.40-0.97)	6.9[d]
Gallbladder	0.72 (0.51-1.01)	0.78 (0.57-1.06)	8.3[d]
Liver	0.73 (0.55-0.98)	0.81 (0.61-1.09)	11.0[d]
Lung	0.74 (0.71-0.77)	0.73 (0.70-0.76)	−1.4
Kidney	0.77 (0.70-0.85)	0.84 (0.77-0.91)	9.1[d]
Small intestine	0.78 (0.60-1.00)	0.81 (0.62-1.05)	3.8
Gastric cardia	0.78 (0.64-0.95)	0.85 (0.69-1.04)	9.0[d]
Endometrial	0.79 (0.68-0.92)	0.98 (0.89-1.09)	24.1[d]
Esophageal squamous	0.80 (0.61-1.06)	0.76 (0.58-1.01)	−5.0[d]
Myeloid leukemia	0.80 (0.70-0.92)	0.85 (0.73-0.97)	6.2[d]
Myeloma	0.83 (0.72-0.95)	0.87 (0.77-0.98)	4.8
Colon	0.84 (0.77-0.91)	0.87 (0.80-0.94)	3.6
Head and neck	0.85 (0.78-0.93)	0.85 (0.77-0.94)	0.0
Rectum	0.87 (0.80-0.95)	0.88 (0.81-0.96)	1.1
Bladder	0.87 (0.82-0.92)	0.88 (0.83-0.94)	1.1
Breast	0.90 (0.87-0.93)	0.93 (0.90-0.96)	3.3
Non-Hodgkin lymphoma	0.91 (0.83-1.00)	0.94 (0.85-1.04)	3.3
Thyroid	0.92 (0.81-1.06)	0.95 (0.81-1.11)	3.3
Gastric noncardia	0.93 (0.73-1.19)	0.92 (0.73-1.15)	−1.1
Soft tissue	0.94 (0.67-1.31)	0.97 (0.70-1.34)	3.2
Pancreas	0.95 (0.83-1.08)	0.98 (0.86-1.12)	3.2
Lymphocytic leukemia	0.98 (0.87-1.11)	0.99 (0.88-1.12)	1.0
Ovary	1.01 (0.91-1.13)	1.03 (0.92-1.15)	2.0
Brain	1.06 (0.93-1.20)	1.06 (0.92-1.22)	0.0
Prostate	1.05 (1.03-1.08)	1.04 (1.01-1.07)	−1.0
Malignant melanoma	1.27 (1.16-1.40)	1.28 (1.17-1.41)	0.8

[a] All models were adjusted for age, sex, smoking status (never, former, current), alcohol consumption (0, 0.1-14.9, 15.0-29.9, and ≥30.0 g/d), education (did not complete high school, completed high school, post–high-school training, some college, completed college), and race/ethnicity (white, black, other). Models for endometrial, breast, and ovarian cancers are additionally adjusted for postmenopausal hormone therapy use (ever, never), oral contraceptive use (ever, never), age at menarche (<10, 10-11, 12-13, ≥14 years), age at menopause (premenopausal, 40-44, 45-49, 50-54, ≥55 years), and parity (0, 1, 2, ≥3 children).

[b] BMI was calculated as weight in kilograms divided by height in meters squared. Categories used for adjustment were as follows: less than 18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, 40.0 or more.

[c] The Surveillance, Epidemiology, and End Results site recode and the *International Classification of Diseases for Oncology, Third Edition*, code[20] corresponding to each cancer type are shown in eTable 3 in the Supplement.

[d] Change of 5% or more in HR after adjustment for BMI.

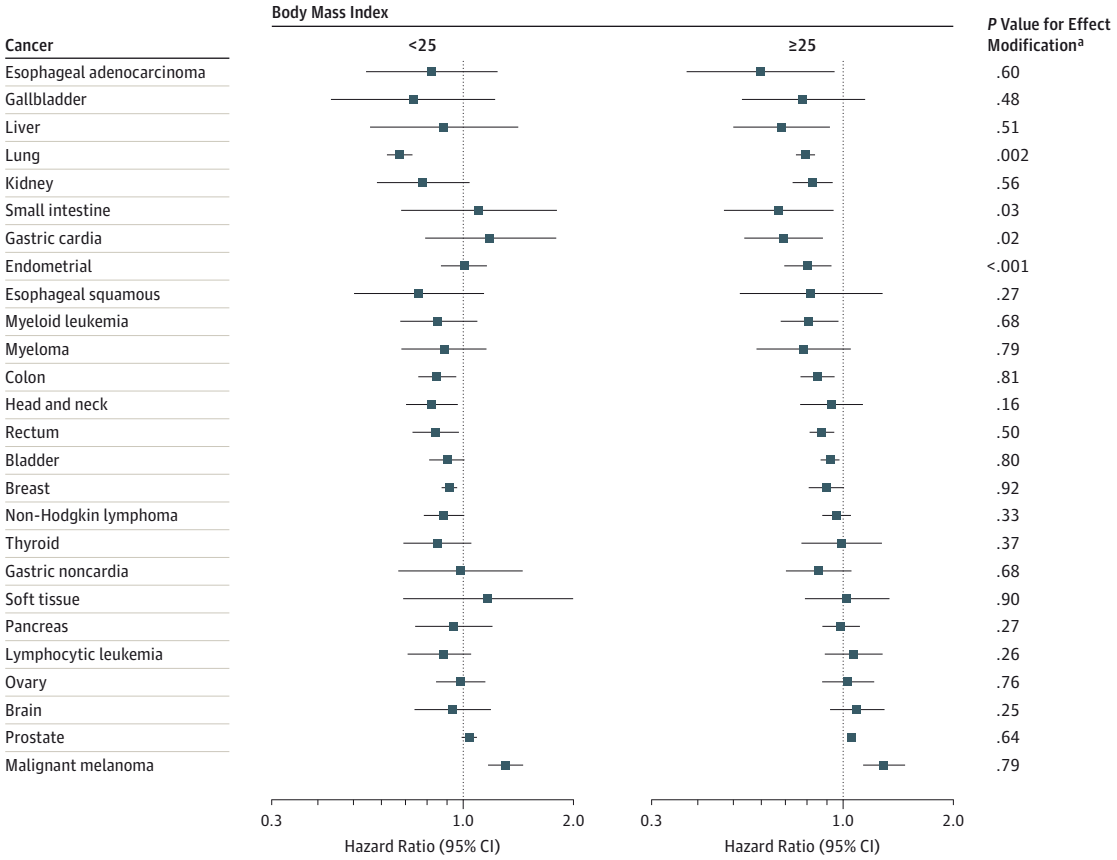
nant melanoma (HR, 1.27 [95% CI, 1.16-1.40]). Over the 26 cancers, the estimated false-discovery rate is 7%. This low false-discovery rate suggests that chance is unlikely to explain any more than 1 to 2 study findings. In aggregate, higher levels of physical activity were associated with a 7% lower risk of total cancer (HR, 0.93 [95% CI, 0.90-0.95]).

Heterogeneity between studies was modest, with nominal heterogeneity ($P < .05$) for esophageal adenocarcinoma, liver cancer, soft-tissue cancer, colon cancer, melanoma, and endometrial cancer. Exact causes of heterogeneity could not be determined with certainty, but for esophageal adenocarcinoma, liver cancer, and soft-tissue cancer, variability in HRs may reflect small case numbers. For colon cancer, associations were weaker in female cohorts, and, for melanoma, associations were stronger in European studies (possibly reflecting skin tone). For endometrial cancer, 1 outlying result appears to drive heterogeneity, but the reason for the outlier is not understood. Despite quantitative heterogeneity, point estimates for each study were generally consistent in direction. In an influence analysis, excluding each study in turn only modestly affected HRs (eTable 6 in the Supplement).

Adjusting for BMI attenuated associations for esophageal adenocarcinoma and cancers of the liver, kidney, and gastric cardia (ie, increase of 5%-11% in HRs) (see **Table 2** and eFigure 3 in the Supplement) and nullified the association for endometrial cancer; that is, the HR increased from 0.79 (statistically significant) to 0.98 (nonsignificant). Associations for liver and gastric cardia were no longer statistically significant in BMI-adjusted models, although HRs were still consistent with 15% to 20% lower risk. Otherwise, the effects of adjustment for BMI were modest, and 10 of 13 inverse associations remained statistically significant after adjustment.

Effect modification by BMI was modest (**Figure 2**) except for a slightly stronger lung cancer association (P for heterogeneity = .002) and a null endometrial cancer association (P for heterogeneity < .001) in those with a BMI lower than 25. Effect modification by smoking history (**Figure 3**) was also modest, except for a null lung cancer association in never smokers (P for heterogeneity < .001) and an inverse myeloma association in never smokers that became positive in current smokers (P for heterogeneity = .002). There was no effect modification of associations by geographic region (eFigure 4 in the Supplement), hormone therapy use (eFigure 5 in the Supplement), sex (eFigure 6 in the Supplement), race (limited subset of cancers) (eFigure 7 in the Supplement), or follow-up time (eFigure 8 in the Supplement), except for myeloma, for which case numbers were small. Restriction to studies with validated questionnaires resulted in no changes in HRs greater than

Figure 2. Summary Multivariable Hazard Ratios and 95% Confidence Intervals for a Higher (90th Percentile) vs Lower (10th Percentile) Level of Leisure-Time Physical Activity by Cancer Type, Stratified by Body Mass Index of Less Than 25 vs 25 or Higher



Multivariable models were adjusted for age, sex, smoking status (never, former, current), alcohol consumption (0, 0.1-14.9, 15.0-29.9, and ≥30.0 g/d), education (did not complete high school, completed high school, post–high-school training, some college, completed college), and race/ethnicity (white, black, other). Models for endometrial, breast, and ovarian cancers are additionally adjusted for postmenopausal hormone therapy use (ever, never), oral contraceptive use (ever, never), age at menarche (<10, 10-11, 12-13, ≥14 years), age at menopause (premenopausal, 40-44, 45-49, 50-54, ≥55 years), and parity (0, 1, 2, ≥3 children). Body mass index is calculated as weight in kilograms divided by height in meters squared. Data markers indicate hazard ratio, and error bars, 95% confidence intervals. Size of the data markers corresponds to the relative weight assigned in the pooled analysis using random-effects meta-analysis.

[a] Indicates the *P* value for effect modification by body mass index.

6%, and associations did not become uniformly stronger or weaker (eTable 7 in the Supplement).

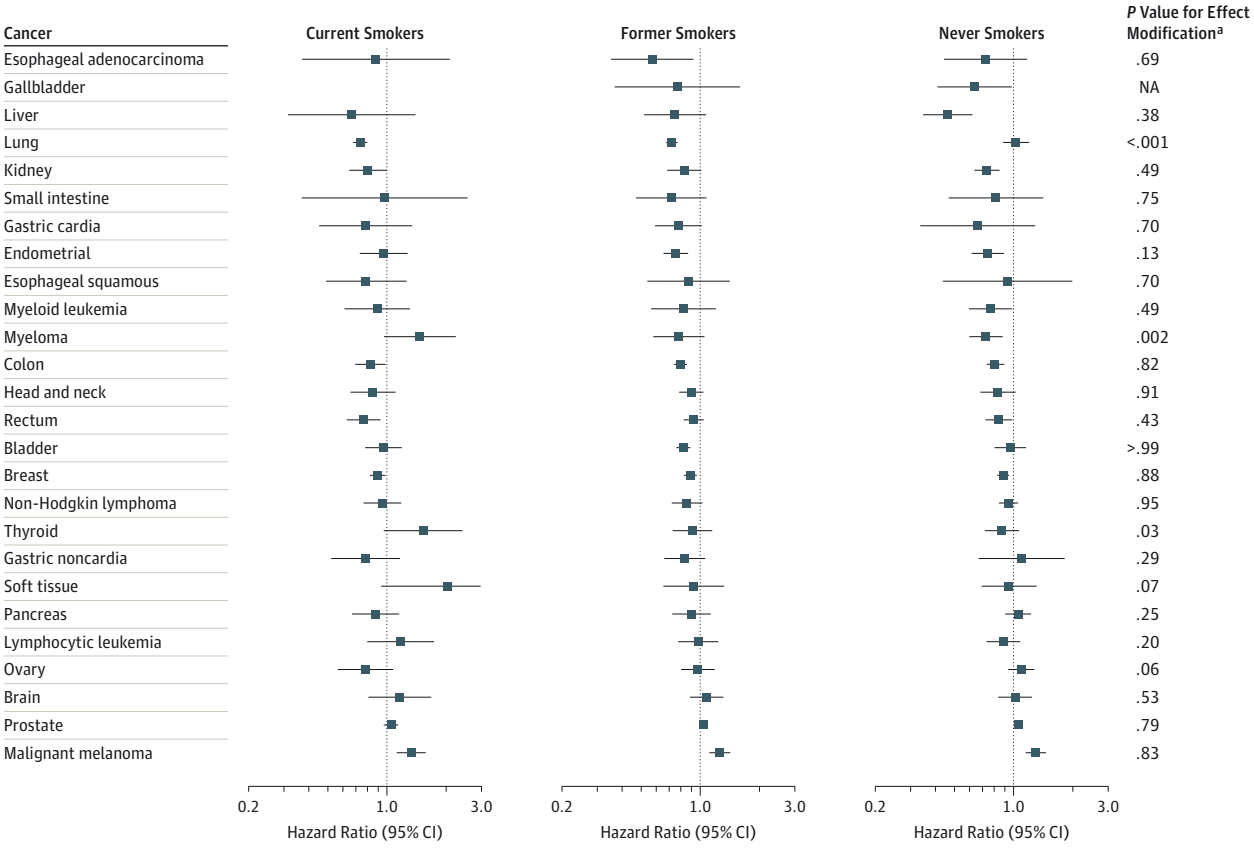
In additional analyses in the NIH-AARP study (eFigure 9 in the Supplement), leisure-time physical activity was inversely associated with risk of ER-positive breast cancers (HR, 0.89 [95% CI, 0.82-0.97]), and especially ER-negative cancers (HR, 0.72 [95% CI, 0.59-0.88]; *P* for heterogeneity = .05). Leisure-time physical activity was associated with higher risk of nonadvanced prostate cancer (HR, 1.08 [95% CI, 1.03-1.12]) but not advanced prostate cancer (HR, 0.99 [95% CI, 0.88-1.10]; *P* for heterogeneity = .14). The leisure-time physical activity–melanoma association was statistically significant in US regions with higher levels of solar UV radiation (HR, 1.26 [95% CI, 1.14-1.38]) but not in regions with lower levels (HR, 1.12 [95% CI, 0.97-1.30]; *P* for heterogeneity = .21). Lastly, adjustment for dietary factors resulted in modest increases in HRs for esophageal adenocarcinoma (7%), liver cancer (5%), and rectal cancer (5%), but for other physical activity–associated cancers, the attenuation was minimal (<5%) (eTable 8 in the Supplement).

Discussion

In this pooled analysis of 1.44 million participants, higher levels of leisure-time physical activity (at the 90th percentile), as compared with lower levels (at the 10th percentile), were associated with lower risk of 13 of 26 types of cancer examined, with risk reductions of 20% or more for 7 of the cancers. Leisure-time physical activity was also associated with higher risk of malignant melanoma, and higher risk of nonadvanced prostate cancer. A higher level of leisure-time physical activity was associated with a 7% lower risk of total cancer.

Our results suggest that leisure-time physical activity may be associated with lower risk of a wider breadth of types

Figure 3. Summary Multivariable Hazard Ratios and 95% Confidence Intervals for a Higher (90th Percentile) vs Lower (10th Percentile) Level of Leisure-Time Physical Activity by Cancer Type, Stratified by Current, Former, and Never Smokers



Multivariable models were adjusted for age, sex, smoking status (never, former, current), alcohol consumption (0, 0.1-14.9, 15.0-29.9, and ≥30.0 g/d), education (did not complete high school, completed high school, post–high-school training, some college, completed college), and race/ethnicity (white, black, other). Models for endometrial, breast, and ovarian cancers are additionally adjusted for postmenopausal hormone therapy use (ever, never), oral contraceptive use (ever, never), age at menarche (<10, 10-11, 12-13, ≥14 years), age at menopause (premenopausal, 40-44, 45-49, 50-54, ≥55 years), and parity (0, 1, 2, ≥3 children). For gallbladder cancer among current smokers, case numbers were inadequate to provide an estimate. Data markers indicate hazard ratio, and error bars, 95% confidence intervals. Size of the data markers corresponds to the relative weight assigned in the pooled analysis using random-effects meta-analysis. NA indicates not applicable.

[a] Indicates the *P* value for effect modification by smoking status.

of cancer than previously described, and they bolster the evidence for associations that were previously only weakly supported. For example, associations for esophageal adenocarcinoma and gastric cardia cancer were among our strongest findings, but previous prospective studies found small effects compared with our own.[28] For kidney and bladder cancers, we observed clear inverse associations, while recent meta-analyses reported nonsignificant associations in prospective studies.[29,30] For myeloid leukemia and myeloma, we found robust inverse associations, whereas a 2015 meta-analysis found null associations.[31] For liver cancer, inverse associations had been observed, but few studies had been conducted[32] and additional confirmatory data were needed. We also observed nonsignificant inverse associations for cancers of the gallbladder and small intestine, while existing studies found no associations.[32,33] Our findings confirm the previously reported inverse associations between physical activity and risk of colon, endometrial, and breast cancers, and further extend the observation of inverse associations to the ER-negative subtype of breast cancers (in the NIH-AARP study).

Our study also systematically explored the role of BMI in physical activity's association with the full spectrum of cancer types. Longitudinal studies[34,35] and randomized exercise trials[36] show that physical activity helps prevent weight gain and that exercise reduces levels of cancer-relevant biomarkers such as estradiol, mostly as a consequence of weight loss.[37,38] These combined observations have given rise to the hypothesis that physical activity reduces cancer risk primarily through lowering body weight. Our finding that physical activity and cancer associations were generally BMI independent argues against this hypothesis for most cancers. However, for esophageal adenocarcinoma and cancers of the liver, gastric cardia, kidney, and endometrium—cancers known to be obesity related[39]—the associations were somewhat BMI dependent, and body mass index may potentially

be a mediating factor that explains why physical activity is related to lower risk of these cancers. Unfortunately, we did not have information about the trajectories of physical activity and body weight and therefore could not distinguish between BMI's mediating and confounding roles.

We additionally observed that leisure-time physical activity was strongly inversely associated with lung cancer and unassociated with endometrial cancer in those with a BMI lower than 25. For lung cancer, this may reflect higher smoking prevalence among the lean, and thus higher potential for residual confounding. For endometrial cancer, this may reflect the effect of removing body weight (because all participants in this group are lean) from the causal path connecting physical activity to lower risk. For all other cancers, there was little evidence for effect modification, suggesting that among the overweight and obese, a higher physical activity level is still associated with lower cancer risk. This is important because not all persons who engage in high levels of physical activity have low body weights. This finding may help encourage those who are overweight or obese to be physically active.

We separately examined risk associations among current, former, and never smokers, and aside from lung cancer and myeloma, found little evidence for effect modification. For lung cancer, variability in the physical activity association by smoking status could reflect an inability to completely adjust for smoking habits among current or former smokers, that is, residual confounding. It is also conceivable, however, that the different findings in current or former smokers—who constitute almost all cases—are indicative of distinct etiologic and biologic features of their lung cancers compared with never smokers.[40] Effect modification by smoking status was not observed for other smoking-related cancers such as head and neck cancer. This provides some evidence against a generic bias due to residual confounding by smoking, although case numbers were too small to rule this out definitively. For myeloma, smoking is not a risk factor and effect modification may therefore be due to small case numbers and/or chance.

Leisure-time physical activity was positively associated with prostate cancer risk, but there is no known biologic rationale to explain this association. Physically active men are more likely than inactive men to receive digital rectal examinations and/or prostate-specific antigen screening,[26] which increases the likelihood of diagnosing indolent prostate cancers. The positive association that we observed could therefore be due to screening bias. To circumvent this potential bias, we analyzed advanced prostate cancers in the NIH-AARP study because advanced cases are less likely to remain indolent, and found no association between physical activity and advanced prostate cancer. This difference in associations for overall prostate cancers and advanced prostate cancers implies that results for overall prostate cancers were influenced by screening bias, although we cannot fully rule out etiologic heterogeneity.

The higher risk of melanoma with increased leisure-time physical activity was notable, particularly because this association has only been examined in 1 prior study. This case-control study found that higher activity levels were associated with a 30% lower melanoma risk,[41] a finding that our analysis refutes. Of the 12 cohorts we examined, 8 found higher activity levels to be associated with at least a 20% higher melanoma risk. Greater incidental sun exposure seems to be the likely reason for this increase in melanoma risk because physical activity is frequently done outdoors in light clothing and has been associated with substantially increased risk of sunburn.[42] Moreover, we found that the physical activity–melanoma association was stronger in high-UV areas, implying that sun exposure is an important factor underlying this association. Physically active people thus appear to be a vulnerable population for melanoma, and cancer prevention efforts focused on physical activity should emphasize sun exposure safety (eg, http://www.cancer.org/healthy/besafeinthesun/).

Physical activity's biological link with cancer has been hypothesized to be mediated through 3 hormonal systems: sex steroids, insulin and insulin-like growth factors, and adipokines.[43] Among other evidence for a link between physical activity and these hormonal systems, randomized exercise trials show that randomization to a 1-year physical activity intervention reduces levels of estrone and estradiol,[37,38] and insulin[44] in postmenopausal women, with effects mediated, at least in part, through reduced adiposity. Several nonhormonal mechanisms have been hypothesized to link physical activity to cancer risk, including inflammation, immune function, oxidative stress, and for colon cancer, reduced gastrointestinal transit time.[43] Some of these nonhormonal mechanisms could potentially explain why physical activity was more robustly inversely associated with ER-negative than ER-positive breast cancer. For some physical activity–associated cancers in our study, for example, esophageal adenocarcinoma or bladder cancer, less is known about the potential mechanisms underlying the physical activity association and our results suggest that further mechanistic research is warranted.

The primary strength of our study is that, to our knowledge, it is the largest ever conducted on physical activity and cancer risk. This afforded us the statistical precision to examine uncommon and rare cancers that together constitute most incident cancers. Another strength is our consistent methodological approach, including restriction to prospective cohort studies, and leisure-time physical activity, as well as analyzing the same large contrast in physical activity level across studies. This approach minimizes heterogeneity, improves consistency of results, and maximizes power. Finally, our results are not susceptible to publication bias because our analysis is not restricted to published data.

The main limitation of our study is that, in the context of an observational study of lifestyle factors, we cannot fully exclude the possibility that residual confounding by diet, smoking, or other factors may affect our results. However, we did control for many of the known cancer risk factors, and adjusted for diet in sensitivity analyses, with little overall effect on results. We also carefully evaluated effects of adjusting for BMI, and evaluated potential residual confounding by smoking by estimating associations separately in never smokers. We

also conducted sensitivity analyses to explore potential screening bias for prostate cancer and the role of sun exposure for melanoma.

An additional limitation is that we used self-reported physical activity, which entails some error in recall. Mitigating this concern is the fact that many physical activity assessments were previously validated and that the discrete, structured nature of leisure-time physical activities makes them comparatively easy to recall.[45] A further concern is that assessments of physical activity differed somewhat by study; however, for most cancers, results were still highly consistent between studies. Finally, not all cohorts assessed moderate- and vigorous-intensity activities separately, and several cohorts lacked key details needed to calculate MET-hours per week of physical activity, a measure that would have enabled benchmarking our findings against national guidelines. Our collaborative group will conduct future studies targeting in greater detail the type, intensity, and amount of physical activity needed to reduce overall cancer risk in subsets with the relevant data.

Conclusions

Increasing levels of leisure-time physical activity were associated with lower risks of 13 of the 26 cancers we investigated, extending our current evidence base beyond colon, breast, and endometrial cancers. Furthermore, our results support that these associations are broadly generalizable to different populations, including overweight or obese individuals, or those with a history of smoking. These findings support promoting physical activity as a key component of population-wide cancer prevention and control efforts.

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Study supervision: Moore, Lee, Weiderpass, Hartge, Matthews.

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REFERENCES

1. Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med*. 2015;175(6):959-967.

2. World Cancer Research Fund, American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: American Institute for Cancer Research; 2007.

3. American Cancer Society. Cancer Facts & Figures 2014. 2014. http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/. Accessed April 7, 2016.

4. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012: online analysis. IARC CancerBase No 11 Lyon. Lyon, France: International Agency for Research on Cancer; 2014. http://globocan.iarc.fr/Pages/online.aspx. Accessed April 20, 2016.

5. Centers for Disease Control and Prevention. Fastats: Exercise or Physical Activity. http://www.cdc.gov/nchs/fastats/exercise.htm. Accessed February 22, 2016.

6. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U; Lancet Physical Activity Series Working Group. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet*. 2012;380(9838):247-257.

7. Lee IM, Manson JE, Ajani U, Paffenbarger RS Jr, Hennekens CH, Buring JE. Physical activity and risk of colon cancer: the Physicians' Health Study (United States). *Cancer Causes Control*. 1997;8(4):568-574.

8. Gaziano JM, Sesso HD, Christen WG, et al. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2012;308(18):1871-1880.

9. Zhang SM, Moore SC, Lin J, et al. Folate, vitamin B_6, multivitamin supplements, and colorectal cancer risk in women. *Am J Epidemiol*. 2006;163(2):108-115.

10. Larsson SC, Håkansson N, Giovannucci E, Wolk A. Folate intake and pancreatic cancer incidence: a prospective study of Swedish women and men. *J Natl Cancer Inst*. 2006;98(6):407-413.

11. Hildebrand JS, Gapstur SM, Campbell PT, Gaudet MM, Patel AV. Recreational physical activity and leisure-time sitting in relation to postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2013;22(10):1906-1912.

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. Moore SC, Rajaraman P, Dubrow R, et al. Height, body mass index, and physical activity in relation to glioma risk. *Cancer Res*. 2009;69(21):8349-8355.

14. Hashibe M, Hunt J, Wei M, Buys S, Gren L, Lee YC. Tobacco, alcohol, body mass index, physical activity, and the risk of head and neck cancer in the prostate, lung, colorectal, and ovarian (PLCO) cohort. *Head Neck*. 2013;35(7):914-922.

15. Howard RA, Leitzmann MF, Linet MS, Freedman DM. Physical activity and breast cancer risk among pre- and postmenopausal women in the US Radiologic Technologists cohort. *Cancer Causes Control*. 2009;20(3):323-333.

16. Steindorf K, Ritte R, Eomois PP, et al. Physical activity and risk of breast cancer overall and by hormone receptor status: the European prospective investigation into cancer and nutrition. *Int J Cancer*. 2013;132(7):1667-1678.

17. Leitzmann MF, Moore SC, Peters TM, et al. Prospective study of physical activity and risk of postmenopausal breast cancer. *Breast Cancer Res*. 2008;10(5):R92.

18. Roswall N, Sandin S, Adami HO, Weiderpass E. Cohort profile: the Swedish Women's Lifestyle and Health cohort [published online June 10, 2015]. *Int J Epidemiol*. doi:10.1093/ije/dyv089.

19. US Department of Health and Human Services. *2008 Physical Activity Guidelines for Americans*. Washington, DC: US Department of Health and Human Services; 2008.

20. World Health Organization. *International Classification of Diseases for Oncology*. 3rd ed. Geneva, Switzerland: World Health Organization; 2000.

21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.

22. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Stat Methodol*. 1995;57(1):289-300.

23. Takkouche B, Cadarso-Suárez C, Spiegelman D. Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. *Am J Epidemiol*. 1999;150(2):206-215.

24. Park Y, Leitzmann MF, Subar AF, Hollenbeck A, Schatzkin A. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. *Arch Intern Med*. 2009;169(4):391-401.

25. Schafer JL. *Analysis of Incomplete Multivariate Data*. New York, NY: Chapman and Hall; 1997.

26. Moore SC, Peters TM, Ahn J, et al. Physical activity in relation to total, advanced, and fatal prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2008;17(9):2458-2466.

27. Peters TM, Schatzkin A, Gierach GL, et al. Physical activity and postmenopausal breast cancer risk in the NIH-AARP diet and health study. *Cancer Epidemiol Biomarkers Prev*. 2009;18(1):289-296.

28. Behrens G, Jochem C, Keimling M, Ricci C, Schmid D, Leitzmann MF. The association between physical activity and gastroesophageal cancer: systematic review and meta-analysis. *Eur J Epidemiol*. 2014;29(3):151-170.

29. Behrens G, Leitzmann MF. The association between physical activity and renal cancer: systematic review and meta-analysis. *Br J Cancer*. 2013;108(4):798-811.

30. Keimling M, Behrens G, Schmid D, Jochem C, Leitzmann MF. The association between physical activity and bladder cancer: systematic review and meta-analysis. *Br J Cancer*. 2014;110(7):1862-1870.

31. Jochem C, Leitzmann MF, Keimling M, Schmid D, Behrens G. Physical activity in relation to risk of hematologic cancers: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2014;23(5):833-846.

32. Behrens G, Matthews CE, Moore SC, et al. The association between frequency of vigorous physical activity and hepatobiliary cancers in the NIH-AARP Diet and Health Study. *Eur J Epidemiol*. 2013;28(1):55-66.

33. Cross AJ, Hollenbeck AR, Park Y. A large prospective study of risk factors for adenocarcinomas and malignant carcinoid tumors of the small intestine. *Cancer Causes Control*. 2013;24(9):1737-1746.

34. Lee IM, Djoussé L, Sesso HD, Wang L, Buring JE. Physical activity and weight gain prevention. *JAMA*. 2010;303(12):1173-1179.

35. Hankinson AL, Daviglus ML, Bouchard C, et al. Maintaining a high physical activity level over 20 years and weight gain. *JAMA*. 2010;304(23):2603-2610.

36. Ennour-Idrissi K, Maunsell E, Diorio C. Effect of physical activity on sex hormones in women: a systematic review and meta-analysis of randomized controlled trials. *Breast Cancer Res*. 2015;17(1):139.

37. Friedenreich CM, Woolcott CG, McTiernan A, et al. Alberta physical activity and breast cancer prevention trial: sex hormone changes in a year-long exercise intervention among postmenopausal women. *J Clin Oncol*. 2010;28(9):1458-1466.

38. Campbell KL, Foster-Schubert KE, Alfano CM, et al. Reduced-calorie dietary weight loss, exercise, and sex hormones in postmenopausal women: randomized controlled trial. *J Clin Oncol*. 2012;30(19):2314-2326.

39. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569-578.

40. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers—a different disease. *Nat Rev Cancer*. 2007;7(10):778-790.

41. Shors AR, Solomon C, McTiernan A, White E. Melanoma risk in relation to height, weight, and exercise (United States). *Cancer Causes Control*. 2001;12(7):599-606.

42. Holman DM, Berkowitz Z, Guy GP Jr, Hartman AM, Perna FM. The association between demographic and behavioral characteristics and sunburn among US adults—National Health Interview Survey, 2010. *Prev Med*. 2014;63:6-12.

43. 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.

44. Friedenreich CM, Neilson HK, Woolcott CG, et al. Changes in insulin resistance indicators, IGFs, and adipokines in a year-long trial of aerobic exercise in postmenopausal women. *Endocr Relat Cancer*. 2011;18(3):357-369.

45. 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.