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.
Physical activity is known to reduce risks of heart disease and all-cause mortality, as well as risks of colon, breast, and endometrial cancers. Less is known, however, about whether physical activity reduces risk of other cancers, which, together, constitute 75% of incident cancers in the United States and 61% of cancers worldwide. Physical inactivity is highly prevalent, with an estimated 51% of people in the United States and 31% of people worldwide not attaining recommended physical activity levels. 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, 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. 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 body weight 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.

### 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.

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). 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.

Seven of the 12 cohorts (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, or, alternately, by inquiring about overall weekly participation in moderate- to vigorous-intensity activities. 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. Of the remaining cohorts, 4 evaluated only vigorous-intensity leisure-time physical activity, and 1 evaluated frequency of moderate- to vigorous-intensity activities, but not time spent. 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.

Cancer-type definitions 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 (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...
of multiple cancer end points. Multiple-imputation procedures\textsuperscript{25-27} 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 non-advanced and advanced prostate cancers. These specific cancers and subtypes were selected on the basis of prior data suggesting subtype specificity of associations.\textsuperscript{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.\textsuperscript{24}
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 (Table 1). Leisure-time physical activity was associated with lower risk for 13 of the 26 types of cancer (Figure 1, eTable 5 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]), gastriccardia (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, 0.72-0.95]), 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 malign-
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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

### Table 2. Comparison of Multivariable Hazard Ratios (HRs)* 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)**

<table>
<thead>
<tr>
<th>Cancer*</th>
<th>HR (95% CI) Not BMI Adjusted</th>
<th>BMI Adjusted</th>
<th>Difference in HR, %</th>
</tr>
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</table>
| Esophageal adenocarcinoma | 0.58 (0.37-0.89) | 0.62 (0.40-0.97) | 6.9*
| Gallbladder | 0.72 (0.51-1.01) | 0.78 (0.57-1.06) | 8.3*
| Liver | 0.73 (0.55-0.98) | 0.81 (0.61-1.09) | 11.0*
| 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*
| 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*
| Endometrial | 0.79 (0.68-0.92) | 0.98 (0.89-1.09) | 24.1*
| Esophageal squamous | 0.80 (0.61-1.06) | 0.76 (0.58-1.01) | −5.0*
| Myeloid leukemia | 0.80 (0.70-0.92) | 0.85 (0.73-0.97) | 6.2*
| 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) | −0.1
| Malignant melanoma | 1.27 (1.16-1.40) | 1.28 (1.17-1.41) | 0.8

*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).

**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.

The Surveillance, Epidemiology, and End Results site code20 corresponding to each cancer type are shown in eTable 3 in the Supplement.

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

The Surveillance, Epidemiology, and End Results site code20 corresponding to each cancer type are shown in eTable 3 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%), and parity (0, 1, 2, 3 or more 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. 

### 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...
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. Longitudinal studies and randomized exercise trials 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. 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—the associations were somewhat BMI dependent, and body mass index may potentially...
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, 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, 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. 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. 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, and insulin 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. 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. 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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Original Investigation  Research