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## Physical Activity in Cancer Prevention and Survival: A Systematic Review

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Supplemental Digital Content

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## Abstract

**Purpose:** This paper reviews and updates the evidence on the associations between physical activity and risk for cancer, and for mortality in persons with cancer, as presented in the *2018 Physical Activity Guidelines Advisory Committee Scientific Report*.

**Methods:** Systematic reviews of meta-analyses, systematic reviews, and pooled analyses were conducted through December 2016. An updated systematic review of such reports plus original research through February 2018 was conducted. This paper also identifies future research needs.

**Results:** In reviewing 45 reports comprising hundreds of epidemiologic studies with several million study participants, the report found strong evidence for an association between highest versus lowest physical activity levels and reduced risks of bladder, breast, colon, endometrial, esophageal adenocarcinoma, renal, and gastric cancers. Relative risk reductions ranged from approximately 10 to 20 percent. Based on 18 systematic reviews and meta-analyses, the report also found moderate or limited associations between greater amounts of physical activity and decreased all-cause and cancer-specific mortality in individuals with a diagnosis of breast, colorectal, or prostate cancer, with relative risk reductions ranging almost up to 40 to 50 percent. The updated search, with 5 meta-analyses and 25 source papers reviewed, confirmed these findings.

**Conclusions:** Levels of physical activity recommended in the 2018 Guidelines are associated with reduced risk and improved survival for several cancers. More research is needed to determine the associations between physical activity and incidence for less common cancers and associations with survival for other cancers. Future studies of cancer incidence and mortality should consider these associations for population subgroups, to determine dose-response relationships between physical activity and cancer risk and prognosis, and to establish mechanisms to explain these associations.

## Keywords

exercise; cancer risk; cancer survivorship

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## INTRODUCTION

In 2018, 1,735,350 new cancer cases and 609,640 cancer deaths are projected to occur in the United States.<sup>(1)</sup> In 2018, there are expected to be over 18 million cancer cases worldwide

and over 9.5 million deaths.(2) An estimated one in three Americans will be diagnosed with an invasive cancer over their lifetimes,(1) and the number of cancer survivors is expected to exceed 20 million by 2026.(3)

Most cancers arise from a complex etiology involving genetic, environmental and lifestyle factors, and their interactions,(4) and there is great need and opportunity for cancer prevention through lifestyle change. Increasingly, recognition of the role of host factors in cancer survival has supported the increased focus on lifestyle changes to improve these factors.(5)

Decades of epidemiologic research have identified a physically active lifestyle as protective against the occurrence of some common cancers, but comprehensive reviews were lacking. The U.S. Department of Health and Human Services (HHS) 2018 Physical Activity Guidelines Advisory Committee (PAGAC) therefore addressed the following question: What is the relationship between physical activity and specific cancer incidence?(6) The PAGAC then investigated the presence and shape of dose-response relationships, whether the relationships varied by age, sex, race/ethnicity, socioeconomic status, or weight status, whether the relationship varies by specific cancer subtypes, and whether the relationship is present in individuals at high risk, such as those with familial predisposition to cancer. The PAGAC also examined the role of sedentary behaviors in the etiology of cancer (presented in Katzmarzyk et al.).(7)

In addition to the questions related to the primary prevention of cancer, the PAGAC also investigated the following question: Among cancer survivors, what is the relationship between physical activity and (1) all-cause mortality, (2) cancer-specific mortality, or (3) risk of cancer recurrence or second primary cancer? Further, the PAGAC considered the presence and shape of dose-response relationships, and whether the relationships vary by age, sex, race/ethnicity, socioeconomic status, or weight status. Finally, the PAGAC explored whether the relationships vary based on frequency, duration, intensity, type (mode), and how physical activity is measured. The PAGAC also considered current knowledge gaps and priorities for future research.

The purpose of this article is to summarize and update epidemiologic evidence on the associations between physical activity and risk of cancer incidence and survival as reviewed by the PAGAC.(6)

## METHODS

This systematic review is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.(8) The systematic review followed an established protocol, and was registered at PROSPERO (#CRD42018096729). The purpose of the PAGAC systematic review was to identify systematic reviews, meta-analyses, and pooled analyses that examined the relationship between physical activity and risks of cancer incidence, and risks of mortality among persons diagnosed with cancer. The purpose of the updated systematic search was to determine whether additional meta-analyses were published after the *2018 Physical Activity Guidelines Advisory Committee Scientific Report*

(2018 Scientific Report) search, and whether individual source studies had been published after the dates of the latest meta-analyses.

### **Search Strategy and Selection Criteria**

For the 2018 Scientific Report, systematic literature searches were conducted using PubMed, Cochrane, and CINAHL databases through December 2016 (see Supplementary Table 1, Supplemental Digital Content 1, 2018 Physical Activity Guidelines Advisory Committee search terms for epidemiologic literature on relationships between physical activity and risk for cancer; and Supplementary Table 2, Supplemental Digital Content 2, 2018 Physical Activity Guidelines Advisory Committee search terms for epidemiologic literature on relationships between physical activity and mortality in persons diagnosed with cancer). (6) Studies were considered potentially eligible if they were systematic reviews, meta-analyses, reports, or pooled analyses published in English through December 2016, and investigated the relationship between all types and intensities of physical activity and risk of invasive cancer of any type in adults, or the relationship between all types and intensities of physical activity and mortality in persons of any age with a diagnosis of cancer.

For the present paper, updated systematic literature searches were conducted for the inclusive dates January 2016 through February 2018 using the same search terms including systematic reviews, meta-analyses, and pooled analyses, and more recent original prospective cohort studies published after the inclusion dates for the cancer-specific systematic reviews/meta-analyses.

### **Data Extraction and Methodological Study Quality Assessment**

The titles, abstracts, and full-text of the identified articles were independently screened, and data were abstracted by two reviewers. Disagreement between reviewers was resolved by discussion or a third person review. For the 2018 Scientific Report, data were extracted for systematic reviews, meta-analyses, and pooled analyses regarding years of source studies inclusion, numbers of studies, type of studies included (e.g., cohort, case-control), whether dose-response relationships were addressed, adjustment for confounders, evaluation of effect modifiers, and effect sizes and statistical significance. For the updated search, two reviewers independently screened the titles, abstracts, and full-text of the identified articles, and abstracted data to determine if new information would change the conclusions of the 2018 Scientific Report.

### **Grading of Evidence**

Grading criteria were established before the review of the evidence was conducted (see Supplementary Table 3, Supplemental Digital Content 3, 2018 Physical Activity Guidelines Advisory Committee grading criteria). (6) These criteria were used to evaluate the epidemiologic evidence included in the systematic reviews and meta-analyses considered by the PAGAC members. The criteria included the applicability, generalizability, risk of bias and study limitations, quantity and consistency of the results across studies as well as the magnitude and precision of the effects. The PAGAC members undertook careful deliberations when reviewing the evidence and consensus on the grade to be assigned to

each cancer site was sought through discussion amongst the PAGAC members in Subcommittees and through regular reports during public PAGAC meetings.

## RESULTS

For the 2018 Scientific Report, 45 systematic reviews, meta-analyses, or pooled analyses were reviewed related to associations between physical activity and cancer risk; 18 systematic reviews, meta-analyses, or pooled analyses were reviewed on the associations between physical activity and cancer survival.<sup>(6)</sup> For the updated search, 145 systematic reviews, meta-analyses, or pooled analyses were identified as potentially relevant, of these five were included in the updated review (exclusions were primarily because of not focusing on cancer etiology or survival). In addition, 25 original source papers were included, out of 1256 identified from the updated search (exclusions were primarily for already being included in the meta-analyses or pooled analyses, or for not focusing on cancer etiology or survival).

In the studies included in the meta-analyses, systematic reviews, and pooled analyses, physical activity was measured by self-report, with different types of physical activity questionnaires. In many studies, participants were presented with a list of typical activities (e.g., walking, running, biking), and asked to indicate the frequency and duration of each activity. Other studies used more general questions about time spent in moderate- or vigorous-intensity activities. Most studies collected information on recreational activities, several also included occupational activities, and only a few included household activities. Some studies added up all of these activities to estimate total physical activity; most limited estimation of total physical activity to leisure time activity. Most of the meta-analyses estimated MET-hours per week of moderate-to-vigorous intensity physical activities where data were available, but the cut-points for “highest” versus “lowest” activity levels varied across studies.

Most of the meta-analyses, as well as a large pooled study,<sup>(9)</sup> were restricted to prospective cohort studies. However, for some of the rarer cancers, meta-analyses or pooled analyses did include case-control studies. Observational studies on cancer survival were restricted to prospective cohort studies of cancer survivors.

For the review of cancer survivors, PAGAC recognized that the definition of cancer recurrence was heterogeneous, rarely examined as an outcome, and therefore eliminated recurrence outcomes from this review. Furthermore, only post-diagnosis physical activity was included in the review of cancer survival.

### Cancer Primary Prevention

The PAGAC evaluated 45 systematic reviews, meta-analyses, and pooled analyses comprising hundreds of epidemiologic studies with several million participants. The PAGAC determined that, when comparing the incidence among individuals in the highest category of physical activity with individuals in the lowest, strong evidence demonstrated reduced risks of bladder, breast, colon, endometrial, esophageal adenocarcinoma, renal and gastric cancers, with relative risk reductions ranging from approximately 10 percent to 20 percent

(Table 1). The PAGAC also found moderate evidence that individuals in the highest category of physical activity had lower risk for lung cancer compared with those in the lowest category of physical activity. The number of available meta-analyses for each cancer type ranged from one to seven. Below are the main results from the most recent, or most comprehensive, meta-analyses reviewed for the 2018 Scientific Report(6) for individual cancers for which the PAGAC found strong or moderate grade evidence of an association between increased physical activity and reduced cancer risk (see also Table 1).

**Bladder Cancer:** The PAGAC identified two meta-analyses/systematic reviews and one pooled analysis on the association between bladder cancer and physical activity. Of these reports, the most comprehensive was a 2014 meta-analysis that found bladder cancer risk was significantly lower for individuals engaging in the highest versus lowest categories of recreational or occupational physical activity level (relative risk (RR)=0.85; 95% confidence interval (CI): 0.74-0.98).(10) The other meta-analysis and pooled analysis found similar results.(6) No new reports were identified in our updated search.

**Breast Cancer:** A total of four meta-analyses/systematic reviews and two pooled analyses were identified that focused on physical activity and breast cancer risk. The most recent and comprehensive report was a 2016 meta-analysis that examined risk of breast cancer by all types of physical activity in which a statistically significant reduction for breast cancer incidence was found when comparing the highest versus the lowest amounts of all types of physical activity combined (odds ratio (OR): 0.88; 95% CI: 0.85-0.91).(11) When examining the associations by type of activity, these authors reported risk reductions for non-occupational physical activity (OR=0.88; 95% CI: 0.85-0.92 from 30 studies) and occupational physical activity (OR=0.87; 95% CI: 0.83-0.90) based on 11 studies). Premenopausal and postmenopausal women had very similar risk reductions for highest versus lowest levels of physical activity (RR=0.87; 95% CI: 0.78-0.96 and RR=0.88; 95% CI: 0.85-0.91, respectively). The other meta-analyses and pooled analyses found similar results.(6) The updated search identified two meta-analyses on the associations between physical activity and breast cancer risk, both of which reported reduced breast cancer risk comparing high versus low levels of physical activity for the total population,(12, 13) although one meta-analysis found no association of physical activity with breast cancer occurring before menopause.(12) The updated search identified five publications of cohort studies (14–18) that investigated the associations of physical activity with breast cancer risk. One cohort study observed that strenuous activity was inversely and significantly associated with reduced breast cancer risk, particularly in certain molecular subtypes.(14) Another study found that increased total, leisure, and occupational physical activity were inversely and significantly associated with reduced breast cancer risk.(15) One study found that increased physical activity in childhood and teenage years was associated with lower risk for breast cancer development,(16) while another found no association between physical activity between menarche and first pregnancy on later breast cancer risk.(17) Finally, a study found statistically significant associations between high versus low levels of physical activity and reduced risk for postmenopausal breast cancer.(18)



**Colon Cancer:** A total of eight meta-analyses/systematic reviews and one pooled analysis on physical activity and colon cancer were identified in the PAGAC literature review. The most recent was a 2016 meta-analysis which reported that risk of colon cancer is significantly reduced for individuals engaging in the highest versus lowest categories of physical activity level (RR=0.81, 95% CI: 0.83-0.93).(19) These findings were similar to those reported in the other meta-analyses.(6) Our updated literature search yielded two additional meta-analyses, both of which supported these findings.(20, 21) The updated search also identified three original research reports of cohort studies that had not been included in any reviewed meta-analyses, which found that high versus low levels of physical activity decrease risk for colon cancer.(22–24)

**Endometrial Cancer:** The PAGAC used information from four meta-analyses/systematic reviews and one pooled analysis on physical activity and endometrial cancer risk with the most recent one published in 2015. That meta-analysis found a statistically significant reduction for endometrial cancer incidence when comparing the highest versus the lowest amounts of all types of physical activity combined (OR=0.80; 95% CI: 0.75-0.85).(25) The meta-analysis further reported risk reductions for recreational (OR=0.84; 95% CI: 0.78-0.91), occupational (OR=0.81; 95% CI: 0.75-0.87), and household (OR=0.70; 95% CI: 0.47-1.02) activities as well as for walking (OR=0.82; 95% CI: 0.69-0.97). Risk was decreased with all intensity levels of physical activity (light, moderate-to-vigorous, and vigorous). The other meta-analyses and pooled analysis found similar results.(6) Two cohort studies identified in the updated search found statistically significant associations between high versus low levels of physical activity and reduced risk of endometrial cancer.(26, 27)

**Esophageal Cancer:** The PAGAC identified three meta-analyses/systematic reviews and one pooled analysis on physical activity and esophageal cancer risk. The most comprehensive was a 2014 meta-analysis(28) that included 24 individual studies of which 9 were cohort and 15 were case-control studies. Risk of esophageal adenocarcinoma was statistically significantly reduced for individuals engaging in highest versus lowest levels of activity (RR=0.79; 95% CI: 0.66-0.94). Conversely, physical activity was not related to risk of squamous cell carcinoma of the esophagus. The other meta-analyses and pooled analysis found similar results.(6) No new reports were identified in our updated search.

**Gastric Cancer:** There were five meta-analyses and one pooled analysis that reported on physical activity and its association with gastric cancer risk. In a 2016 meta-analysis,(29) risk of gastric cancer was statistically significantly reduced for individuals engaging in highest versus lowest levels of activity (RR=0.81; 95% CI: 0.73-0.89). The other meta-analyses and pooled analysis found similar results.(6) No new reports were identified in our updated search.

**Renal Cancer:** The PAGAC identified one meta-analysis/systematic review and one pooled analysis of physical activity and renal cancer. The meta-analysis, published in 2013, reported that risk of renal cancer was significantly lower for individuals engaging in the highest versus lowest categories of physical activity level (RR=0.88; 95% CI: 0.79-0.97).

(30) The pooled analysis found similar results.(6) No new reports were identified in our updated search.

**Lung Cancer:** The PAGAC used information from six meta-analyses and one pooled analysis on physical activity and risk of lung cancer. Using data from the most recent and comprehensive meta-analysis, the PAGAC found evidence of a 25 percent relative reduction in lung cancer risk with highest versus lowest levels of physical activity (RR=0.75; 95% CI: 0.68-0.84).(31) The other meta-analyses and pooled analysis found similar results.(6) The PAGAC could not rule out effect modification by tobacco use and therefore considered the evidence to be of a moderate grade. The updated search yielded two publications of cohort studies on physical activity and risk of lung cancer.(32, 33) Both studies assessed the association between physical activity and risk for lung cancer within categories of smoking (e.g., current, former, or never smoker), and both found lack of association of physical activity with reduced lung cancer in some or all smoking status categories.

**Other Cancers:** For some other cancer sites, very few meta-analyses and systematic reviews had been published at the time of the original review for the 2018 Scientific Report. Hence, the PAGAC determined that limited evidence suggested an association between higher physical activity and decreased risks of hematologic, head and neck, ovarian, pancreatic, and prostate cancers. No grade could be assigned for brain cancer given the paucity of evidence. The PAGAC found limited evidence of no association of physical activity with risk of thyroid or rectal cancer. Finally, for all remaining cancer sites, there were no published studies that could be considered for this report.

Six publications on the associations between physical activity and risk of hematologic cancers were identified in the updated literature search. One study found that high versus low levels of physical activity were associated with reduced risk for myeloid neoplasms (myelodysplastic syndromes, acute myeloid leukemia, myeloproliferative neoplasms), chronic lymphocytic leukemia, small lymphocytic lymphoma, and mature B cell lymphomas, but not plasma cell disorders.(34) Three studies found varying associations of physical activity with non-Hodgkin lymphoma or B-cell non-Hodgkin lymphoma: one found no association with either,(35) one finding a non-significant reduced risk of non-Hodgkin lymphoma,(36) and one no association with B-cell non-Hodgkin lymphoma.(37) Finally, one study of physical activity and risk of multiple myeloma was identified, which found no statistically significant associations.(38) One report on the association between physical activity and risk of head and neck cancer found statistically significant decreases in risk with increasing hours/week spent in vigorous activity.(39) The updated literature search identified two cohort studies of physical activity and ovarian cancer; one found no association between physical activity and reduced risk for ovarian cancer,(40) and one suggested increased risk for ovarian cancer with high physical activity levels.(41) Two publications presented results of cohort studies that examined the association between physical activity and risk of pancreatic cancer: one found a negative association in men but not women,(42) while the other found a negative association in persons aged under 60 years but not in older individuals.(43)



In 2018, a meta-analysis of leisure-time physical activity and risk of prostate cancer was published, focusing on dose-response effects; it found no association of leisure time physical activity with risk of total, local, or advanced prostate cancer.(44) Two cohort studies of prostate cancer risk in relation to physical activity were identified; one found no statistically significant associations between physical activity and risk,(45) and one observed a statistically significant reduction only in risk of advanced prostate cancer in active versus inactive men.(46)

The updated search also found publications focused on hepatobiliary, (47) carcinoid tumors of the small intestine,(48) squamous cell skin cancer,(49) and testicular cancers (50)that the PAGAC did not review for the 2018 Scientific Report. None provided enough evidence to reverse the PAGAC decision that evidence is lacking on the role of physical activity in risk for any of these cancers.

### **Associations of Physical Activity with Cancer by Dose-Response and Subgroups**

**Dose-Response:** A dose-response relationship between physical activity and specific cancer risk was evident for several cancers (Table 1), but given the inconsistent methods of measuring and categorizing physical activity levels in the various studies, meta-analyses, and pooled analyses, it was not possible to determine exact levels of physical activity that provide given levels of effect.

**Cancer Subtypes:** Investigation by cancer subtype showed that increased physical activity is associated with reduced risk of breast cancer regardless of hormone receptor status, and of colon cancer originating both proximally and distally. Conversely, although high levels of physical activity were associated with reduced adenocarcinoma of the esophagus, no statistically significant effect was observed for squamous cell cancer of the esophagus. Little information was available for other subtypes of cancer.

**Population Subgroups:** Effects of physical activity on specific cancer risk were seen for both women and men for colon and renal cancers, while for other cancers such as bladder, esophageal, gastric, lung, and pancreatic, differences by sex could not be ruled out. Little information was available on differences in physical activity effect on cancer risk by age or socioeconomic status. Few estimates were available for specific racial/ethnic groups other than Whites. For several cancers, individuals of Asian ancestry appeared to have similar protection from physical activity as do non-Asian individuals. The pooled analysis suggested that, similar to Whites, physical activity reduces risks of lung, colon, and breast cancers in African Americans.(9). For some U.S. populations (Latino, Native American, Pacific Islander), data are so sparse that systematic reviews, meta-analyses, and pooled analyses have not presented data on these racial/ethnic populations. Weight status affected the association between physical activity and risk of several cancers, including breast, endometrial, lung, ovarian, and thyroid, and possibly for esophageal adenocarcinoma and gastric cardia cancers.

## Mortality in Persons Diagnosed with Cancer

The National Cancer Institute states that an individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life.(51) Systematic reviews and meta-analyses on the relationship between physical activity and mortality among cancer survivors were available only for three cancers: breast, colorectal, and prostate cancer (Table 2).

**Breast Cancer:** Data from six meta-analyses show a consistent inverse association between amounts of physical activity after diagnosis and cancer-specific and all-cause mortality in breast cancer survivors. Estimates from a 2015 meta-analysis of eight cohorts found that highest versus lowest levels of physical activity were associated with a 48 percent reduction in risk for all-cause mortality (RR=0.52; 95% confidence interval (CI): 0.43-0.64). (52) A 2016 meta-analysis of ten cohorts found that highest versus lowest levels of post-diagnosis physical activity were associated with a 38 percent reduction in risk of breast cancer-specific mortality (RR=0.62; 95% CI: 0.48-0.80).(53) A pooled analysis addressed the association between meeting the 2008 Physical Activity Guidelines(54) recommended activity levels and breast cancer survival. The project found that engaging in 10 or more MET-hours per week was associated with a 27 percent reduction in all-cause mortality (hazard ratio (HR)=0.73; 95% CI: 0.66-0.82) and a 25 percent reduction in breast cancer-specific mortality (HR=0.75; 95% CI: 0.65-0.85).(55) The updated literature search identified two additional prospective cohort studies of breast cancer that examined the association between post-diagnosis physical activity and overall survival(56) and breast cancer specific survival.(57) In both of these cohort studies, higher levels of physical activity were associated with improved survival outcomes.

**Colorectal Cancer:** Data from six meta-analyses found a consistent inverse association between amounts of physical activity after diagnosis and all-cause mortality and colorectal cancer-specific mortality in colorectal cancer survivors. A 2016 meta-analysis including seven cohort studies showed a 42 percent reduced risk of all-cause mortality in survivors with highest versus lowest levels of physical activity (RR=0.58; 95% CI: 0.49-0.68).(58) A different 2016 meta-analysis of six cohorts found that highest versus lowest levels of post-diagnosis physical activity were associated with a 38 percent reduction in risk of colorectal cancer-specific mortality (relative risk (RR)=0.62; 95% CI: 0.45-0.86).(53) One meta-analysis assessed dose-response using five cohort studies.(59) In comparisons of less active to more active individuals, each 5, 10, or 15 MET-hours per week increase in post-diagnosis physical activity was associated with a 15 percent (95% CI: 10%-19%), 28 percent (95% CI: 20%-35%), and 35 percent (95% CI: 28%-47%) lower risk for all-cause mortality. Results for colorectal cancer-specific mortality were virtually identical. The updated literature review identified two additional prospective cohort studies on physical activity and colorectal cancer survival. The first cohort study noted a 25% reduction in mortality associated with highest versus lowest levels of leisure time physical activity (HR=0.75; 95% CI, 0.61-0.91).(60) The second cohort study found an approximate 50% reduced risk of overall mortality associated with highest versus lowest post-diagnosis total physical activity (HR= 0.53; 95% CI, 0.36-0.80).(61)

**Prostate Cancer:** Data from three available meta-analyses show an inverse association between amounts of physical activity after diagnosis and cancer-specific mortality in prostate cancer survivors. Estimates from a 2016 meta-analysis of three cohort studies found that highest versus lowest levels of physical activity were associated with a 38 percent reduction in risk for prostate cancer-specific mortality (RR=0.62; 95% CI: 0.47-0.82).(53) A review of the papers included in the systematic reviews indicates that highest versus lowest levels of total, recreational, non-sedentary occupational, and vigorous physical activity, as well as greater MET-hours per week or greater numbers of hours per week, were statistically significantly related to reduced risk for all-cause mortality.(62–64) One additional cohort study that included assessment of physical activity that was done at least one year post-diagnosis was found in the updated literature review.(65) Higher levels of physical activity significantly reduced prostate cancer-specific mortality in this study.

The PAGAC assigned grades of only Moderate or lower to the associations for all three of these cancers, because of the considerable chance of reverse causation. That is, individuals who have cancer may feel more fatigue and be less physically active as a result.

## DISCUSSION

We found strong evidence that physical activity reduces the risk of cancers of the breast, colon, endometrium, bladder, stomach, esophagus (adenocarcinoma) and kidney and moderate evidence for an association with lung cancer risk, with 10 to 20% reductions in relative risks. We found limited evidence that physical activity is associated with reduced risk for prostate cancer overall. The evidence for an association with hematologic, head and neck, ovary, and pancreas cancers remains limited mainly because of the lack of research that has been done on these cancers. Furthermore, for brain cancer and other cancer sites not listed here, there is insufficient evidence to determine the nature of the association with physical activity at this time.

The epidemiologic evidence on the association between physical activity and survival after cancer is still emerging with preliminary results supporting 40-50% relative risk reductions for mortality for breast, colon and prostate cancers with high versus low levels of physical activity.

There were several limitations to our work. The evidence relied on epidemiologic studies, with a lack of clinical trial evidence in either preventing cancer or improving survival in persons with cancer. Furthermore, most of the studies in persons diagnosed with cancer did not control adequately for treatment type or completion, nor for undiagnosed progression of disease, all of which can interfere with physical activity ability and therefore could have been major confounders of the relationships between physical activity and cancer survival.

Given the varying methods of physical activity ascertainment and classification in source papers and meta-analyses, the PAGAC could not determine the specific levels of physical activity that correspond to the reported levels of risk reduction. Furthermore, while dose-response associations were estimated in some papers and meta-analyses, the results varied such that exact dose-response relationships cannot be described even for individual cancers.

Nevertheless, for several cancers, dose-response relationships were evident. Most importantly, there did not appear to be a lower threshold below which no effect was evident. In other words, almost any level of physical activity likely confers some benefit.

Almost all epidemiologic data on physical activity and cancer risk and survival focuses on aerobic activity. The PAGAC, therefore, was only able to consider this type of activity. Furthermore, several of the studies provided information only on leisure-time, recreational activity. The effects of occupational, household, transportation and other activities on cancer risk and survival have therefore not been established.

The data in meta-analyses were not consistent enough or classified with sufficient precision for the PAGAC to determine the exact nature of physical activity-cancer relationships across population subgroups such as by age, race/ethnicity, socioeconomic status, or weight status. Nevertheless, where data were available, they pointed to likely benefit of physical activity across a wide range of population groups.

The PAGAC did not perform its own meta-analyses, and therefore relied on the methods of classifying data on physical activity, cancers, and covariates in the published meta-analyses. All physical activity data in the observational studies were collected via self-report, with resulting potential for measurement error due to recall error and reporting bias. Very few observational studies have included device-based measures of physical activity.

The PAGAC recommended future research in the areas of cancer prevention. There is a need for large prospective epidemiologic studies of the associations of physical activity on risk for specific cancers that have not been adequately studied. More epidemiologic studies of effects of physical activity on risk of cancer in specific age, racial, ethnic, and socioeconomic groups are needed. The methods of data collection and classification of activity amount varied across studies. Greater consistency and data harmonization across studies is needed, so that dose-response relationships can be established. Defining dose-response relationships will be critical to develop physical activity guidelines for cancer prevention. Most of the data available in meta-analyses and pooled analyses were on aerobic physical activity, typically added together into total leisure-time activity. Therefore, there is need for epidemiologic studies to determine effects of specific types of physical activity on cancer risk and survival.

Finally, to reduce the chance of confounding and error in testing the effect of physical activity on cancer risk, there remains a need for randomized controlled clinical trials testing exercise effects on cancer incidence. Randomized trials in high-risk individuals could be more cost-effective, as trials with smaller sample sizes or shorter follow-up durations are more feasible than trials in the general, at-risk population. Furthermore, randomized clinical trials testing the effects of physical activity on biomarkers of cancer, as well as animal models, have provided important mechanistic information to support the relationship between physical activity and reduced cancer risk.(66–69)

For cancer survival, the PAGAC identified several research needs. Because of the increasing length of cancer survivorship, there is need to continue long-term follow-up of cohorts of cancer survivors, with repeated self-report and device-based measures of physical activity, to

determine long-term associations of physical activity with recurrence and survival. In addition, continued follow-up of established large epidemiologic cohorts will allow for identification of individuals with less common cancers, to determine associations between physical activity level and survival from these other cancers. Given the strong potential for confounding by cancer treatment, stage, and progression, there is need for randomized controlled trials and cohort studies of physical activity and cancer survival and recurrence, aimed at eliminating effects of possible confounders. There is also need for prospective cohort studies and randomized controlled trials to determine effects of physical activity on cancer survival and recurrence in understudied groups, such as survivors from diverse ages, races, ethnicities, and socioeconomic groups; individuals with metastatic cancer; individuals with cancers other than colorectal, prostate, and female breast cancer; and patients treated with cardiotoxic drugs, radiotherapy, and hormonal treatments. Although the original and updated searches identified only studies of cancers in adults, the authors are aware that at least one study in childhood survivors was published after our updated search was completed;(70) more research is needed in this population. Of note, two ongoing randomized clinical trials will provide more definitive data on the dose and type of physical activity needed for improved survival in persons diagnosed with colon and prostate cancers. (71, 72)

In summary, levels of physical activity recommended in the 2018 Guidelines(73) are associated with reduced risk for several cancers, notably some of the most common cancers. The PAGAC also recognizes the potential benefit of these levels of physical activity in improving survival for individuals diagnosed with some common cancers. Given the significant impact of cancer on quality of life, financial stability, and mortality, the reduction in risk, and improved prognosis, of common cancers from high levels of physical activity could have a large public health impact. Substantial reductions in the incidence of cancer, mortality from cancer, and cancer-related costs would be expected if currently inactive individuals became more physically active. Therefore, the PAGAC suggests that all individuals should be encouraged to engage in recommended levels of physical activity to reduce risk for developing cancer and for improving cancer prognosis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HHS staff provided general administrative support to the Committee and assured that the Committee adhered to the requirements for Federal Advisory Committees. HHS also contracted with ICF, a global consulting services company, to provide technical support for the literature searches conducted by the Committee. HHS and ICF staff collaborated with the Committee in the design and conduct of the searches by assisting with the development of the analytical frameworks, inclusion/exclusion criteria, and search terms for each primary question; using those parameters, ICF performed the literature searches.

## Conflicts of Interest and Source of Funding

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**Table 1:**

2018 Physical Activity Guidelines Advisory Committee Evidence on Relationship between Physical Activity and Risk of Developing Invasive Cancer

Cancer	Overall Evidence Grade	Approximate % Relative Risk Reduction	Dose-response? Grade
Bladder	Strong	15%	Yes, moderate
Breast	Strong	12 – 21%	Yes, strong
Colon	Strong	19%	Yes, strong
Endometrium	Strong	20%	Yes, moderate
Esophagus (adenocarcinoma)	Strong	21%	No, limited
Gastric	Strong	19%	Yes, moderate
Renal	Strong	12%	Yes, limited
Lung	Moderate	21 – 25%	Yes, limited
Hematologic	Limited	Variable effect sizes	Not assignable
Head & Neck	Limited	Variable effect sizes	Not assignable
Ovary	Limited	8%	Yes, limited
Pancreas	Limited	11%	No, limited
Prostate	Limited	Variable effect sizes	Not assignable
Brain	Grade not assignable	Variable effect sizes	Not assignable
Thyroid	Limited	0	Not assignable
Rectal	Limited	0	Not assignable



**Table 2:**

2018 Physical Activity Guidelines Advisory Committee Evidence on Relationship Between Physical Activity and Mortality in Cancer Survivors

<b>All-cause Mortality</b>		
<b>Cancer</b>	<b>Evidence Grade</b>	<b>Approximate % Relative Risk Reduction</b>
Breast	Moderate	48%
Colorectal	Moderate	42%
Prostate	Limited	37-49%
<b>Cancer-specific Mortality</b>		
Breast	Moderate	38%
Colorectal	Moderate	38%
Prostate	Moderate	38%

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