PART F. CHAPTER 4. CANCER PREVENTION

Table of Contents

INTRODUCTION

In 2017, 1,688,780 new cancer cases and 600,920 cancer deaths are projected to occur in the United States.[1] On average, 38 percent of American women and 42 percent of American men will be diagnosed with an invasive cancer over their lifetimes.[2] Although several genetic causes of cancer have been identified, most cases of cancer are due to the environment or lifestyle.[3] In addition to lack of physical activity, other known lifestyle and preventable causes of cancer include tobacco use, alcohol intake, diet, obesity, and behaviors that increase exposure to oncogenic viruses. Therefore, there is great need and possibilities for cancer prevention through lifestyle change.

There are more than 100 types of cancer based on body site or cell of origin. Furthermore, most cancers include subtypes defined by anatomy, histology, or genomics. Cancer types and subtypes often differ in etiology or natural course. Therefore, studying the association of physical activity with cancer risk is tantamount to determining the effect of physical activity on scores of endpoints. In this report, subtypes of cancer sites are listed where etiologies, including physical activity exposure, are known to vary by subtype.

Decades of epidemiologic research have identified a physically active lifestyle as protective against the occurrence of some common cancers. The 2008 Physical Activity Guidelines Advisory Committee concluded that a moderate, inverse relationship existed between increased levels of physical activity and reduced risks of colon and breast cancers.[4] The 2008 Committee also found some evidence of reductions in risk of lung, endometrial, and ovarian cancers with increased physical activity, but no change in risk of prostate or rectal cancers.[4] Information was deemed too sparse to make conclusions for other cancers. The *Physical Activity Guidelines Advisory Committee Report, 2008*[4] provided probable risk reduction levels, based on reviews of individual reports; no meta-analyses were performed, and none were found from the literature at that time. Since that report was released, the epidemiologic literature has grown enough to allow the use of meta-analytic and pooled analysis techniques to provide robust estimates of the effect of physical activity on occurrence of both common and rarer cancers.

Interest in understanding the health effects associated with sedentary behavior (sitting) is also increasing. The 2008 Advisory Committee did not review the evidence on the association between sedentary behavior and cancer incidence. However, since 2008, an emerging literature has accumulated with respect to the association between sedentary time and cancer incidence and the Cancer Prevention Subcommittee included a question on this issue. (For additional information on the health effects associated with sedentary behavior, see *Part F. Chapter 2. Sedentary Behavior*.)

The 2008 Scientific Report also cited some mechanisms that may explain the associations between physical activity and cancer risk, but did not perform a systematic review.[4] Given the extremely large literature in this area,[5-8] including human experimental, observational, animal models, and other laboratory work, the Cancer Prevention Subcommittee was not able to perform a systematic review of the literature on mechanisms linking physical activity to cancer. However, the Subcommittee recognizes that this topic is a critical area of research that needs further attention and helps provide more understanding of how physical activity is related to cancer.

Finally, while many of the reviewed cancers occur in children as well as adults (e.g., leukemia, lymphoma), the etiology of these cancers often differs significantly in children versus adults. In addition, the usual long latency period for physical activity to protect against cancer development in adults will likely not be relevant to cancers occurring in children. For this reason, the literature review on physical activity and cancer risk has been limited to adults. Therefore, the Subcommittee limited its search to cancers in adults.

REVIEW OF THE SCIENCE

Overview of Questions Addressed

This chapter addresses two major questions and related subquestions:

1. What is the relationship between physical activity and specific cancer incidence?
    a) Is there a dose-response relationship? If yes, what is the shape of the relationship?
    b) Does the relationship vary by age, sex, race/ethnicity, socioeconomic status, or weight status?
    c) Does the relationship vary by specific cancer subtypes?
    d) Is the relationship present in individuals at high risk, such as those with familial predisposition to cancer?

2. What is the relationship between sedentary behavior and cancer incidence?
   a) Is there a dose-response relationship? If yes, what is the shape of the relationship?
   b) Does the relationship vary by age, sex, race/ethnicity, socioeconomic status, or weight status?
   c) Is the relationship independent of levels of light, moderate, or vigorous physical activity?
   d) Is there any evidence that bouts or breaks in sedentary behavior are important factors?

Data Sources and Process Used to Answer Questions

Systematic literature searches were conducted to answer Questions 1 and 2. The databases searched included PubMed, Cochrane, and CINAHL. The literature search to address Question 1 was limited to systematic reviews, meta-analyses, and pooled analyses. The literature search strategy to address Question 2 was expanded to also include original research articles, and was conducted in two steps. Step 1 involved a search for existing systematic reviews and meta-analyses that could address the question. Step 2 involved a de novo literature search of more recent original research studies published after the systematic reviews and meta-analyses. Question 2 is the same as the cancer component of Question 4 in the sedentary behavior chapter (for details, see *Part F. Chapter 2. Sedentary Behavior*.)

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 collected information on recreational activities, several also included occupational activities, and only a few included household activities. Some estimated total physical activity, adding up all of these activities; most limited estimation of amount of activity to leisure time activity. Most of the meta-analyses estimated MET-hours per week of moderate and vigorous physical activities where data were available, but the cut-points for “highest” versus “lowest” activity levels varied across studies. Although most studies assigned a MET value of 6 for vigorous activities, some assigned a value of 8.

Most of the meta-analyses, as well as the large pooled study,[9] were restricted to prospective cohort studies in order to minimize error from reporting that might occur because of recall of past physical activity levels that is required in case-control studies. However, for some more rare cancers, meta-analyses or pooled analyses did include case-control studies. For this reason, the Subcommittee did not exclude results from systematic reviews, meta-analyses, or pooled analyses in making conclusions about the associations between physical activity and risk for specific cancers.

Question 1. What is the relationship between physical activity and specific cancer incidence?

a) Is there a dose-response relationship? If yes, what is the shape of the relationship?
b) Does the relationship vary by age, sex, race/ethnicity, socioeconomic status, or weight status?
c) Does the relationship vary by specific cancer subtypes?
d) Is the relationship present in individuals at high risk, such as those with familial predisposition to cancer?

Sources of evidence: Meta-analyses, systematic reviews, pooled analyses

Cancers for Which Physical Activity Shows Strong Evidence of a Protective Effect

Bladder Cancer

Conclusion Statements

Strong evidence demonstrates that greater amounts of physical activity are associated with reduced risk of developing bladder cancer. **PAGAC Grade: Strong.**

Moderate evidence indicates a dose-response relationship between increasing physical activity levels and decreasing risk of bladder cancer. **PAGAC Grade: Moderate.**

Limited evidence suggests that the effects of physical activity on bladder cancer risk are lower for men than for women. **PAGAC Grade: Limited.** Insufficient evidence is available to determine whether the effects of physical activity on risk of bladder cancer differ by specific age, race/ethnicity, socioeconomic groups, or weight status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the effects of physical activity are similar for all types of bladder cancer. **PAGAC Grade: Not assignable**

Insufficient evidence is available to determine whether the effects of physical activity on bladder cancer risk differ in individuals at elevated risk of bladder cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

Based on data from 2010 to 2014, the incidence rate of bladder cancer was 19.8 per 100,000 men and women per year.[10] The number of deaths was 4.4 per 100,000 men and women per year. Several factors increase risk of bladder cancer, including smoking, exposure to certain occupational toxins, and arsenic in drinking water.[11] Bladder cancer is more common in individuals older than age 55 years than in younger individuals, in men than in women, and in individuals with a personal or family history of cancer of the urinary tract.

To examine the association between physical activity and risk of bladder cancer, the Subcommittee reviewed one published meta-analysis.[12] The meta-analysis contained data from 11 cohort and 4 case-control studies. The Subcommittee also reviewed one pooled analysis of 12 large prospective cohort studies[9] and meta-analysis data from the World Cancer Research Fund, which included data from 12 cohort studies.[13]

Evidence on the Overall Relationship

A considerable body of epidemiologic data exists on the association between physical activity and risk of developing bladder cancer. The meta-analysis reported that risk of bladder cancer 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).[12] Most studies adjusted for multiple potential confounding factors, including age, body mass index (BMI), and other bladder cancer risk factors. Similar to these findings, the pooled analysis of 12 cohort studies found a statistically significant relationship between the 90th versus 10th percentile level for leisure time physical activity and decreased risk of bladder cancer (RR=0.87; 95% CI: 0.82-0.92).[9] In contrast, the World Cancer Research Fund meta-analysis summary result for highest versus lowest physical activity, which did not include studies focused on occupational physical activity, showed a non-statistically significant effect (RR=0.94, 95% CI: 0.83-1.06).[13]

Dose-response: The meta-analysis examined the dose-response relationship by quartiles of physical activity in each study. Compared with the least active quartile, those in quartiles 2, 3, and 4 had RR (95% CIs) of 0.90 (0.83-0.97), 0.86 (0.77-0.96), and 0.83 (0.72-0.95), respectively.[12] The pooled analysis of 12 cohort studies found a significant linear relationship between increasing leisure time physical activity percentile and decreasing risk of bladder cancer ($P_{overall}$<0.0001; $P_{non\text{-}linear}$=0.59).[9]

Evidence on Specific Factors

Sex: The meta-analysis found some differences in physical activity effect on bladder cancer risk between men (RR=0.92, 95% CI: 0.82-1.05) and women (RR=0.83; 95% CI: 0.73-0.94).[12] Although the pooled analysis found that the effect size of physical activity on risk of bladder cancer was similar in men and women, the association was statistically significant only in women ($P_{heterogeneity}$=0.81).[9]

Age: None of the analyses provided data within specific age groups.

Race/ethnicity: All but one study in the meta-analysis were conducted in the United States and Europe; the one study in Asia (men only) showed a non-statistically significant association of physical activity with bladder cancer risk (RR=0.94; 95% CI: 0.77-1.15).[12]

Socioeconomic status: None of the analyses presented data on the effect of socioeconomic status on the association between physical activity and bladder cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: The pooled analysis examined associations between the 90th percentile versus 10th percentile of physical activity level by BMI. Risk of bladder cancer associated with physical activity level did not differ for those with BMI <25.0 kg/m^2 versus BMI $\geq$25 kg/m^2 ($P_{interaction}$ = 0.80).[9]

Cancer subtype: Neither the meta-analysis nor the pooled analysis provided data by subtype of bladder cancer.

Individuals at high risk: No information was provided in the meta-analysis or in the pooled analysis about the effects of physical activity in individuals at elevated risk of bladder cancer.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Breast Cancer

Conclusion Statements

Strong evidence demonstrates that greater amounts of physical activity are associated with a lower risk of breast cancer. **PAGAC Grade: Strong.**

Strong evidence demonstrates that a dose-response relationship exists between greater amounts of physical activity and lower breast cancer risk. **PAGAC Grade: Strong.**

Moderate evidence indicates that greater amounts of physical activity are associated with a greater risk reduction in all women regardless of body mass index. **PAGAC Grade: Moderate.** Insufficient evidence is available to determine whether the amount of physical activity and risk of breast cancer incidence varies by age. **PAGAC Grade: Not assignable.** Limited evidence suggests that the relationship between physical activity and breast cancer does not vary by race/ethnicity. **PAGAC Grade: Limited.** Insufficient evidence is available to determine whether the relationship between physical activity and breast cancer varies by socioeconomic status. **PAGAC Grade: Not assignable.**

Limited, but inconsistent, evidence suggests that the relationship between physical activity and breast cancer varies by specific histologic types of breast cancers. **PAGAC Grade: Limited**.

Limited evidence suggests that the relationship between physical activity and breast cancer is apparent in women at increased breast cancer risk, as an enhanced effect of physical activity was associated with premenopausal breast cancer in women with a positive family history of breast cancer. **PAGAC Grade: Limited.**

Review of the Evidence

Based on data from 2010 to 2014, the incidence rate of female breast cancer was 124.9 per 100,000 women per year. The number of deaths was 21.2 per 100,000 women per year.[14] Most commonly, breast cancer occurs in ducts of the breast (ductal carcinoma); lobular carcinoma and inflammatory breast cancer are less common. Breast cancers are typically categorized by estrogen receptor (ER) and progesterone receptor (PR) status (positive (+)/negative (-)), as well as by presence of human epidermal growth factor type 2 receptor (HER2/neu positive (+)/negative (-)). Breast tumors can be further characterized by grade, which is the degree of cellular abnormality seen microscopically. Stage of breast cancer is determined by both pathological and clinical diagnosis. In situ (or Stage 0) breast cancer is that which has not invaded based the lining of the duct or lobule. By definition, Stages 1-4 is invasive breast cancer that has spread to local or distant tissues

The major risk factors for breast cancer, besides increasing age and physical inactivity, are: inherited changes in genetic factors, a first degree family history of breast cancer, increased mammographic density, atypical hyperplasia, radiation therapy, alcohol intake, early age at menarche and late age at menopause, first full-term pregnancy after age 30 years and nulliparity, long term use of menopausal hormone therapy, overweight or obesity after menopause, and White race.[15]

The Subcommittee used information from four meta-analyses[16-19] and two pooled analyses.[9, 20] The meta-analysis by Wu et al[16] included 31 prospective cohort studies published to November 2012. The meta-analysis by Neilson et al[17] included 80 reports from 67 different studies published to June 2015. The meta-analysis by Pizot et al[18] included 38 prospective cohort studies published between 1987 and 2014. The meta-analysis by Liu et al[19] included 126 cohort studies that examined a variety of cancers. Of these, nine studies were included in the breast cancer analysis and five of them were used in the dose-response analysis. The pooled analysis by Gong et al[20] included four studies combined in the African American Breast Cancer Consortium. The pooled analysis by Moore et al[9] included nine cohort studies with 35,178 breast cancer cases. All types of physical activity were included in the meta-analyses by Wu et al[16] and Pizot et al[18]; recreational physical activity only was included in the meta-analyses by Neilson et al[17] and Liu et al[19] and the pooled analysis by Moore et al.[9] The pooled analysis by Gong et al[20] included vigorous physical activity but did not specify what type of activity was specifically recorded and used as the exposure assessment. The meta-analysis by Neilson et al[17] was likewise restricted to moderate-to-vigorous recreational physical activity. The dose-response relationship was tested in all of these meta-analyses and pooled analyses,[9, 16-20] and evidence for a linear statistically significant association between greater amounts of physical activity and lower breast cancer risk was observed in four of these meta-analyses.[16-19]

Evidence on the Overall Relationship

The meta-analysis by Wu et al[16] estimated that the highest versus the lowest categories of all types of physical activity in the 38 cohort studies they included was associated with a decreased risk of breast cancer (RR=0.88; 95% CI: 0.85-0.90). Wu et al[16] also presented the results stratified by menopausal status. For premenopausal women, the random effects model estimates were 0.77 (95% CI: 0.69-0.86) and for postmenopausal women the effect estimates were 0.88 (95% CI: 0.87-0.92).[16] These authors also presented the results for the association between breast cancer incidence and physical activity by type of activity. For occupational activity, the relative risk was 0.84 (95% CI: 0.73-0.96); for non-occupational activity, it was 0.87 (95% CI: 0.82-0.91); for recreational activity, it was 0.87 (95% CI: 0.83-0.91); for household activity, it was 0.89 (95% CI: 0.83-0.95), and for walking, it was 0.87 (95% CI: 0.79-0.96).[16]

Neilson et al[17] reported all results for the association between physical activity and breast cancer risk stratified by menopausal status. Data from 36 case-control and 13 cohort studies were combined to estimate the relative risk of premenopausal breast cancer associated with moderate-to-vigorous recreational activity; for postmenopausal women, data from 38 case-control and 26 cohort studies were combined. For premenopausal women, the estimated odds ratio (OR) was 0.80 (95% CI: 0.74-0.87) and for postmenopausal women, the odds ratio was 0.79 (95% CI: 0.74-0.84).

Pizot et al[18] presented the results for all types of physical activity combined. These authors found a statistically significant reduction for breast cancer incidence when comparing the highest versus the lowest amounts of all types of physical activity combined (OR: 0.88; 95% CI: 0.85-0.91). When examining the associations by type of activity, they 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). Pizot et al[18] also reported the results for the association between all types of physical activity combined and breast cancer risk by menopausal status. 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). Pizot et al[18] also provided risk estimates for studies that used comparable methods for assessing physical activity. Risk reductions were greater in studies that measured physical activity in hours per week (RR=0.81; 95% CI: 0.76-0.87) than in MET-hours per week (RR=0.87; 95% CI: 0.83-0.91) or in other units (RR=0.89; 95% CI: 0.85-0.92).[18]

Liu et al[19] reported decreased risk of overall breast cancer incidence when they compared participants with the highest to the lowest amounts of leisure time physical activity (RR=0.88; 95% CI: 0.84-0.91).

In their pooled analysis from the African American Breast Cancer Epidemiology and Risk Consortium, Gong et al[20] reported that any vigorous activity versus none was associated with a reduction in odds of breast cancer incidence of 0.88 (95% CI: 0.81-0.96).

Moore et al[9] compared participants in the 90th percentile to those in the 10th percentile of physical activity in their pooled analysis and found a statistically significant association with breast cancer incidence (hazard ratio (HR)=0.90; 95% CI: 0.87-0.93).

Dose-response: Evidence for a linear statistically significant association between greater amounts of physical activity and lower breast cancer risk was observed in four of the meta-analyses.[16-19] Using data from three studies, Wu et al[16] observed a statistically significant linear relationship between higher amounts of non-occupational physical activity and lower breast cancer risk. The risk of breast cancer was 2 percent lower (RR=0.98; 95% CI: 0.97-0.99) for every 25 MET-hours per week increment in non-occupational activity (roughly equivalent to 10 hours per week of light household activity). Using data on recreational activity from seven studies, Wu et al[16] estimated that the risk of breast cancer was 3 percent lower (RR=0.97; 95% CI: 0.95-0.98) for every 10 MET-hours per week increment in recreational activity (roughly equivalent to 4 hours per week of walking at 2 miles per hour). Wu et al[16] also found a linear relationship between breast cancer risk and moderate plus vigorous recreational activity using data from eight studies. The risk of breast cancer was 5 percent lower (RR=0.95; 95% CI: 0.93-0.97) for every 2 hours per week increment in moderate plus vigorous activity.[16] When examining vigorous recreational activity only with data from eight studies, Wu et al[16] found that the risk of breast cancer was 5 percent lower (RR=0.95; 95% CI: 0.92-0.97) for every 2 hours per week spent in this level of recreational activity.

Neilson et al[17] plotted dose-response curves across levels of moderate-to-vigorous recreational activity by menopausal status and found a statistically significant, curvilinear dose-response relationship for both menopausal groups. The authors speculated that this curvilinear dose-response association suggested a point of diminishing returns when moderate-to-vigorous recreational activity went beyond 20 to 30 MET-hours per week. However, the 95% confidence intervals were wide at the upper levels of activity, which precluded any definitive conclusions about the nature of this dose-response relationship at very high levels of activity. Neilson et al[17] also plotted dose-response curves with respect to activity duration (hours per week) using data from 13 studies and they found a clear inverse linear association with postmenopausal breast cancer risk. For premenopausal breast cancer risk, using data from 10 studies they observed a J-shaped, statistically significant non-linear trend with an inflection point around 3 hours per week. These studies were distinct from those in the MET-hours per week analysis. The authors investigated the possible reasons for this J-shaped association and suggested that measurement error, covariate adjustment, and heterogeneity across these studies might partially explain these unexpected findings. The study by Neilson et al[17] is the only meta-analysis to examine the dose-response relationships separately for premenopausal and postmenopausal breast cancer.

Pizot et al[18] performed dose-response analyses with 11 studies that reported physical activity in MET-hours per week and with 11 studies that reported duration of physical activity in hours per week and noted statistically significant dose-response relationships between amounts of physical activity and breast cancer risk without evidence for a threshold.

Liu et al[19] also found a statistically significant decreasing risk for breast cancer across categories of leisure time physical activity estimated in MET-hours per week.

Gong et al[20] tested for a linear trend across categories of hours per week of vigorous physical activity and found evidence for a statistically significant trend, although the dose-response association was not very evident with the highest category of physical activity (7 hours per week), which was associated with a risk of 0.86 (95% CI: 0.68-1.10) compared with the lowest category (<2 hours per week), which had a risk of 0.90 (95% CI: 0.81-1.01).

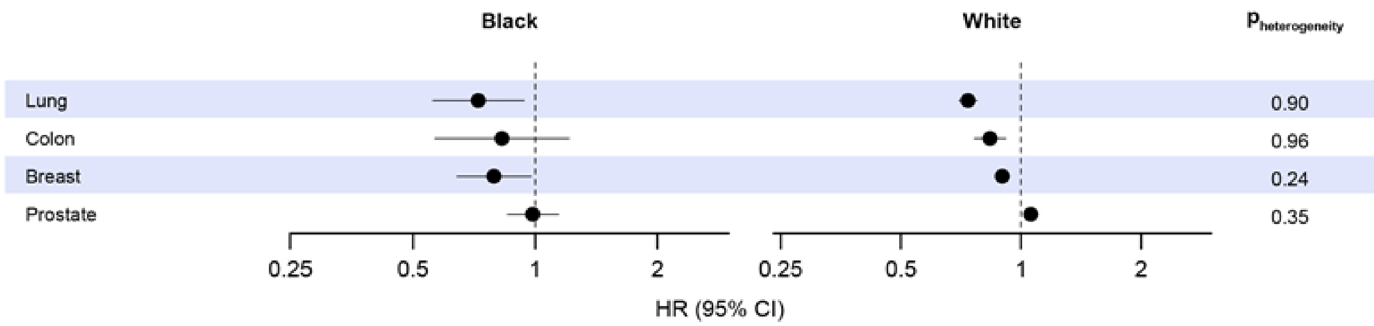
Finally, Moore et al[9] also found a linear dose-response relationship between increasing levels of leisure time physical activity and decreased breast cancer risk (*P*<0.0001).

Evidence on Specific Factors

Age: Only the pooled analysis by Gong et al[20] reported results by age (<50 years versus ≥50 years) and found comparable risk reductions for both age groups of 15 and 12 percent that were borderline statistically significant. Several of these meta-analyses and pooled analyses did examine the effects of physical activity on breast cancer risk by menopausal status, which could be a proxy for age. Overall, there appears to be a somewhat greater breast cancer risk reduction associated with higher amounts of physical activity among postmenopausal women than premenopausal women.

Race/ethnicity: The pooled analysis by Gong et al[20], which included only American women of African ancestry, reported a statistically significant 12 percent decreased risk associated with vigorous physical activity. Neilson et al[17] presented the results for studies by racial groups and found statistically significant reductions in premenopausal breast cancer risk for White, White-Hispanic, and Asian women. For postmenopausal women, statistically significant reductions in breast cancer risk also were evident for White-Hispanic and Asian women. No statistically significant risk reductions were found for Hispanic or Black women in either menopausal category.[17] The Moore et al[9] pooled analysis found similar associations between highest versus lowest physical activity level and breast cancer risk in black and white women (*P* heterogeneity = 0.24) (Figure F4-1). No other studies presented their results by race/ethnic groups.

Figure F4-1. Summary Multivariable Hazard Ratios and 95% Confidence Intervals (CI) for a Higher (90th percentile) versus Lower (10th percentile) Level of Leisure-Time Physical Activity, by Cancer Type, Stratified by Race/Ethnicity



Source: Reproduced with permission from [Moore et al[9], Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. 2016. 176(6):816–825]. Copyright©(2016) American Medical Association. All rights reserved.

Socioeconomic status: None of the analyses presented data on the effect of socioeconomic status on the association between physical activity and breast cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: A statistically significant effect modification of the association between breast cancer incidence and physical activity by BMI was found in the meta-analysis by Neilson et al,[17] with greater risk reductions found in both premenopausal and postmenopausal women with a BMI <25 kg/m^2 (RR=0.85; 95% CI: 0.73-0.99 and RR=0.84; 95% CI: 0.77-0.92, respectively) than in women with a BMI ≥25 kg/m^2 (RR=0.99; 95% CI: 0.98-1.00 and RR=0.88; 95% CI: 0.82-0.95, respectively). Pizot et al[18] reported risk reductions in breast cancer incidence for both women with low and high BMI (RR=0.84; 95% CI: 0.78-0.90 and RR=0.87; 95% CI: 0.81-0.93). In contrast, in the Moore et al[9] pooled analysis no effect modification by BMI was observed for the association between leisure time physical activity and breast cancer incidence.

Cancer subtype: The association between physical activity and different breast cancer subtypes was considered in four of these meta-analyses and pooled analyses but the findings were inconsistent.[16, 17, 19, 20] Wu et al[16] found stronger risk reductions for invasive breast cancers than in situ tumor stage cancers (RR=0.81; 95% CI: 0.73-0.91 versus RR=0.86; 95% CI: 0.74-0.99). These results also were found in the meta-analysis by Liu et al,[19] in which greater risk reductions for invasive cancers compared with in situ breast cancers were found. Wu et al[16] also reported that women with estrogen receptor negative/progesterone receptor negative breast cancer tumors had a greater reduction in risk compared with estrogen receptor positive/progesterone receptor positive breast cancer cases (RR=0.77; 95% CI: 0.65-0.90 and RR=0.93; 95% CI: 0.87-0.98). Gong et al[20] reported a statistically significant inverse association with vigorous physical activity for estrogen receptor positive breast cancer (OR=0.88; 95% CI: 0.80-0.98) but not for estrogen receptor negative breast cancer (OR=0.93; 95% CI: 0.82-1.06). Pizot et al[18] observed stronger risk reductions for women with estrogen receptor negative breast cancer (OR=0.80; 95% CI: 0.83-0.90) than for estrogen receptor positive breast cancers (OR=0.89; 95% CI: 0.83-0.95) associated with physical activity. Neilson et al[17] found statistically significant associations between moderate-to-vigorous recreational activity and ductal and lobular tumor histology in postmenopausal women but observed no inverse associations for mucinous or tubular breast cancers. They also stratified their study results by hormone receptor status and found inverse and statistically significant associations for estrogen receptor positive/progesterone receptor positive premenopausal and postmenopausal breast cancers. In addition, they found that tumors with several combinations of hormone receptor and HER2/neu status were also protected with high levels of physical activity including: 1) estrogen receptor positive, 2) progesterone receptor positive, 3) estrogen receptor positive/progesterone receptor negative, 4) HER2 positive, or 5) HER2 negative/estrogen receptor positive/progesterone receptor positive postmenopausal breast cancer. In addition, physical activity protected against: 1) estrogen receptor negative/progesterone receptor negative, HER2 negative, or p53 premenopausal breast cancers. No clear pattern of greater risk reductions by tumor grade was seen.[17]

Other factors: No effect modification by geographic location (i.e., America, Europe, Asia) was observed in the meta-analysis by Wu et al.[16] No other analyses examined effect modification of the association between physical activity and breast cancer incidence by geographic location. The pooled analysis by Gong et al[20] of African Americans suggested that having no family history of breast cancer conferred greater risk reduction associated with physical activity than having a positive family history. Neilson et al[17] found limited evidence that a positive family history of breast cancer was associated with a greater risk reduction than no family history in premenopausal women (RR=0.28; 95% CI: 0.14-0.58 versus RR=0.72; 95%CI: 0.58-0.88). For postmenopausal women, the effect of physical activity on reducing breast cancer risk in women with and without a family history of breast cancer was nearly equal (RR=0.85; 95% CI: 0.70-1.02 versus RR=0.83; 95% CI: 0.75-0.92). The stratified analyses in the meta-analysis by Neilson et al[17] for premenopausal women with a family history of breast cancer were based on only three studies and must be interpreted with caution.

In the analyses by Gong et al[20] and Neilson et al,[17] physical activity conferred a greater benefit for breast cancer risk reduction among parous women as compared to nulliparous women. In the Neilson et al[17] meta-analysis, premenopausal parous women had a 36 percent risk reduction (OR=0.64; 95% CI: 0.46-0.90) associated with higher amounts of moderate-to-vigorous recreational activity.

The meta-analysis by Pizot et al,[18] showed a statistically significant effect modification between hormone replacement therapy use and breast cancer risk. A beneficial effect of physical activity was observed only in those women who never used hormone replacement therapy while ever users had no risk reductions associated with physical activity. Neilson et al[17] found that not using hormone replacement therapy and ever use were both associated with statistically significant reduced breast cancer risks but that the effects were stronger in non-users than ever users.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Colon Cancer

Conclusion Statements

Strong evidence demonstrates that greater amounts of recreational, occupational, or total physical activity are associated with a lower risk of developing colon cancer. **PAGAC Grade: Strong.**

Strong evidence demonstrates a dose-response relationship between increasing physical activity levels and decreasing risk of colon cancer. **PAGAC Grade: Strong.**

Strong evidence demonstrates that the effects of physical activity on colon cancer risk are evident in both men and women. **PAGAC Grade: Strong.** Insufficient evidence is available to determine whether the effects of physical activity on risk of colon cancer differ by specific age, race/ethnic, or socioeconomic groups in the United States. **PAGAC Grade: Not assignable.** Moderate evidence indicates that weight status does not affect the associations between physical activity and colon cancer risk. **PAGAC Grade: Moderate.**

Strong evidence demonstrates that greater amounts of physical activity are associated with a lower risk of developing both proximal and distal colon cancer. **PAGAC Grade: Strong.**

Insufficient evidence is available to determine whether the effects of physical activity on colon cancer risk differ in individuals at elevated risk of colon cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

Colon cancer is the third most commonly diagnosed cancer in the United States in both men and women.[21] Based on data from 2010-2014, the incidence rate of colon cancer in the United States was 28.2 per 100,000 men and women per year. Risk factors for colon cancer include: increased age, African-American race or Jewish ethnicity, family history of colorectal cancer, personal history of adenomatous colorectal polyps, history of certain inflammatory bowel conditions, a known family history of a hereditary colorectal cancer syndrome, diabetes mellitus, smoking, obesity, alcohol intake, and eating red and processed meats.[22]

To examine the association between physical activity and risk of colon cancer, 8 systematic reviews were reviewed[19, 23-29] of which 7[19, 23-28] included meta-analyses, as well as one pooled analysis of 12 large prospective cohort studies.[9] The Subcommittee also reviewed meta-analysis data from the World Cancer Research Fund.[30, 31] Because the association of physical activity with colon and rectal cancer differs by site (see the section on rectal cancer, below), the Subcommittee did not include studies where colorectal cancer was the outcome of interest because the relationship between physical activity and colon cancer likely would be obscured. The reviews contained data from between 8 and 21 epidemiologic studies.

Evidence on the Overall Relationship

A large body of epidemiologic data exists on the association between physical activity and risk of developing colon cancer. The most recent meta-analysis 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] Other meta-analyses found similar effect sizes showing inverse associations between highest versus lowest levels of physical activity and risk of developing colon cancer.[23-27, 30, 31] Most studies adjusted for multiple potential confounding factors, including age, BMI, and colon cancer risk factors, although adjustment for colon cancer screening (which could be related to physical activity level) was not typically done. To address this issue, one meta-analysis examined the associations between physical activity and colon cancer risk before 1993 (before testing fecal occult blood was widely used), between 1993 and 1999, and after 1999 when colon cancer screening (by endoscopy) became widely available.[28] The risk estimates for physical activity and colon cancer risk did not differ between the time periods. Studies published before 1993 (RR=0.74; 95% CI: 0.67-0.82); those published between 1993 and 1999 (RR=0.78, 95% CI: 0.70-0.86); and those published after 1999 (RR=0.78; 95% CI: 0.73-0.83) demonstrated similar risk reductions for this association.

Dose-response: A dose-response relationship is apparent, with risk decreasing at higher levels of physical activity. A dose-response meta-analysis of three cohort studies found that per 30 minutes per day of recreational physical activity, the relative risk of colon cancer was 0.88 (95% CI: 0.80-0.96).[31] In contrast, dose-response estimates per 5 MET-hours per week of total physical activity were significant only for distal colon cancer, with a relative risk of 0.92 (5 studies, 95% CI: 0.89-0.96).[31] One meta-analysis estimated dose-response by percentile of physical activity, and found a linear reduction in risk across the 20th to 95th percentiles and estimated risk reductions between these two percentiles of 0.13 in men and 0.14 in women.[23] This same meta-analysis plotted risk for colon cancer by leisure time physical activity in those studies with MET-hours per week or MET-minutes per week data, and found dose-response risk reductions in both men and women. The pooled analysis of 12 cohort studies found a significant relationship between increasing leisure time physical activity percentile and decreased risk of colon cancer ($P_{overall}<0.0001$; $P_{non\text{-}linear}=0.4$).[9]

Evidence on Specific Factors

Sex: Meta-analyses found that physical activity reduced colon cancer risk in both men and women, and there were no statistically significant differences in this effect by sex overall,[23] or for proximal or distal colon cancer.[24, 26]

Age: None of the analyses or the systematic review provided data within specific age groups.

Race/ethnicity: Studies in the United States and Europe were primarily in Caucasians. One systematic review of Japanese studies reported on data from two cohort and six case-control studies, and found that the association of increased physical activity with reduced risk for colon cancer was stronger in men than women, and stronger in proximal than distal cancer.[29] The pooled analysis of 12 cohort studies examined the association between the 90th percentile versus 10th percentile of physical activity level in Black and White individuals (Figure F4-1).[9] The hazard ratio was similar in the two groups ($P_{heterogeneity}$= 0.96).

Socioeconomic status: None of the analyses or the systematic review presented data on the effect of socioeconomic status on the association between physical activity and colon cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: The pooled analysis examined associations between the 90th percentile versus 10th percentile of physical activity level by BMI. Risk of colon cancer for those with BMI <25.0 kg/m^2 did not differ from that of individuals with BMI $\geq$25 kg/m^2 (*P*-value for effect modification=0.81).[9]

Cancer subtype: Two meta-analyses were conducted on studies that included data by anatomic subsite.[24, 26] Comparing most to least active individuals, the relative risks for proximal colon cancer were almost identical in the two reports: 0.73 (95% CI: 0.66-0.81)[24] and 0.76 (95% CI: 0.70-0.83).[26] Similarly, the relative risks for distal colon cancer were almost identical in the two reports: 0.74 (95% CI: 0.68-0.80)[24] and 0.77 (95% CI: 0.71-0.83).[26] A dose-response meta-analysis of three cohort studies found that per 30 minutes per day of recreational physical activity, the relative risks of proximal and distal colon cancer were 0.89 (95% CI: 0.82-0.96), and 0.87 (95% CI: 0.77-0.98), respectively.[31]

Individuals at high risk: No information was provided in the systematic review or analyses about effects of physical activity in individuals at elevated risk of colon cancer.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Endometrial Cancer

Conclusion Statements

Strong evidence demonstrates that greater amounts of physical activity are associated with a lower risk of endometrial cancer. **PAGAC Grade: Strong.**

Moderate evidence indicates that a dose-response relationship exists between greater amounts of physical activity and lower endometrial cancer risk. **PAGAC Grade: Moderate.**

Moderate evidence indicates that greater amounts of physical activity are associated with a greater risk reduction in women with a body mass index of greater than 25 kg/m^2 compared to women with a body mass index of less than 25 kg/m^2. **PAGAC Grade: Moderate.** Insufficient evidence is available to determine whether the association between physical activity and risk of endometrial cancer varies by age, race/ethnicity, or socioeconomic status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether specific histologic types of endometrial cancers modify the relationships between amounts of physical activity and risk of endometrial cancer. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the effects of physical activity on endometrial cancer risk differ in individuals at elevated risk of endometrial cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

Based on data from 2010 to 2014, the incidence rate of endometrial cancer was 25.7 per 100,000 women per year.[32] The number of deaths was 4.6 per 100,000 women per year. Several factors increase risk of endometrial cancer, including obesity and having metabolic syndrome, hyperinsulinemia, nulliparity, early age at menarche, late age at menopause, polycystic ovarian syndrome, first degree relative with endometrial cancer, and Lynch syndrome.[32]

The Subcommittee used information from four meta-analyses[19, 33-35] and one pooled analysis.[9] The meta-analysis by Keum et al[33] included 20 studies (10 cohort and 10 case-control studies) published to September 2013. The meta-analysis by Moore et al[34] included nine prospective studies published to December 2009. The meta-analysis by Schmid et al[35] included 33 studies (15 prospective cohort studies, 3 retrospective cohort studies, 1 case-cohort study and 14 case-control studies). The meta-analysis by Liu et al[19] included 126 cohort studies. Of these, nine studies were a binary endometrial cancer analysis and five of them were used in the dose-response analysis. The pooled analysis[9] included 9 cohort studies with 5,346 endometrial cancer cases. Recreational physical activity was included in two of the meta-analyses[19, 33] and the pooled analysis.[9] Moore et al[34] included recreational and occupational activity in their review and Schmid et al[35] included recreational, occupational, and household activity and walking in their review. The dose-response relationship was examined in three of the meta-analyses[19, 33, 35] and in the pooled analysis.[9]

Evidence on the Overall Relationship

The meta-analysis by Keum et al[33] found that the highest versus lowest categories of leisure time physical activity in the 20 studies they included were associated with a decreased risk of endometrial cancer (RR=0.82; 95% CI: 0.75-0.90). The meta-analysis by Moore et al[34] reported that the highest versus lowest amounts of recreational physical activity were associated with a statistically significant reduction in endometrial cancer incidence (RR=0.73; 95% CI: 0.58-0.93). These authors also presented the results for highest versus lowest amounts of occupational physical activity and found similar risk reductions (OR=0.79; 95% CI: 0.71-0.88). Schmid et al[35] presented the results for all types of physical activity combined as well as by type of activity. These authors 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). When examining the associations by type of activity, they 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). Schmid et al[35] also presented their results by the intensity of physical activity and reported that endometrial cancer risk was decreased with all intensity levels of physical activity (light, moderate-to-vigorous, and vigorous) and these risk reductions were all statistically significant. The greatest reduction in endometrial cancer incidence was associated with light-intensity physical activity for which a relative risk of 0.65 was observed (95% CI: 0.49-0.86). Moderate-to-vigorous and vigorous-intensity physical activity had similar associations, with endometrial cancer risk of RR=0.83 (95% CI: 0.71-0.96) and 0.80 (95% CI: 0.72-0.90), respectively.[35] Liu et al[19] reported a null association for overall endometrial cancer incidence when they compared participants with the highest to the lowest amounts of leisure time physical activity (RR=0.94; 95% CI: 0.77-1.15). Moore et al[9] compared participants in the 90th percentile to those in the 10th percentile of physical activity and found a statistically significant decreased risk of endometrial cancer (HR=0.79; 95% CI: 0.68-0.92).

Dose-response: Keum et al[33] observed a non-linear statistically significant relationship between greater amounts of leisure time physical activity and lower endometrial cancer risk. They estimated that per 3 MET-hours per week, the relative risk was 0.98 (95% CI: 0.95-1.00) and per 1 hour per week, the RR was 0.95 (95% CI: 0.93-0.98). Schmid et al[35] restricted their assessment of dose-response to studies that reported their results in MET-hours per week and to account for variability in the range of MET-hour levels in the individual studies, they performed analyses summarizing studies that provided the risk estimates for 3-8, 9-20 and greater than 20 MET-hours as compared to less than 3 MET-hours of physical activity per week. They obtained relative risks of 0.94 (95% CI: 0.74-1.20), 0.79 (95% CI: 0.64-0.98), and 0.87 (95% CI: 0.71-1.06) for 3-8, 9-20 and greater than 20 MET-hours as compared to less than 3 MET-hours of physical activity per week. In addition, within the range of 0 to approximately 40 MET-hours per week of recreational physical activity, they observed a non-linear inverse dose-response relationship for recreational physical activity with endometrial cancer risk ($P_{non\text{-}linearity}$<0.05), which indicated a 5 percent reduced risk of endometrial cancer for those engaging in 12 MET-hours per week of recreational activity compared to those not engaging in regular physical activity (RR=0.95 (95% CI: 0.91-0.99). Liu et al[19] estimated the hazard ratios across categories of leisure time physical activity from 0 to 40 MET-hours per week in increments of between 10 and 20 MET-hours per week. They found no evidence for a linear dose-response trend (*P*-trend=0.46). However, Moore et al[9] did observe a statistically significant linear dose-response trend (*P*<0.0001) between greater amounts of physical activity and lower endometrial cancer risk.

Evidence on Specific Factors

Age: None of the analyses presented their results stratified by different age groups, hence, no conclusions can be made regarding the role of age on the association between physical activity and endometrial cancer.

Race/ethnicity: No conclusions can be made regarding the role of race/ethnicity in the association between physical activity and endometrial cancers because none of the analyses considered these factors.

Socioeconomic status: None of the analyses presented data on the effect of socioeconomic status on the association between physical activity and endometrial cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: A statistically significant effect modification of the association between endometrial cancer incidence and physical activity by BMI was found in the meta-analysis by Schmid et al,[35] with a greater risk reduction found in women with a BMI ≥25 kg/m^2 (OR=0.69 (95% CI: 0.52-0.91) than in women with a BMI <25 kg/m^2 (OR=0.97; 95% CI: 0.84-1.13). In the Moore et al[9] pooled analysis, effect modification by BMI was observed for the association between leisure time physical activity and endometrial cancer incidence. This pooled analysis showed no effect of physical activity on endometrial cancer incidence for women with a BMI <25 kg/m^2 but stronger risk reductions were observed for those with a BMI ≥25 kg/m^2 (Note: no risk estimates were provided in the Moore et al[9] pooled analysis).

Cancer subtype: None of the analyses considered the association with physical activity for different endometrial cancer subtypes.

Other factors: No effect modification by geographic location (i.e., America, Europe, Asia) was observed in the meta-analyses by Keum et al[33] or Schmid et al.[35] Likewise, no effect modification was observed by use or hormone therapy, oral contraceptives, menopausal status, or parity.[33, 35] There was some indication that smokers who were more physically active as compared to the least active smokers had a greater reduction in endometrial cancer incidence (RR=0.79 (95% CI: 0.71-0.87) than non-smokers who were the most active compared to the least active (RR=0.87 (95% CI: 0.73-1.03).[33]

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Esophageal Cancer

Conclusion Statements

Strong evidence demonstrates that greater amounts of recreational, occupational, or total physical activity are associated with a lower risk of developing adenocarcinoma of the esophagus. **PAGAC Grade: Strong.**

Limited evidence suggests that greater amounts of physical activity are not associated with a lower risk of developing squamous cell carcinoma of the esophagus. **PAGAC Grade: Limited.**

Limited evidence suggests a dose-response relationship between physical activity and risk of adenocarcinoma of the esophagus. **PAGAC Grade: Limited.**

Available evidence is insufficient to determine whether the effects of physical activity on esophageal cancer risk differ by age, sex, race/ethnicity, weight status, socioeconomic status, or in individuals at elevated risk of esophageal cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

Based on data from 2010-2014, the incidence rate of esophageal cancer in the United States was 4.2 per 100,000 men and women per year, and deaths from this cancer were 4.1 per 100,000.[36] Esophageal cancer is classified into two main types: adenocarcinoma, which occurs in the lower part of the esophagus, and squamous cell carcinoma, which develops in the upper part. Risk factors for esophageal adenocarcinoma include obesity, Barrett's esophagus, smoking, and gastro-esophageal reflux disease.[37] Risk factors for squamous cell carcinoma of the esophagus include smoking, alcohol use, and exposure to some forms of human papilloma virus.[38]

The Subcommittee reviewed evidence of associations between physical activity and esophageal cancer risk. Three meta-analyses were reviewed,[39-41] and one pooled analysis of six cohort studies.[9] Because the biology and etiology of the two types of esophageal cancers differ considerably, the Subcommittee focused on results that were separate for these types rather than for all esophageal cancer combined.

Two dozen epidemiologic studies on the association between physical activity and risk of developing esophageal cancer have been published. Some meta-analyses limited the evidence to studies with incidence outcomes only,[40] while others included studies with either incidence or mortality as the disease indicator.[39]

Evidence on the Overall Relationship

In the most comprehensive meta-analysis of physical activity and esophageal cancer risk,[39] 24 individual studies were available for the meta-analysis, of which 9 were cohort and 15 were case-control studies. This meta-analysis found that 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 (RR=0.94; 95% CI: 0.41-2.16). Other meta-analyses found similar effect sizes showing inverse associations between highest versus lowest levels of physical activity and risk of developing adenocarcinoma of the esophagus, but not squamous cell esophageal cancer.[40, 41] When all types of esophageal cancer were combined, adjustment for smoking, adiposity, and alcohol intake did not substantially alter effect sizes. Similar trends were seen in the pooled analysis (adenocarcinoma HR=0.58, 95% CI: 0.37-0.89; squamous cell esophageal cancer HR=0.80, 95% CI: 0.61-1.06).[9]

Dose-response: One meta-analysis performed dose-response analyses for all esophageal cancers combined from five studies.[41] The meta-analysis reported that the middle and highest tertiles or quartiles of physical activity were associated with reductions of 12 percent (RR=0.88 95% CI: 0.7-1.1) and 24 percent (RR-0.76; 95% CI: 0.60-0.97), respectively.[41] However, given that these analyses were only for combined adenocarcinoma and squamous cell carcinoma, the dose-response relationship cannot be accurately defined. The pooled analysis estimated dose-response using within-study percentile; with increasing percentile of physical activity, incidence of esophageal adenocarcinoma was statistically significantly and linearly decreased ($P<0.0001$).[9] Because the percentiles were not defined for dose, the dose-response relationship cannot be accurately determined.

Evidence on Specific Factors

Age: None of the analyses reported effects of physical activity by specific age groups.

Sex: Analysis by sex was performed for all esophageal cancers combined in all reviewed meta-analyses; risk reduction was higher for women than men, but data were not presented for adenocarcinoma of the esophagus.[39-41] However, given that these analyses were only for adenocarcinoma and squamous cell carcinoma combined, the relationship within sex cannot be accurately defined. In the pooled analysis, similar effects of physical activity on reduced risk for adenocarcinoma of the esophagus were seen for both men and women ($P_{\text{effect modification}}$=0.75). Given the discrepancies between the meta-analysis and the pooled analysis, the Subcommittee could not determine whether physical activity reduces risk for esophageal cancer in both sexes.

Race/ethnicity: Studies included primarily Caucasian and Asian populations, with little difference observed between the two populations for combined adenocarcinoma and squamous cell carcinoma of the esophagus. No analyses were available for adenocarcinoma by race/ethnicity.

Socioeconomic status: None of the analyses presented data on the effect of socioeconomic status on the association between physical activity and esophageal cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: The pooled analysis[9] examined the effect of highest versus lowest level of physical activity on esophageal adenocarcinoma in individuals with BMI <25 kg/m^2 versus ≥25 kg/m^2. The analysis found similar effect sizes in the two groups, although the statistically significant effect was limited to those in the overweight/obese group ($P_{\text{effect modification}}$=0.60). BMI did not change the effect of physical activity on squamous cell carcinoma of the esophagus ($P_{\text{effect modification}}$ =0.60). Because no information was available from a meta-analysis, the Subcommittee could not conclude that weight status was unrelated to physical activity effect.

Individuals at high risk: No information was provided in the analyses about effects of physical activity in individuals at elevated risk of esophageal cancer.

Cancer subtype: In the most comprehensive meta-analysis of physical activity and esophageal cancer risk,[39] 24 individual studies were available for the meta-analysis, of which 9 were cohort and 15 were case-control studies. This meta-analysis found that 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 for squamous cell carcinoma of the esophagus (RR=0.94; 95% CI 0.41-2.16).

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Gastric Cancer

Conclusion Statements

Strong evidence demonstrates that greater amounts of physical activity are associated with a lower risk of developing gastric cancer. **PAGAC Grade: Strong.**

Moderate evidence indicates that as levels of physical activity increase, risk of gastric cancer decreases. **PAGAC Grade: Moderate.**

Insufficient evidence is available on whether the effects of physical activity on gastric cancer risk vary by sex, age, race/ethnicity, socioeconomic groups, or weight status. **PAGAC Grade: Not assignable.**

Moderate evidence indicates that as levels of physical activity increase, the risk of both subtypes of gastric cancer—cardia and non-cardia adenocarcinoma—decreases. **PAGAC Grade: Moderate.**

Insufficient evidence is available to determine whether the effects of physical activity on gastric cancer risk differ in individuals at elevated risk of gastric cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

In the United States, the incidence rate of gastric cancer is 7.3 per 100,000 men and women per year, based on data from 2010 to 2014.[42] The major risk factor for this cancer is infection with Helicobacter pylori. Other risk factors include smoking, genetics, some industrial chemicals, and regular intake of highly salted foods. Gastric cancer is classified into two main subtypes: cardia adenocarcinoma and noncardia adenocarcinoma. Biologically, cardia gastric cancer is similar to the adjacent esophageal adenocarcinoma.

Evidence on the Overall Relationship

The Subcommittee reviewed five meta-analyses on the associations between physical activity and gastric cancer[39, 40, 43-45] and one pooled analysis of seven cohort studies.[9] Because the biology and etiology of the two subtypes of gastric cancers may differ, results that were separate for these subtypes, as well as all gastric cancer combined, were reviewed.

Considerable evidence indicates that physical activity is associated with a reduced risk of gastric cancer. Some meta-analyses limited studies to those with incidence outcomes only,[40, 44] while one included studies with either incidence or mortality as the outcome.[39] This latter found no difference in effect size when studies with fatal cases as endpoints were removed.

In the most comprehensive meta-analysis of physical activity and incident gastric cancer risk,[44] 22 individual studies were available for the meta-analysis, of which 10 were cohort and 12 were case-control studies. This meta-analysis found that 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). Similar results were found in the other meta-analyses and the pooled analysis.[9, 39, 40, 43, 45] Adjustment for smoking, adiposity, and alcohol intake did not substantially alter effect sizes.

Dose-response: One meta-analysis estimated dose-response analyses for all gastric cancers combined.[45] Compared with the least active individuals, those in the middle activity tertile had an adjusted odds ratio of 0.91 (95% CI: 0.82-1.02), and those in the highest tertile had an adjusted odds ratio of 0.78 (95% CI: 0.68-0.90) ($P_{\text{difference between groups}} = 0.08$).[45] The pooled analysis estimated dose-response using within-study percentile.[9] With increasing percentile of physical activity, incidence of gastric cardia cancer was statistically significantly, but non-linearly, decreased ($P_{\text{overall}} = 0.02$, $P_{\text{non-linear}} = 0.0037$). With increasing percentile of physical activity, incidence of gastric noncardia cancer was statistically significantly decreased ($P_{\text{overall}} = 0.015$, $P_{\text{non-linear}} = 0.58$).

Evidence on Specific Factors

Age: None of the analyses reported the effects of physical activity on gastric cancer by age group.

Sex: Analysis by sex was performed for all gastric cancers combined. Risk reduction was statistically significant in men (RR=0.87; 95% CI: 0.77-0.99), but not women (RR=0.77; 95% CI: 0.53-1.12).[44]

Race/ethnicity: Studies included primarily Caucasian and Asian populations, with little difference between the two. In one meta-analysis,[44] 3 of 10 cohort studies and 6 of 12 case-control studies were of Asian populations. The relative risk of high versus low physical activity on all gastric cancer combined was 0.82 (95% CI: 0.74-0.90).

Socioeconomic status: None of the analyses presented data on the effect of socioeconomic status on the association between physical activity and gastric cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: The pooled analysis examined the effect of 90th versus 10th percentile of level of physical activity on gastric cancer in individuals with BMI <25 kg/m^2 versus ≥25 kg/m^2.[9] The study found that high physical activity level was associated with decreased gastric cardia cancer in individuals with BMI ≥25 kg/m^2, but not in those with BMI <25 kg/m^2 (*P* for effect modification: 0.02). In contrast, physical activity was not statistically significantly associated with risk for gastric noncardia cancer in either BMI category.

Cancer subtype: The analyses estimated overall associations by cancer subtype (gastric cardia versus noncardia). In the largest meta-analysis, high physical activity levels were associated with noncardia (RR=0.62; 95% CI: 0.52-0.75), but not gastric cardia cancer (RR=0.80; 95% CI: 0.64-1.01).[44] In contrast, pooled analysis found a significant association between 90th versus 10th percentile of level of physical activity and risk of gastric cardia cancer (HR=0.80; 95% CI: 0.64-0.95), but no significant association with gastric noncardia cancer.[9]

Individuals at high risk: No information was provided in the analyses about effects of physical activity in individuals at elevated risk of gastric cancer.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Renal Cancer

Conclusion Statements

Strong evidence demonstrates that greater amounts of physical activity are associated with reduced risk of developing renal cancer. **PAGAC Grade: Strong.**

Limited evidence suggests that a dose-response relationship exists between increasing physical activity levels and decreasing risk of renal cancer. **PAGAC Grade: Limited.**

Limited evidence suggests that the effects of physical activity on renal cancer risk are similar for men and women. **PAGAC Grade: Limited.** Limited evidence suggests that the effects of physical activity on renal cancer risk do not vary by weight status. **PAGAC Grade: Limited.** Insufficient evidence is available to determine whether the effects of physical activity on risk of renal cancer differ by specific age, race/ethnic, or socioeconomic groups. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the effects of physical activity are similar for all subtypes of renal cancer. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the effects of physical activity on renal cancer risk differ in individuals at elevated risk of renal cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

Based on data from 2010 to 2014, the incidence rate of renal cancer was 15.6 per 100,000 men and women per year. The number of deaths was 3.9 per 100,000 men and women per year.[46] Several factors increase risk of renal cancer, including smoking, obesity, exposure to certain occupational toxins, hypertension, and history of some rare medical conditions.[47] Renal cancer is more common in men than in women and in individuals with a personal or family history of cancer of the urinary tract.

To examine the association between physical activity and risk of renal cancer, the Subcommittee reviewed one published meta-analysis.[48] The meta-analysis contained data from 11 cohort and 8 case-control studies. The Subcommittee also reviewed 1 pooled analysis of 11 large prospective cohort studies[9] and meta-analysis data from the World Cancer Research Fund, which included data from 12 cohort studies.[49]

Evidence on the Overall Relationship

A considerable body of epidemiologic data exists on the association between physical activity and risk of developing renal cancer. The meta-analysis (19 cohort studies, of which 2 used renal cancer mortality as the endpoint) 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).[48] Most studies adjusted for multiple potential confounding factors, including age, BMI, and renal cancer risk factors. When the analysis was limited to the 17 cohort studies that did not use renal cancer mortality as the endpoint, risk estimates were similar (RR=0.88; 95% CI: 0.80-0.98). Similar to these findings, the pooled analysis of 11 cohort studies found a statistically significant relationship between the 90th versus 10th percentile level for leisure time physical activity and decreased risk of renal cancer (RR=0.77; 95% CI: 0.70-0.85).[9] The World Cancer Research Fund meta-analysis found similar results for highest versus lowest: 1) total physical activity (RR=0.89; 95% CI: 0.72-1.10); 2) occupational physical activity (RR=0.96; 95% CI: 0.76-1.23); and 3) recreational physical activity (RR=0.84; 95% CI: 0.70-1.01).[49]

Dose-response: The meta-analysis did not examine the dose-response relationship of physical activity with renal cancer risk. The pooled analysis of 11 cohort studies found a significant linear relationship between increasing leisure time physical activity percentile and decreasing risk of renal cancer ($P_{overall}$<0.0001; $P_{non\text{-}linear}$=0.624).[9]

Evidence on Specific Factors

Sex: The meta-analysis found some differences in the effects of physical activity on renal cancer risk between men (RR=0.91; 95% CI: 0.81-1.03) and women (RR=0.85; 95% CI: 0.57-1.29).[48] In that meta-analysis, studies that presented data for men and women combined had a combined relative risk of 0.85 (95% CI: 0.73-0.98). The pooled analysis found that the effect size of physical activity on risk for renal cancer was similar, and statistically significant, in both men and women.[9]

Age: None of the analyses provided data within specific age groups.

Race/ethnicity: All but three studies in the meta-analysis were conducted in the United States and Europe; a meta-analysis of the three studies in Asia showed no association of physical activity with renal cancer risk (RR=1.00; 95% CI: 0.83-1.20).[48]

Socioeconomic status: None of the analyses presented data on the effect of socioeconomic status on the association between physical activity and renal cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: The pooled analysis examined associations between the 90th percentile versus 10th percentile of physical activity level by BMI. Risk of renal cancer associated with physical activity level did not differ for those with BMI <25.0 kg/m^2 versus BMI $\geq$25 ($P_{interaction}$ = 0.39).[9]

Cancer subtype: Neither the meta-analyses nor the pooled analysis provided data by subtype of renal cancer.

Individuals at high risk: No information was provided in the meta-analyses or pooled analysis about effects of physical activity in individuals at elevated risk of renal cancer.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Cancers for Which Physical Activity Shows Moderate Evidence of a Protective Effect

Lung Cancer

Conclusion Statements

Moderate evidence indicates that greater amounts of physical activity are associated with a lower risk of lung cancer. **PAGAC Grade: Moderate.**

Limited evidence suggests that a dose-response relationship exists between greater amounts of physical activity and lower lung cancer risk. **PAGAC Grade: Limited.**

Limited evidence suggests that the relationship between amount of physical activity and risk of lung cancer does not vary by age. **PAGAC Grade: Limited.** Limited evidence suggests that greater amounts of physical activity are associated with a greater risk reduction in females than in males. **PAGAC Grade: Limited.** Limited evidence suggests that greater amounts of physical activity are associated with a greater risk reduction in those with a body mass index of less than 25 kg/m^2 than in those with higher body mass index. **PAGAC Grade: Limited.** Insufficient evidence is available to determine whether this relationship varies by race/ethnicity or socioeconomic status because these factors have yet to be examined in the studies conducted to date. **PAGAC Grade: Not assignable.**

Limited evidence suggests that specific histologic types of lung cancers do not modify the relationships between amounts of physical activity and risk of lung cancer incidence. **PAGAC Grade: Limited.**

Moderate evidence indicates that greater amounts of physical activity are associated with a greater risk reduction in current and former smokers than in never smokers. **PAGAC Grade: Moderate.**

Review of the Evidence

Between 2010 and 2014, the incidence rate of lung and bronchus cancer was 55.8 per 100,000 men and women per year. The number of deaths was 44.7 per 100,000 men and women per year.[50] Lung cancer is the number one cause of cancer mortality in the U.S. The main risk factor for lung cancer is both active and passive tobacco use. Other risk factors include occupational exposures (including arsenic, radon, chloromethyl ethers, chromium, nickel, polycyclic aromatic hydrocarbons), outdoor air pollution (i.e., particulate matter) and dietary intake (i.e., low fruit and vegetable intake).

The Subcommittee used information from six meta-analyses[19, 51-55] and one pooled analysis.[9] The meta-analysis by Sun et al[51] included 14 prospective cohort studies published to May 2012 with 1,644,305 participants. The meta-analysis by Buffart et al[52] included seven prospective cohort studies published to November 2011. The meta-analysis by Schmid et al[53] included 25 studies (18 prospective cohort, 6 case-control, and 1 nested case-control) published to September 2015 that included 3,147,747 participants and 29,123 cases. The Brenner et al[55] meta-analysis included 28 studies (6 case-control and 22 cohort) published to May 2015. The Zhong et al[54] meta-analysis included 18 studies (12 cohort and 6 case-control) published to January 2014 that included 2,648,470 participants and 26,453 cases. The Liu et al[19] meta-analysis included 126 cohort studies, which included 15 studies in a lung cancer analysis and a pooled analysis[9] that included 12 cohort studies with 19,133 cases. All types of physical activity were included in two of the meta-analyses[51, 54] and leisure time/recreational physical activity was included in the four remaining meta-analyses.[19, 52, 53, 55] The pooled analysis[9] included only leisure time/recreational physical activity in their report. The dose-response relationship was tested in one of the reviews only[52] and no evidence for an association was found. The analyses in the Buffart et al[52] review were restricted to smokers only.

Evidence on the Overall Relationship

The first meta-analysis published by Sun et al[51] found risk reductions for both medium and high levels of physical activity compared to low levels with relative risks of 0.87 (95% CI: 0.83-0.90) and 0.77 (95% CI: 0.73-0.81), respectively. The meta-analysis by Buffart et al,[52] which was restricted to smokers only, reported reductions for moderate, moderate-to-vigorous, and vigorous physical activity amounts compared to low amounts that were all statistically significant decreases (moderate: RR=0.79; 95% CI: 0.70-0.90; moderate-to-vigorous physical activity: RR=0.87; 95% CI: 0.81-0.93; vigorous physical activity: RR=0.74; 95% CI: 0.67-0.82). Brenner et al[55] reported a 25 percent reduction in lung cancer risk when comparing the highest versus lowest amounts of physical activity in all studies combined (RR=0.75; 95% CI: 0.68-0.84). Schmid et al[53] similarly reported a 21 percent reduction in lung cancer risk when comparing the highest versus lowest amounts of physical activity (RR=0.79; 95% CI: 0.72-0.87). Zhong et al[54] reported reductions for both moderate amounts of physical activity (0.87; 95% CI: 0.84-0.90) and high amounts of physical activity (RR=0.75; 95% CI: 0.68-0.84). Liu et al[19] reported an analysis for overall lung cancer that compared the highest to the lowest amounts of leisure time physical activity that was a null association (RR=0.99; 95% CI: 0.97-1.01). Moore et al[9] compared the 90th percentile to the 10th percentile of physical activity and found a statistically significant risk reduction of about 26 percent (HR=0.74; 95% CI: 0.71-0.77).

Dose-response: The dose-response relationship was not examined in any of the studies with the exception of the Moore et al[9] pooled analysis that provided dose-response curves for the association between physical activity and lung cancer incidence. There was a statistically significant linear trend (P_{trend}<0.0001) between greater amounts of physical activity and lower lung cancer risk.

Evidence on Specific Factors

Age: Brenner et al[55] examined sub-group effects by age and found no statistically significant differences by age subgroups.

Sex: Buffart et al[52] examined the association by sex (this study examined smokers only) and found a stronger protective effect of higher levels of physical activity among women than among men (RR=0.68; 95% CI: 0.57-0.82 and RR=0.85; 95% CI: 0.77-0.93, respectively).

Race/ethnicity: No conclusions can be made regarding the role of race or ethnicity in the association between physical activity and lung cancers. None of the meta-analyses reported on these population subgroups, preventing any systematic conclusions related to these factors. The Moore et al[9] pooled analysis, however, found similar associations between highest versus lowest physical activity level and lung cancer risk in Black and White individuals ($P_{heterogeneity}$=0.90) (Figure F4-1).[9]

Socioeconomic status: None of the analyses presented data on the effect of socioeconomic status on the association between physical activity and lung cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: A statistically significant effect modification by BMI was found in the Moore et al[9] pooled analysis, with stronger reductions for participants with BMI <25 kg/m^2 than for those ≥25 kg/m^2.

Cancer subtype: Schmid et al[53] examined the effects by different histologic type and no statistically significant differences by cancer subtype were found.

Other factors: Clear effect modification by smoking status was found by Moore et al,[9] with strong reductions for the association between physical activity and lung cancer observed for current and former smokers but not for never smokers ($P_{effect\ modification}$<0.001). Zhong et al[54] found similar magnitude risk reductions for former, current, and never smokers. These risk reductions ranged between 24 to 26 percent and were statistically significant. Schmid et al[53] also reported effect modification by smoking status, with substantial risk reductions for the association between physical activity and lung cancer for former smokers (RR=0.68; 95% CI: 0.51-0.90), current smokers (RR=0.80; 95% CI: 0.70-0.90) but not for never smokers (RR=1.05; 95% CI: 0.78-1.40). Likewise, Brenner et al[55] reported no association between physical activity and lung cancer for never smokers (RR=0.96; 95% CI: 0.79-1.18) whereas former smokers had a risk reduction between higher amounts of physical activity and lung cancer (RR=0.77; 95% CI: 0.69-0.85) as did current smokers (RR=0.77; 95% 0.72-0.83).

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Cancers for Which Physical Activity Shows Limited Evidence for a Protective Effect

Hematologic Cancers

Conclusion Statements

Limited evidence suggests a null relationship between physical activity and leukemia incidence. Limited evidence suggests that physical activity has a protective effect on lymphoma and myeloma such that greater amounts of physical activity reduce the risk of lymphoma and myeloma. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether a dose-response relationship exists between greater amounts of physical activity and reduced risk of hematologic cancers. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether sex modifies the relationship between physical activity and Hodgkin lymphoma, with a risk reduction observed with physical activity for females only. **PAGAC Grade: Not assignable.** Insufficient evidence is available to determine whether body mass index, smoking, or alcohol affect the relationship between physical activity and risk of developing other hematologic cancers, or whether this relationship varies by sex, age, race/ethnicity, or socioeconomic status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between physical activity varies by specific types of hematologic cancers. **PAGAC Grade: Not assignable**.

Insufficient evidence is available to determine whether the effects of physical activity on hematologic cancers differ in individuals at elevated risk of hematologic cancers. **PAGAC Grade: Not assignable**.

Review of the Evidence

Hematologic cancers, which include cancers that originate in the blood cells, have three main types: 1) leukemia (cancer of the blood and bone marrow, including chronic myeloid leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, acute lymphocytic leukemia, and other subtypes); 2) lymphoma (cancer of the lymphatic system with Hodgkin lymphoma and non-Hodgkin lymphoma as the two main types); and 3) myeloma (cancer of the plasma cells). Between 2010 and 2014, the incidence rate of leukemia was 13.7 per 100,000 men and women per year. The number of deaths was 6.8 per 100,000 men and women per year.[56] For non-Hodgkin lymphoma, the incidence rate for this same time period was 19.5 per 100,000 men and women per year. The number of deaths was 5.9 per 100,000 men and women per year.[57] For Hodgkin lymphoma, the incidence rate was 2.6 per 100,000 men and women per year. The number of deaths was 0.3 per 100,000 men and women per year.[58] For myeloma, the incidence rate was 6.6 per 100,000 men and women per year. The number of deaths was 3.3 per 100,000 men and women per year.[59]

The main known risk factors for leukemia are: radiation, chemical exposures (e.g., benzene), chemotherapy, Down syndrome, and having a family history of leukemia. The main risk factors for lymphoma are: age older than 50 years, male sex, Caucasian race, having an autoimmune disease, HIV/AIDS, high fat and meat diet, and pesticide exposure. For myeloma, the main risk factors are: African American race, age older than 50 years, male sex, obesity, and exposure to radiation and the petroleum industry.

The Subcommittee used information from three meta-analyses[19, 60, 61] and two pooled analyses.[9, 62] The meta-analysis by Jochem et al[60] included 23 studies (15 cohort and 8 case-control studies) conducted up to 2013 with 19,334 hematologic cancers. The meta-analysis by Vermaete et al[61] included 12 studies (7 case-control and 5 cohort studies) also published by 2013 with 9,511 lymphomas. The third meta-analysis, by Liu et al,[19] included 126 cohort studies conducted to the end of 2014 that included 8 studies used in the lymphoid neoplasm analysis (number of cases not specified). The pooled analysis by Aschebrook-Kilfoy et al[62] was based on the InterLymph Non-Hodgkin Lymphoma Subtypes Project, which included 14 case-control studies published by the end of 2011, included 324 cases of Mycosis fungoides and Sézary syndrome (rare cutaneous T-cell lymphomas). The Moore et al[9] pooled analysis included 12 U.S. and European cohort studies of which 10 cohorts reported on myeloid leukemia with 1,692 cases, 9 cohorts on myeloma with 2,161 cases, 11 cohorts for non-Hodgkin lymphoma with 6,953 cases, and 10 cohorts for lymphocytic leukemia with 2,160 cases. All types of physical activity were included in two of the meta-analyses[60, 61] and leisure-type physical activity was included in the third meta-analysis.[19] The first pooled analysis[62] included all types of physical activity combined, and the second pooled analysis[9] included only recreational and leisure time physical activity in their report.

Evidence on the Overall Relationship

None of the analyses that were identified combined all types of hematologic cancers to provide an overall estimate of the association with physical activity. Rather, separate estimates were provided in each review given the different etiologies of these cancers.

A null association between physical activity and leukemia was reported in two analyses (RR=0.97; 95% CI: 0.84-1.13[60]; HR=0.98; 95% CI: 0.87-1.11[9]), with the latter study reporting on lymphocytic leukemia.

For non-Hodgkin lymphoma, a non-statistically significant risk reduction of about 8 to 9 percent was found in 3 of the reviews that considered this hematologic cancer when comparing the highest versus the lowest levels of physical activity (RR=0.91; 95% CI: 0.82-1.00[60]; 0.92; 95% CI: 0.81-1.04[61]; HR=0.91; 95% CI: 0.83-1.00[9]).

For Hodgkin lymphoma, a non-statistically significant risk reduction of about 16 to 18 percent was reported in 2 reviews that included this hematologic cancer (RR=0.86; 95% CI: 0.58-1.26[60]; OR=0.82; 95% CI: 0.47-1.42[61]).

Two studies reported on all types of lymphoma combined in association with physical activity and reported a 10 percent reduction in all types of lymphoma with greater amounts of physical activity (pooled RR=0.90; 95% CI: 0.81-0.99[60] and pooled OR=0.90; 95% CI: 0.79-1.02[61]). Another meta-analysis reported on lymphoid neoplasms combined and reported a null association between greater amounts of physical activity and lymphoid neoplasms (RR=0.97; 95% CI: 0.86-1.10).[19]

Two studies reported separate results for multiple myeloma/myeloma, with risk reductions ranging from 14 to 17 percent (RR=0.86; 95% CI: 0.68-1.09[60]; HR=0.83; 95% CI: 0.72-0.95[9]) when comparing the highest to lowest levels of physical activity in these studies.

Other rare types of hematologic cancers also were reported separately in the meta-analysis by Jochem et al[60] and no associations between physical activity and risk of follicular lymphoma and large B-cell lymphoma (RR=0.98; 95% CI: 0.85-1.11) and chronic lymphocytic lymphoma/small lymphocytic lymphoma (RR=0.99; 95% CI: 0.75-1.29) were observed. Finally, the InterLymph NHL subtypes project reported on the associations between moderate and vigorous physical activity and mycosis fungoides and Sezary syndrome as well. For moderate physical activity, the fully adjusted odds ratio was 0.46 (95% CI: 0.22-0.97) and for vigorous physical activity, the odds ratio was 0.58 (95% CI: 0.32-1.08).[62]

Dose-response: Moore et al[9] observed a statistically significant trend between increasing percentiles of physical activity and decreasing risk of myeloid leukemia (P_{trend}=0.0035), myeloma (P_{trend}=0.007) and non-Hodgkin lymphoma (P_{trend}=0.007). Two other analyses that also examined the dose-response trends did not find any evidence of an association between increasing physical activity levels and all hematologic cancers combined[60] or for mycosis fungoides and Sezary syndrome.[62]

Evidence on Specific Factors

Age: None of the analyses reported on the effects of physical activity for different age groups for any specific hematologic cancers.

Sex: Only one meta-analysis examined effect modification by sex[60] and no statistically significant effect modification was observed. Different risk estimates were found, however, for Hodgkin lymphoma for which a statistically significant risk reduction was observed for women but not for men (RR=0.56; 95% CI: 0.37-0.86 and RR=1.04; 95% CI: 0.58-1.87), respectively.

Race/ethnicity: No conclusions can be made regarding the role of race or ethnicity in the association between physical activity and hematologic cancers. None of these analyses reported on these population subgroups, preventing any systematic conclusions related to these factors.

Socioeconomic status: None of the analyses presented data on the effect of socioeconomic status on the association between physical activity and hematologic cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: No effect modification by BMI was found in the Moore et al[9] pooled analysis or adiposity in the Jochem et al[60] meta-analysis.

Cancer subtype: As described above, hematologic cancers are comprised of several different cancer sites and the results are described above. No studies to date have provided results on specific subtypes within each of these hematologic cancers.

Other factors: No effect modification by alcohol or smoking status was found for any of the hematologic cancers in the meta-analysis by Jochem et al.[60] Moore et al[9] reported an effect modification by smoking status for myeloma but none for the other hematologic cancers.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Head and Neck Cancers

Conclusion Statements

Limited evidence suggests that greater amounts of physical activity are associated with a lower risk of head and neck cancer incidence. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether a dose-response relationship exists between physical activity and head and neck cancer incidence. **PAGAC Grade: Not assignable.**

Limited evidence suggests that the relationship between physical activity and head and neck cancer incidence does not vary by age, sex, BMI, or smoking. **PAGAC Grade: Limited.** Insufficient evidence is available to determine whether this relationship varies by race/ethnicity or socioeconomic status because these factors have yet to be examined in the studies conducted to date. **PAGAC Grade: Not assignable.**

Limited evidence suggests that this relationship varies by specific types of head and neck cancers. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether the effects of physical activity on head and neck cancers differ in individuals at elevated risk of head and neck cancers. **PAGAC Grade: Not assignable.**

Review of the Evidence

In 2014, an estimated 346,902 people were living with head and neck cancers in the United States.[63] These cancers include cancers that originate in the oral cavity, pharynx, larynx, paranasal sinuses and nasal cavity, and salivary glands. The main known risk factors for head and neck cancers are tobacco and alcohol use and infection with human papillomavirus.[64]

The Subcommittee used information from two pooled analyses.[9, 65] The pooled analysis by Nicolotti et al[65] combined 4 case-control studies from the International Head and Neck Consortium (INHANCE) that included 2,289 cases and 5,580 controls, and the Moore et al[9] pooled analysis included 12 U.S. and European cohort studies; of these, 11 cohorts reported on head and neck cancers with 3,985 cases. Both of these pooled analyses included only recreational and leisure time physical activity in their reports.

Evidence on the Overall Relationship

The INHANCE pooled analysis observed a risk reduction for all head and neck cancers combined for both moderate recreational physical activity (OR=0.78; 95% CI: 0.66-0.91) and high recreational physical activity (OR=0.72; 95% CI: 0.46-1.16). The pooled analysis by Moore et al[9] reported a risk reduction for all head and neck cancers when comparing the 90th to 10th percentile of study participants' physical activity levels (HR=0.85; 95% CI: 0.78-0.93).

Dose-response: No dose-response analyses were conducted in either of these pooled analyses.

Evidence on Specific Factors

Age: The INHANCE pooled analysis[65] examined results stratified by age and reported a decreased risk for study participants ages 45 years or older (OR=0.66; 95% CI: 0.48-0.91) but not for participants younger than age 45 years (OR=0.76; 95% CI: 0.17-3.52). No stratification on age was reported in the Moore et al[9] pooled analysis.

Sex: No effect modification by sex was observed in the INHANCE consortium analysis. For all head and neck cancers combined, the risk reductions for both females (OR=0.64; 95% CI: 0.27-1.54) and males (OR=0.75; 95% CI: 0.38-1.46) were similar in magnitude and non-statistically significant. No consideration of effect modification by sex was made in the pooled analysis by Moore et al.[9]

Race/ethnicity: No conclusions can be made regarding whether or not the inverse relationship between physical activity and head and neck cancer varies by race or ethnicity. The studies did not report on these population subgroups, preventing any systematic conclusions related to these factors.

Socioeconomic status: Neither pooled analysis presented data on the effect of socioeconomic status on the association between physical activity and head and neck cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: No effect modification by BMI was found in the Moore et al[9] pooled analysis.

Cancer subtype: Only the INHANCE consortium[65] considered specific subtypes of head and neck cancer and reported risk reductions for oral cavity and pharyngeal cancers but not for laryngeal cancers. For oral cavity cancers, moderate amounts of physical activity (OR=0.74; 95% CI: 0.56-0.97) and high amounts of physical activity (OR=0.53; 95% CI: 0.32-0.88) were both associated with around a 25 percent and nearly 50 percent risk reductions, respectively, compared to the least active study participants. For pharyngeal cancers, both moderate and high amounts of physical activity were also associated with risk reductions of about 30 percent to 40 percent (OR=0.67; 95% CI: 0.53-0.85) and OR=0.58; 95% CI: 0.38-0.89). The associations for laryngeal cancer and physical activity were inconsistent with other head and neck cancers. For moderate amounts of physical activity, a non-statistically significant reduction was observed, and for high amounts of physical activity, an increased risk was reported (OR=0.81; 95% CI: 0.60-1.11) and OR=1.73; 95% CI: 1.04-2.88), respectively. The Moore et al[9] pooled analysis did not report on specific types of head and neck cancers separately.

Other factors: No effect modification by smoking status was found in either pooled analysis and no evidence exists regarding the relationship among individuals at high risk of head and neck cancers.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Ovarian Cancer

Conclusion Statements

Limited evidence suggests a weak relationship between greater levels of physical activity and lower risk of ovarian cancer. **PAGAC Grade: Limited.**

Limited evidence suggests that no dose-response relationship exists between greater amounts of physical activity and lower ovarian cancer risk. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether the relationship between physical activity and ovarian cancer is modified by age, race/ethnicity, socioeconomic status, or weight status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between physical activity and ovarian cancer is modified by specific histologic types of ovarian cancers. **PAGAC Grade: Not assignable**

Insufficient evidence is available to determine whether the effects of physical activity on ovarian cancer risk differ in individuals at elevated risk of ovarian cancer. **PAGAC Grade: Not assignable**

Review of the Evidence

Based on data from 2010 to 2014, the incidence rate of ovarian cancer was 11.7 per 100,000 women per year. The number of deaths was 7.4 per 100,000 women per year.[66] The risk factors for ovarian cancer include obesity; nulliparity; first degree family history of ovarian, breast or colorectal cancer; family cancer syndromes (e.g., hereditary breast and ovarian cancer syndrome, hereditary nonpolyposis colon cancer); personal history of breast cancer; and estrogen-only therapy after menopause. Ovarian cancer risk is decreased with oral contraceptive use of at least 3 to 6 months and some forms of injectable hormonal contraceptive.[67]

The Subcommittee used information from two meta-analyses[19, 68] and two pooled analyses.[9, 69] The meta-analysis by Zhong et al[68] included 19 studies (9 prospective cohort and 10 case-control studies) published between 1984 and June 2014. The meta-analysis by Liu et al[19] included 126 cohort studies, which included 9 studies in an ovarian cancer analysis. The pooled analysis from the Ovarian Cancer Association Consortium (OCAC) by Cannioto et al[69] included 9 case-control studies published to September 2016 with 8,309 cases and 12,612 controls. The pooled analysis[9] included 9 cohort studies with 2,880 ovarian cancer cases. Recreational physical activity was included in one meta-analysis[19] and in both the pooled analyses,[9, 69] and non-occupational physical activity was included in the meta-analysis by Zhong et al.[68] The dose-response relationship was tested in two of the meta-analyses[19, 68] and in the pooled analysis.[9]

Evidence on the Overall Relationship

The pooled-analysis published by Cannioto et al[69] found chronic physical inactivity compared to some physical activity was associated with an increased risk of ovarian cancer (OR=1.34; 95% CI: 1.14-1.57). The meta-analysis by Zhong et al[68] reported that any non-occupational physical activity versus none was associated with a borderline statistically significant reduction in ovarian cancer incidence (RR=0.92; 95% CI: 0.84-1.00). These authors also presented the results for moderate and high amounts of non-occupational physical activity compared to low amounts and found similar risk reductions (OR=0.91; 95% CI: 0.85-0.99 and OR=0.89; 95% CI: 0.79-1.01, respectively). Liu et al[19] reported a null association for overall ovarian cancer when they compared participants with the highest to the lowest amounts of leisure time physical activity (RR=0.96; 95% CI: 0.74-1.26). Moore et al[9] compared participants in the 90^{th}

percentile to those in the 10^{th} percentile of physical activity and found no association with ovarian cancer incidence (HR=1.01; 95% CI: 0.91-1.13).

Dose-response: Zhong et al[68] observed a non-statistically significant relationship between increasing amounts of non-occupational physical activity and decreasing ovarian cancer risk. In addition, Zhong et al[68] reported that a 2 MET-hours per week or 2 hours per week increment in non-occupational activity conferred a relative risk of ovarian cancer risk of 0.98 (95% CI: 0.96-1.01) and 0.97 (95% CI: 0.94-1.01), respectively. Liu et al[19] estimated the hazard ratios across categories of leisure time physical activity, from 0 to 80 MET-hours per week in increments of between 10 and 20 MET-hours per week. They found no evidence for a linear dose-response trend (P_{trend}=0.28). Moore et al[9] also found no evidence for a linear dose-response trend (P_{trend}=0.77).

Evidence on Specific Factors

Age: None of the analyses presented their results stratified by different age groups. As a result, no conclusions about the role of age on the association between physical activity and ovarian cancer can be made.

Race/ethnicity: No effect modification by race on the association between recreational physical activity and ovarian cancer incidence was observed in the pooled analysis by Cannioto et al.[69] No other analyses considered the effect of race/ethnicity on this association.

Socioeconomic status: None of the analyses presented data on the effect of socioeconomic status on the association between physical activity and ovarian cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: A statistically significant effect modification by BMI was found by Cannioto et al,[69] with a greater increased risk associated with physical inactivity in women with a BMI <25 kg/m^2 (OR=1.33; 95% CI: 1.19-1.49) than in women with a BMI ≥25 kg/m^2 (OR=1.21; 95% CI: 1.09-1.34). In the Moore et al[9] pooled analysis, no effect modification by BMI was observed for the association between leisure time physical activity and ovarian cancer incidence.

Cancer subtype: Zhong et al[54] examined the effects by different ovarian cancer subtype (borderline and invasive tumors) and no statistically significant differences by cancer subtype were found. No other analyses considered the association with physical activity for different ovarian cancer subtypes.

Other factors: No effect modification by menopausal status was observed in the pooled analysis by Cannioto et al.[69] No other analyses considered menopausal status or any other factors as potential effect modifiers of the association between physical activity and ovarian cancer incidence.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Pancreatic Cancer

Conclusion Statements

Limited evidence suggests that greater amounts of physical activity are associated with a lower risk of developing pancreatic cancer. **PAGAC Grade: Limited.**

Limited evidence suggests that a dose-response association does not exist between physical activity and pancreatic cancer. **PAGAC Grade: Limited.**

Limited evidence suggests that the effects of physical activity on pancreatic cancer risk do not vary by sex. **PAGAC Grade: Limited.** Insufficient evidence is available to determine whether the effects of physical activity on pancreatic cancer risk vary by age, race/ethnicity, socioeconomic groups, or weight status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the effects of physical activity on pancreatic cancer risk differ by cancer subtypes. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the effects of physical activity on pancreatic cancer risk differ in individuals at elevated risk for pancreatic cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

Pancreatic cancer is the third leading cause of cancer mortality in the United States, and its incidence is rising,[70] possibly due to increasing prevalence of obesity and diabetes, two risk factors for the disease.[71, 72] Based on data from 2010 to 2014, the incidence rate of pancreatic cancer in the United States was 12.5 per 100,000 men and women per year and the number of deaths was 10.9 per 100,000 men and women per year.[73]

Evidence on the Overall Relationship

The Subcommittee reviewed five systematic reviews on the association between physical activity and risk of pancreatic cancer,[19, 74-77] of which four,[19, 75-77] included meta-analyses. The Subcommittee also reviewed one pooled analysis of 10 cohort studies.[9] In the most recent of the 4 meta-analyses of physical activity and pancreatic cancer risk,[75] 26 individual studies were available for the meta-analysis, of which three quarters represented cohort studies. Some studies included in the meta-analyses and systematic review used mortality as a proxy for incidence. Because the five-year survival rate for pancreatic cancer is only seven percent, mortality provides a reasonable estimate for incidence. The Farris et al[75] meta-analysis suggests that risk of pancreatic cancer is statistically significantly reduced for individuals engaging in highest versus lowest levels of activity (RR=0.89; 95% CI: 0.82-0.96), but the effect was stronger in case-control studies.[75] Similar results were seen in the systematic review and other meta-analyses.[19, 74, 76, 77] The pooled analysis found no association between high levels of physical activity and risk of pancreatic cancer (HR=0.93; 95% CI: 0.83-1.08).[9]

Dose-response: Dose-response relationships were assessed in three meta-analyses.[19, 75, 76] However, the analyses found no statistically significant associations between increased dose of physical activity and risk of pancreatic cancer, including assessments of duration, frequency, and energy expenditure.[19, 76] Similarly, the pooled analysis did not find evidence of a dose-response relationship between physical activity level and risk of pancreatic cancer ($P_{overall}$ = 0.08, $P_{non\text{-}linear}$ = 0.36).

Evidence on Specific Factors

Age: One meta-analysis[75] examined the association of physical activity with pancreatic cancer by age, and found that only in studies with median age younger than 50 years was physical activity associated with reduced risk (RR=0.61; 95% CI: 0.50-0.75). In comparison, the estimates for studies with median ages 50 to 60 years and older than 60 years were RR=0.93 (95% CI: 0.87-1.01) and RR=1.00 (95% CI: 0.89-1.12), respectively.

Sex: Meta-analyses found similar effects of physical activity on pancreatic cancer risk in males and females, although neither subgroup analysis was statistically significant. In contrast, those studies that combined sexes showed significant effects (RR=0.79; 95% CI: 0.68-0.91).[75]

Race/ethnicity: Studies included primarily Caucasian individuals. One meta-analysis reported results by geographic area of included studies (United States, Canada, Europe, Asia), and found that effect size was similar across areas but was of marginal statistical significance within areas.[75]

Socioeconomic status: None of the analyses or the systematic review presented data on the effect of socioeconomic status on the association between physical activity and pancreatic cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: One meta-analysis reported that adjustment for adiposity somewhat attenuated the association between physical activity and pancreatic cancer risk in cohort studies.[76] In the pooled analysis, BMI status did not change the lack of association between physical activity and risk of pancreatic cancer development.[9]

Cancer subtype: None of the analyses or the systematic review reported on effects of physical activity on subtypes of pancreatic cancer (adenocarcinoma vs. neuroendocrine tumors). However, 95 percent of pancreatic cancers are adenocarcinomas.

Individuals at high risk: No information was provided in the systematic review or analyses about effects of physical activity in individuals at elevated risk of pancreatic cancer.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Prostate Cancer

Conclusion Statements

Limited evidence suggests a weak relationship between greater levels of physical activity and lower prostate cancer risk. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether a dose-response relationship exists between higher levels of physical activity and lower prostate cancer risk. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the association between physical activity and prostate cancer varies by age, race/ethnicity, weight status, socioeconomic status, or smoking status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between physical activity and prostate cancer varies by tumor sub-type, as risk reductions were observed with increased levels of physical activity in both men with aggressive versus non-aggressive prostate cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

Between 2010 and 2014, the incidence rate of prostate cancer was 119.8 per 100,000 men per year. The number of deaths was 20.1 per 100,000 men per year.[78] The main risk factors for prostate cancer are: older age, family history of prostate cancer, elevated endogenous androgen exposure, high dietary fat and dairy products intake, and possibly some occupational exposures.[79]

The Subcommittee used information from two meta-analyses[19, 80] and one pooled analysis.[9] The first meta-analysis by Liu et al[80] included 43 studies (19 prospective cohort studies and 24 case-control studies) published to May 2011 with 88,294 cases. The second meta-analysis by Liu et al[19] included 126 cohort studies; of these, 18 were included in a prostate cancer analysis. The Moore et al[9] pooled analysis included 12 cohort studies; of these, 7 were included in the prostate cancer analysis with 46,890 cases. All types of physical activity were included in the first meta-analysis by Liu et al[80] and leisure time physical activity was included in second meta-analysis by Liu et al[19] and the pooled analysis by Moore et al.[9]

Evidence on the Overall Relationship

The first meta-analysis published by Liu et al[80] found risk reductions for all types of physical activity. For total physical activity, when comparing the highest versus lowest amounts of physical activity, a 10 percent risk reduction was observed that was statistically significant (RR=0.90; 95% CI: 0.84-0.95). Occupational physical activity showed larger reductions than did total physical activity, with a relative risk of 0.81 (95% CI: 0.73-0.91), while recreational physical activity showed smaller risk reductions, with a relative risk of 0.95 (95% CI: 0.80-1.00), respectively. In the Liu et al[19] meta-analysis, when the association between the highest to the lowest amounts of leisure time physical activity was assessed as a binary analysis, the relative risk was 0.93 (95% CI: 0.85-1.01) for overall prostate cancers. Moore et al[9] compared the 90th percentile to the 10th percentile of physical activity and found a moderate risk increase of about 5 percent for higher amounts of physical activity (HR=1.05; 95% CI: 1.03-1.08).

Dose-response: Evidence for a dose-response relationship between increasing percentiles of physical activity and slightly increased prostate cancer risk was found in the Moore et al[9] pooled analysis (P_{trend}<0.0048). No other meta-analyses examined the dose-response relationship between physical activity and prostate cancer risk.

Evidence on Specific Factors

Age: Liu et al[80] examined sub-group effects by age and found stronger risk reductions for men ages 20 to 65 years versus men older than age 65 years.

Race/ethnicity: Liu et al[80] examined the associations between physical activity and population source. For total physical activity, they found stronger risk reductions for European and American populations than for Canadian and Asia-Pacific study populations. In addition, they examined race as an effect modifier and found larger risk reductions for Blacks (RR=0.74; 95% CI: 0.57-0.95) than for Whites (RR=0.86; 95% CI: 0.77-0.97). The Moore et al[9] pooled analysis found similar lack of associations between highest versus lowest physical activity level and prostate cancer risk in Black and White men ($P_{heterogeneity}$=0.35) (Figure F4-1).[9] No studies examined effect modification by socioeconomic status.

Socioeconomic status: None of the analyses presented data on the effect of socioeconomic status on the association between physical activity and prostate cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: No evidence for effect modification by BMI was found in either the meta-analysis by Liu et al[80] or the Moore et al[9] pooled analysis for participants with BMI <25 kg/m^2 compared to those with BMI ≥25 kg/m^2.

Cancer stage and subtype: Liu et al[80] examined the associations between physical activity and prostate cancer risk by cancer stage. They found no effect modification for localized versus advanced prostate cancer stage. Liu et al[19] examined the effects of physical activity within subgroups of prostate cancer defined by tumor aggressiveness. For non-aggressive prostate cancer, the relative risk was 0.98 (95% CI: 0.79-1.21) and for aggressive prostate cancer, the relative risk was 0.89 (95% CI: 0.71-1.12).

Other factors: No effect modification by smoking status was found by Moore et al.[9] Liu et al[80] considered the associations between physical activity and prostate cancer stage by history of prostate specific antigen (PSA) testing and found that men with a previous history of a test had no benefit from physical activity (RR=1.05; 95% CI: 0.92-1.20) while those with no previous PSA test did have a non-statistically significant reduction in risk of prostate cancer (RR=0.83; 95% CI: 0.63-1.11).

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Brain Cancer

Conclusion Statements

Insufficient evidence is available to determine whether a relationship between physical activity and overall brain cancer incidence exists. **PACAC Grade: Not assignable.** Limited evidence suggests that physical activity decreases the risk of certain types of brain cancer. Specifically, a reduced risk is observed for glioma and meningioma. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether a dose-response relationship exists between physical activity and brain cancer incidence. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between physical activity and brain cancer incidence varies by age, sex, race/ethnicity or socioeconomic status because these factors have yet to be examined in the studies conducted to date. **PAGAC Grade: Not assignable.** Insufficient evidence is available to determine whether the relationship between physical activity and brain cancer incidence varies by body mass index. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between physical activity and brain cancer incidence differs in individuals at high risk of brain cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

In 2014, an estimated 162,341 people were living with brain and other nervous system cancers in the United States.[81] Brain cancer has many different types and the causes of brain cancer remain unknown.

The Subcommittee used information from one meta-analysis[82] and one pooled analysis.[9] The meta-analysis included four studies of meningioma (three cohort and one case-control study) and five studies of glioma (three cohort and two case-control studies).[82] The pooled analysis by Moore et al[9] included 12 U.S. and European cohort studies; of these, 10 cohorts were included in the brain cancer analysis, with 2,110 cases. The Niedermaier et al[82] meta-analysis included 2,982 meningioma cases from 9 studies and 3,057 glioma cases from 7 studies. The type of physical activity assessed in the studies included in the meta-analysis[82] was not specified and the pooled analysis by Moore et al[9] was restricted to leisure time physical activity.

Evidence on the Overall Relationship

Some evidence of an inverse relationship between physical activity and certain types of brain cancer was found. For meningioma, a reduced risk was reported when comparing study participants with the highest versus the lowest levels of physical activity (RR=0.73; 95% CI: 0.61-0.88).[82] Similarly, a reduced risk of glioma was reported with higher levels of physical activity (RR=0.86; 95% CI: 0.76-0.97).[82] This risk reduction for brain cancer (no brain cancer sub-type specified) was not observed in the pooled analysis.[9] In that study, when comparing the 90th to 10th percentile of study participants' physical activity levels, the hazard ratio was 1.06 (95% CI: 0.93-1.20).

Dose-response: No dose-response analysis was conducted in the meta-analysis because of the heterogeneous physical activity assessments done in the studies that were assessed.[82] The pooled analysis[9] found no evidence for a dose-response relationship between increasing percentiles of physical activity and brain cancer risk.

Evidence on Specific Factors

Age: The two analyses adjusted for age but did not stratify their results by age group, therefore providing no evidence for effect modification by age.

Sex: No effect modification by sex was observed in the meta-analysis by Niedermaier et al[82] and no consideration of sex was made in the pooled analysis by Moore et al.[9]

Race/ethnicity: No conclusions can be made regarding whether or not the inverse relationship between physical activity and brain cancer varies by race or ethnicity. The studies did not report on these population subgroups, preventing any systematic conclusions related to these factors.

Socioeconomic status: None of the analyses presented data on the effect of socioeconomic status on the association between physical activity and brain cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: No effect modification by BMI was found in either of the two analyses.[9, 82]

Cancer subtype: Only the meta-analysis by Niedermaier et al[82] considered specific subtypes of brain cancer and found risk reductions for both meningioma and glioma.

Other factors: No effect modification by smoking status was found in the pooled analysis.[9] No studies considered the effect of physical activity among individuals at high risk of brain cancer.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Cancers for Which Physical Activity Shows Evidence for No Effect

Thyroid Cancer

Conclusion Statements

Moderate evidence indicates that greater amounts of physical activity are not associated with risk of developing thyroid cancer. **PAGAC Grade: Moderate.**

Insufficient evidence is available to determine whether physical activity levels and risk of thyroid cancer have a dose-response relationship. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the effects of physical activity on thyroid cancer differ by specific sex, age, race/ethnicity, or socioeconomic groups. **PAGAC Grade: Not assignable.** Insufficient evidence is available to determine whether weight status affects the association between physical activity and thyroid cancer risk. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the association of physical activity with thyroid cancer risk differs by subtype of thyroid cancer. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the association of physical activity with thyroid cancer risk differs in individuals at elevated risk of thyroid cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

The incidence and mortality of thyroid cancer are increasing in the United States.[83] Based on data from 2010 to 2014, the incidence rate of thyroid cancer was 14.2 per 100,000 men and women per year. The number of deaths was 0.5 per 100,000 men and women per year. Although the increase in incidence is in part due to increased screening, the increased mortality suggests that part of the increase in incidence is real. Risk factors for thyroid cancer include being female, radiation exposure, some hereditary conditions, low iodine intake, and obesity.[84, 85]

The Subcommittee reviewed evidence of associations between physical activity and thyroid cancer risk. One meta-analysis was reviewed,[86] as well as one pooled analysis of 5 cohorts,[87] and one pooled analysis of 11 cohort studies.[9]

Evidence on the Overall Relationship

A small number of epidemiologic studies have examined the association between physical activity and risk of developing thyroid cancer. In the meta-analysis of physical activity and thyroid cancer risk, data from eight cohort and three case-control studies were included.[86] The meta-analysis suggests that risk for thyroid cancer is not associated with high versus low levels of activity (RR=1.06; 95% CI: 0.79-1.42). When the meta-analysis was limited to cohort studies, physical activity was associated with increased risk of thyroid cancer (RR=1.28; 95% CI: 1.01-1.63).[86] The five-cohort pooled analysis found no significant association between physical activity and thyroid cancer risk (RR=1.18; 95% CI: 1.00-1.39).[87] The pooled analysis of 11 cohorts similarly found no statistically significant association between high levels of physical activity and thyroid cancer risk (RR=0.92; 95% CI: 0.81-1.06).[9]

Dose-response: The larger pooled analysis[9] showed no statistically significant associations between increased dose of physical activity and risk of thyroid cancer.

Evidence on Specific Factors

Age: Risk estimates by age were presented only in the pooled analysis of five cohorts.[87] They observed statistically significant differences according to age at diagnosis (P-$_{\text{interaction}}$=0.03), whereby the association was strongest for thyroid cancers diagnosed before age 50 years (80 cases, HR=2.58; 95% CI: 1.41-4.74, P_{trend}=0.002) compared to thyroid cancers diagnosed at ages 50 to 59 years (127 cases, HR=1.09; 95% CI: 0.72-1.66, P_{trend}=0.68) or at ages 60 years or older (611 cases, HR=1.11; 95% CI: 0.92-1.34, P_{trend}=0.28).[87] Given that this subgroup association was evident only in a subset[87] of all of the studies that have addressed thyroid cancer and physical activity,[9, 86] the Subcommittee could not determine that high levels of physical activity increases risk of thyroid cancer in young individuals.

Sex: The relative risk estimates for women in the individual studies stratified by sex (approximately half) reflect the overall risk estimate. The pooled analysis found similar risk estimates between men and women (both showing no statistically significant associations). In the smaller pooled analysis, association was non-statistically significantly stronger in men (HR=1.40; 95% CI: 1.06-1.86) compared to women (HR=1.07; 95% CI: 0.87-1.32; $P_{interaction}$=0.21).[87]

Race/ethnicity: The studies included in these analyses were primarily from Caucasian individuals. Studies in the meta-analysis[86] that showed data for Asians had similar relative risks to those from the U.S. and European studies.

Socioeconomic status: None of the analyses presented data on the effect of socioeconomic status on the association between physical activity and thyroid cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: The pooled analysis of five cohorts found the association for high versus low physical activity was statistically significantly stronger among participants with BMI ≥25 kg/m^2 (HR=1.34; 95% CI: 1.09-1.64) compared to those with BMI <25 kg/m^2 (HR=0.92; 95% CI: 0.69-1.22; $P_{interaction}$=0.03).[87] The pooled analysis of 11 cohorts, in contrast, found no difference in effect by BMI <25 kg/m^2 versus ≥25 kg/m^2 ($P_{effect\ modification}$ = 0.37).[9]

Cancer subtype: Neither the meta-analysis nor the larger pooled analysis reported on the effects of physical activity by subtypes of thyroid cancer (papillary, follicular, medullary, anaplastic). In the pooled analysis of five cohorts, the association was non-statistically significantly stronger for follicular thyroid cancer (HR=1.55; 95% CI: 1.03-2.35) compared to papillary thyroid cancer (HR=1.18; 95% CI: 0.97-1.44; $P_{interaction}$= 0.24).[87]

Individuals at high risk: No information was provided in the meta-analysis or pooled analyses about effects of physical activity in individuals at elevated risk of thyroid cancer.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Rectal Cancer

Conclusion Statements

Limited evidence suggests that greater amounts of physical activity are not associated with risk of developing rectal cancer. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether a dose-response relationship between increasing physical activity levels and decreasing risk of rectal cancer exists. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the effects of physical activity on rectal cancer risk differ by sex, age, race/ethnicity, weight status, or socioeconomic groups in the United States. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the effects of physical activity on rectal cancer risk differ by subtype of rectal cancer. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the effects of physical activity on rectal cancer risk differ in individuals at elevated risk for rectal cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

Based on data from 2010-2014, the incidence rate of rectal cancer in the United States was 11.8 per 100,000 men and women per year.[21] Risk factors for rectal cancer include: increased age, obesity, personal history of adenomatous colorectal polyps, family history of colorectal cancer, certain genetic polymorphisms, inflammatory bowel disease, alcohol use, and cigarette smoking.[30, 88, 89]

To examine the association between physical activity and risk of rectal cancer, the Subcommittee reviewed four systematic reviews[19, 23, 26, 29] of which three[19, 23, 26] included meta-analyses. The Subcommittee also reviewed one pooled analysis of 12 large prospective cohort studies[9] and meta-analysis data from the World Cancer Research Fund.[30, 31] The reviews contained data from between 5 and 14 epidemiologic studies.

Evidence on the Overall Relationship

A considerable body of epidemiologic data exists on the association between physical activity and risk of developing rectal cancer. The most recent published meta-analysis (nine cohort studies) reported that risk of rectal cancer did not differ for individuals engaging in the highest versus lowest categories of physical activity level (RR=1.07; 95% CI: 0.93-1.24).[19] Other meta-analyses similarly found no associations between highest versus lowest levels of physical activity and risk of developing rectal cancer.[23, 26, 30, 31] Most studies adjusted for multiple potential confounding factors, including age, BMI, and rectal cancer risk factors, although adjustment for colorectal cancer screening (which could be related to physical activity level) was not typically done. In contrast to these findings, the pooled analysis of 12 cohort studies found a statistically significant relationship between the 90th versus 10th percentile level for leisure time physical activity and decreased risk of rectal cancer (RR=0.87; 95% CI: 0.80-0.95).[9] It is not clear why the results of the pooled analysis differ from those of the meta-analyses. The pooled analysis included only a subset of studies contained in the meta-analyses. In addition, the pooled analysis compared the top versus bottom decile of physical activity, while the meta-analyses used whatever the source studies reported as high or low activity levels, typically top and bottom quartiles.

Dose-response: Given the lack of overall associations between physical activity and risk of rectal cancer, none of the meta-analyses examined dose-response relationships. The pooled analysis of 12 cohort studies found a significant U-shaped relationship between increasing leisure time physical activity percentile and risk of rectal cancer ($P_{overall}$=0.0002; $P_{non\text{-}linear}$=0.0008).[9]

Evidence on Specific Factors

Sex: The pooled analysis found that the effect of physical activity on risk of rectal cancer was statistically significant in men, but not women ($P_{heterogeneity}$=0.09).[9]

Age: None of the analyses or the systematic review provided data within specific age groups.

Race/ethnicity: Studies in the United States and Europe were primarily in Caucasians. A systematic review of Japanese studies reported on data from two cohort and six case-control studies, and found no association of higher physical activity with risk of rectal cancer.[29]

Socioeconomic status: None of the analyses or the systematic review presented data on the effect of socioeconomic status on the association between physical activity and rectal cancer incidence. Hence, no conclusions can be made on this factor.

Weight status: The pooled analysis examined associations between the 90th percentile versus 10th percentile of physical activity level by BMI. Risk of rectal cancer for those with BMI <25.0 kg/m^2 did not differ from that of individuals with BMI $\geq$25 kg/m^2 ($P_{effect\ modification}$=0.50).[9]

Cancer subtype: None of the analyses or the systematic review considered the association with physical activity for different rectal cancer subtypes.

Individuals at high risk: No information was provided in the systematic review or analyses about effects of physical activity in individuals at elevated risk of rectal cancer.

For additional details on this body of evidence, visit: https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio.

Other Cancers

No systematic reviews or meta-analyses included sufficient information to make conclusions about the associations between physical activity and occurrence of other cancers, including liver, gallbladder, small intestine, soft tissue, or melanoma. However, the pooled analysis by Moore et al,[9] provided some data on these cancers that are useful to note. Statistically significantly reduced risks were observed for the 90th versus 10th percentile of physical activity level for liver cancer (HR=0.73; 95% CI: 0.55-0.98). Statistically significantly increased risks were seen for malignant melanoma (HR=1.27; 95% CI: 1.16-1.40). No statistically significant associations were observed for cancers of the small intestine (HR=0.78; 95% CI: 0.60-1.00), soft tissue (HR=0.94; 95% CI: 0.67-1.31), and gallbladder (HR=0.72; 95% CI: 0.51-1.01).

Question 2. What is the relationship between sedentary behavior and cancer incidence?

a) Is there a dose-response relationship? If yes, what is the shape of the relationship?
b) Does the relationship vary by age, sex, race/ethnicity, socioeconomic status, or weight status?
c) Is the relationship independent of levels of light, moderate, or vigorous physical activity?
d) Is there any evidence that bouts or breaks in sedentary behavior are important factors?

Sources of evidence: Meta-analyses, systematic reviews, original research articles

Conclusion Statements

Moderate evidence indicates a significant relationship between greater time spent in sedentary behavior and higher risk of incident cancer, particularly for endometrial, colon, and lung cancer. **PAGAC Grade: Moderate.**

Limited evidence suggests the existence of a direct dose-response relationship between sedentary behavior and incident endometrial, colon, and lung cancers. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and incident cancer varies by age, sex, race/ethnicity, socioeconomic status, or weight status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between sedentary behavior and incident cancer varies by amount of moderate-to-vigorous physical activity. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether bouts or breaks in sedentary behavior are important factors in the relationship between sedentary behavior and incident cancer. **PAGAC Grade: Not assignable.**

Review of the Evidence

Sources of evidence included systematic reviews and meta-analyses published from January 2000 to February 21, 2017, and recent original research articles published between January 2014 and April 25, 2017. The sources of evidence were identified through the same search that was used to provide evidence for Question 4 in *Part F. Chapter 2. Sedentary Behavior*. Further details about the search strategy are provided in that chapter.

For details on the review of the evidence to address Question 2, the reader is referred to *Part F. Chapter 2: Sedentary Behavio*r. Briefly, two meta-analyses examined the association between sedentary behavior and total cancer incidence,[90, 91] and reported summary relative risk estimates of 1.20 (95% CI: 1.12-1.28)[90] and 1.13 (95% CI: 1.05-1.21)[91] for highest versus lowest levels of sedentary behavior.

Two meta-analyses examined the association between sedentary behavior and endometrial cancer, and both reported a significant association when comparing the highest versus lowest levels of sedentary time: a relative risk of 1.36 (95% CI: 1.15-1.60) was reported by Schmid and Leitzmann,[92] and a relative risk of 1.28 (95% CI: 1.08-1.53) was reported by Shen et al.[90] The meta-analysis by Shen et al[90] reported a statistically significant association between sedentary behavior and combined colorectal cancer (RR= .30; 95% CI: 1.12-1.49); whereas Schmid and Leitzmann[92] reported a statistically significant association for colon cancer (RR=1.28; 95% CI: 1.13-1.45) but not for rectal cancer (RR=1.03; 95% CI: 0.89-1.19). These two meta-analyses also examined the association between sedentary behavior and lung cancer, and both reported a statistically significant association when comparing the highest versus lowest levels of sedentary time: a relative risk of 1.21 (95% CI: 1.03-1.43) was reported by Schmid and Leitzmann,[92] and a relative risk of 1.27 (95% CI: 1.06-1.52) was reported by Shen et al.[90] It is important to note that many studies reported significant associations between sedentary behavior and incident cancer risk using statistical models that included an estimate of moderate-to-vigorous physical activity as a covariate.

OVERALL SUMMARY AND CONCLUSIONS

In reviewing 45 systematic reviews, meta-analyses, and pooled analyses comprising hundreds of epidemiologic studies with several million study participants, the Subcommittee determined that strong evidence linked highest versus lowest physical activity levels to reduced risks of bladder, breast, colon, endometrial, esophageal adenocarcinoma, renal, and gastric cancers, with risk reductions ranging from approximately 10 percent to 20 percent. The Subcommittee found evidence of a 25 percent reduction in lung cancer risk with highest versus lowest levels of physical activity, but could not rule out confounding by tobacco use and therefore considered the association to be a lower grade of strength. The Subcommittee determined that limited evidence suggested an association between increased physical activity and decreased risks of hematologic, head and neck, ovary, pancreas, and prostate cancers. No grade could be assigned for brain cancer. The Subcommittee found limited evidence of no effect of physical activity on risk of thyroid or rectal cancer. Finally, due to lack of evidence, the Subcommittee did not review several other cancer sites.

A dose-response relationship between physical activity and specific cancer risk was evident, 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.

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.

Effects of physical activity on specific cancer risk were clearly seen for both women and men for colon and renal cancers, while for other cancers such as bladder, esophagus, gastric, lung, and pancreas, 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 race/ethnic groups other than Whites. For several cancers, individuals of Asian race 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, but is not related to prostate cancer risk in African Americans. For some particular 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 race/ethnic populations. Weight status affected the association between physical activity and risk of several cancers, including breast, endometrium, lung, ovary, and thyroid, and possibly for esophageal adenocarcinoma and gastric cardia cancers.

The Subcommittee's review of the literature on sedentary behavior and risk of endometrial, colon, and lung cancers found that highest versus lowest levels of sedentary time increased risks of these cancers by a statistically significant range of 20 percent to 35 percent, with an evidence grade of strong. Conclusions could not be drawn for associations between sedentary time and other specific cancers.

In summary, the Subcommittee's review of the extensive epidemiologic literature resulted in convincing evidence linking increased physical activity to lower risk of several commonly occurring cancers in adults, as well as possible lower risk of several other cancers in adults. These effects appear to apply broadly across sex, most cancer subtypes, and, for most cancers, regardless of weight status. Most of the existing data on physical activity and cancer risk come from studies of Whites. The existing data on other racial and ethnic groups, including African Americans and Asians, suggest that physical activity confers similar benefits. Although data on diverse racial and ethnic groups are insufficient, there are no data to say that physical activity will not help individuals of all races and ethnicities.

Table F4-1. Summary of Associations of Physical Activity and Sedentary Behavior with Specific Cancers, with Subcommittee-assigned Evidence Grade

Cancer	Evidence Grade*
Physical activity protects:	
Bladder, breast, colon, endometrium, esophagus (adenocarcinoma), renal, gastric	Strong
Lung	Moderate
Hematologic, head & neck, ovary, pancreas, prostate	Limited
Brain	Not assignable
No effect of physical activity:	

Cancer	Evidence Grade*
Thyroid	Limited
Rectal	Limited
Sedentary behavior increases risk:	
Endometrium, colon, lung	Moderate

Note: *Evidence grade refers to strength of evidence in the literature regarding associations between physical activity and cancer risk. For effect sizes and directions of these associations, see reviews of evidence with specific cancers.

Comparing 2018 Findings with the 2008 Scientific Report

The *Physical Activity Guidelines Advisory Committee Report, 2008*[4] concluded that evidence supported a moderate, inverse relation between physical activity and the development of colon and breast cancer. In that report, few studies detailed the associations by subgroups (age, sex, weight status, cancer site) or by particular types of physical activity. It further concluded that there was no association between physical activity and the development of prostate or rectal cancer.

The 2008 Scientific Report[4] did not comment on the associations between physical activity and risk of bladder, gastric, endometrial, renal, hematological, head and neck, pancreatic, ovarian, brain, or thyroid cancers because few studies in these cancers were available at that time. Further, given that the evidence of associations between sedentary behavior and cancer incidence has largely been published since 2008, the prior report did not include information on this exposure.

The 2008 Scientific Report[4] reviewed some mechanisms that may explain the associations between physical activity and cancer risk, but the review was not systematic.

Public Health Impact

In 2017, an estimated 1,688,780 Americans will be diagnosed with a new cancer and 600,920 individuals will die of cancer.[1] From our review, regular aerobic physical activity likely confers substantial beneficial effects on reducing risks for occurrence of several cancers, notably some of the most commonly occurring cancers (e.g., breast, colon, and lung cancers), as well as several obesity-related cancers (e.g., postmenopausal breast, colon, esophageal adenocarcinoma, and renal). Given the significant impact of cancer on quality of life, financial stability, and mortality, the reduction in risk 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 Subcommittee believes that all individuals should be encouraged to engage in recommended levels of physical activity in order to reduce risk for developing cancer.

NEEDS FOR FUTURE RESEARCH

1. Conduct epidemiologic studies of effects of physical activity on risk of cancer for specific cancer sites that have not been adequately studied, preferably large prospective cohort studies.

   Rationale: Very little evidence exists on the relationship between physical activity and the risk of cancer at several sites, particularly the rare cancers. Therefore additional pooled datasets and meta-analyses may be needed. Additional studies would provide the data necessary for the useful insights that would be possible through analyses of pooled datasets and meta-analyses.

2. Conduct epidemiologic studies of effects of physical activity on risk of cancer in specific race, ethnic, and socioeconomic groups.

   Rationale: Few studies have had sufficiently large numbers of participants from specific racial, ethnic, or socioeconomic subgroups to assess the effects of physical activity on risk of developing cancer. This additional research is particularly important, as many groups are at high risk of cancer (i.e., African Americans are at increased risk for colon, prostate, and breast cancers), are typically diagnosed with more advanced disease (i.e. individuals from low socioeconomic groups or others without access to medical care), and are often insufficiently active.

3. Conduct studies to test effect modification by age on the associations between physical activity and cancer risk.

   Rationale: Some evidence suggests that risk for some cancers such as colon and breast is increasing in younger age groups, who are also less active today than in previous generations. It would be important to know whether physical activity can be protective in this younger age group.

4. Conduct epidemiologic studies, preferably prospective cohort studies, to determine effects of specific types of physical activity on cancer risk.

Rationale: Few data are available on the associations of specific activities on cancer risk. It would be useful to know whether moderate-intensity activities such as walking are sufficient to provide protection. Also, insufficient data exist on associations of other activities such as muscle-strengthening activity on cancer risk.

5. Conduct epidemiologic studies, preferably prospective cohort studies, to more precisely determine dose-response effect of physical activity on cancer risk.

   Rationale: All data in available studies have been from self-reported recall of usual activities. Collecting data with device-based measures of activity will be important, as will determining precise measures of dose of activity.

6. Conduct randomized controlled clinical trials testing exercise effects on cancer incidence.

   Rationale: All available data are from observational studies, which could suffer from confounding effects of other variables. Randomized trials in high risk individuals could be more cost-effective, as trials with smaller sample sizes or shorter follow-up durations might be feasible.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67(1):7-30. doi:10.3322/caac.21387.

2. American Cancer Society. Lifetime risk of developing or dying from cancer. https://www.cancer.org/cancer/cancer-basics/lifetime-probability-of-developing-or-dying-from-cancer.html. Updated March 23, 2016. Accessed January 3, 2018.

3. Vineis P, Wild CP. Global cancer patterns: causes and prevention. *Lancet*. 2014;383(9916):549-557. doi:10.1016/S0140-6736(13)62224-2.

4. Physical Activity Guidelines Advisory Committee. *Physical Activity Guidelines Advisory Committee Report, 2008*. Washington, DC: U.S. Department of Health and Human Services; 2008.

5. McTiernan A. Mechanisms linking physical activity with cancer. *Nat Rev Cancer*. 2008;8(3):205-211. doi:10.1038/nrc2325.

6. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. *Nat Rev Cancer*. 2017;17(10):620-632. doi:10.1038/nrc.2017.78.

7. Ashcraft KA, Peace RM, Betof AS, Dewhirst MW, Jones LW. Efficacy and mechanisms of aerobic exercise on cancer initiation, progression, and metastasis: a critical systematic review of in vivo preclinical data. *Cancer Res*. 2016;76(14):4032-4050. doi:10.1158/0008-5472.CAN-16-0887.

8. Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. *Cell Metab*. October 2017. pii:S1550-4131(17)30567-3. doi:10.1016/j.cmet.2017.09.015.

9. Moore SC, Lee IM, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med*. 2016;176(6):816-825. doi:10.1001/jamainternmed.2016.1548.

10. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: bladder cancer. https://seer.cancer.gov/statfacts/html/urinb.html. Accessed January 3, 2018.

11. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol*. 2013;63(2):234-241. doi:10.1016/j.eururo.2012.07.033.

12. 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. doi:10.1038/bjc.2014.77.

13. World Cancer Research Fund International, American Institute for Cancer Research. *Continuous Update Project Report: Diet, Nutrition, Physical Activity and Bladder Cancer*; 2015. http://www.wcrf.org/bladder-cancer-2015. Accessed January 16, 2018.

14. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: female breast cancer. https://seer.cancer.gov/statfacts/html/breast.html. Accessed January 3, 2018.

15. National Cancer Institute. Breast cancer risk in American women. https://www.cancer.gov/types/breast/risk-fact-sheet. Accessed January 3, 2018.

16. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res Treat*. 2013;137(3):869-882. doi:10.1007/s10549-012-2396-7.

17. Neilson HK, Farris MS, Stone CR, et al. Moderate-vigorous recreational physical activity and breast cancer risk, stratified by menopause status: a systematic review and meta-analysis. *Menopause*. 2017;24(3):322-344. doi: 10.1097/GME.0000000000000745.

18. Pizot C, Boniol M, Mullie P, et al. Physical activity, hormone replacement therapy and breast cancer risk: a meta-analysis of prospective studies. *Eur J Cancer*. 2016;52:138-154. doi:10.1016/j.ejca.2015.10.063.

19. Liu L, Shi Y, Li T, et al. Leisure time physical activity and cancer risk: evaluation of the WHO's recommendation based on 126 high-quality epidemiological studies. *Br J Sports Med*. 2016;50(6):372-378. doi:10.1136/bjsports-2015-094728.

20. Gong Z, Hong CC, Bandera EV, et al. Vigorous physical activity and risk of breast cancer in the African American breast cancer epidemiology and risk consortium. *Breast Cancer Res Treat*. 2016;159(2):347-356. doi:10.1007/s10549-016-3936-3.

21. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: colorectal cancer. https://seer.cancer.gov/statfacts/html/colorect.html. Accessed January 3, 2018.

22. American Cancer Society. Colorectal cancer risk factors. https://www.cancer.org/cancer/colon-rectal-cancer/causes-risks-prevention/risk-factors.html. Accessed January 3, 2018.

23. Harriss DJ, Atkinson G, Batterham A, et al; Colorectal Cancer, Lifestyle, Exercise And Research Group. Lifestyle factors and colorectal cancer risk (2): a systematic review and meta-analysis of associations with leisure-time physical activity. *Colorectal Dis*. 2009;11(7):689-701. doi:10.1111/j.1463-1318.2009.01767.x.

24. Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2012;104(20):1548-1561. doi:10.1093/jnci/djs354.

25. Johnson CM, Wei C, Ensor JE, et al. Meta-analyses of colorectal cancer risk factors. *Cancer Causes Control*. 2013;24(6):1207-1222. doi:10.1007/s10552-013-0201-5.

26. Robsahm TE, Aagnes B, Hjartaker A, Langseth H, Bray FI, Larsen IK. Body mass index, physical activity, and colorectal cancer by anatomical subsites: a systematic review and meta-analysis of cohort studies. *Eur J Cancer Prev*. 2013;22(6):492-505. doi:10.1097/CEJ.0b013e328360f434.

27. Kyu HH, Bachman VF, Alexander LT, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *BMJ*. 2016;354:i3857. doi:10.1136/bmj.i3857.

28. Wolin KY, Yan Y, Colditz GA, Lee IM. Physical activity and colon cancer prevention: a meta-analysis. *Br J Cancer*. 2009;100(4):611-616. doi:10.1038/sj.bjc.6604917.

29. Pham NM, Mizoue T, Tanaka K, et al; Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Physical activity and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol*. 2012;42(1):2-13. doi:10.1093/jjco/hyr160.

30. World Cancer Research Fund International, American Institute for Cancer Research. *Continuous Update Project Report: Diet, Nutrition, Physical Activity and Colorectal Cancer*. http://www.aicr.org/continuous-update-project/reports/colorectal-cancer-2017-report.pdf. Published 2017. Accessed October 11, 2017.

31. World Cancer Research Fund International, American Institute for Cancer Research. *Continuous Update Project Report: Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer*. http://www.wcrf.org/sites/default/files/Colorectal-Cancer-2011-Report.pdf. Published 2011. Accessed October 11, 2017.

32. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: uterine cancer. https://seer.cancer.gov/statfacts/html/corp.html. Accessed January 3, 2018.

33. Keum N, Ju W, Lee DH, et al. Leisure-time physical activity and endometrial cancer risk: dose-response meta-analysis of epidemiological studies. *Int J Cancer*. 2014;135(3):682-694. doi:10.1002/ijc.28687.

34. Moore SC, Gierach GL, Schatzkin A, Matthews CE. Physical activity, sedentary behaviours, and the prevention of endometrial cancer. *Br J Cancer*. 2010;103(7):933-938. doi:10.1038/sj.bjc.6605902.

35. Schmid D, Behrens G, Keimling M, Jochem C, Ricci C, Leitzmann M. A systematic review and meta-analysis of physical activity and endometrial cancer risk. *Eur J Epidemiol*. 2015;30(5):397-412. doi:10.1007/s10654-015-0017-6.

36. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: esophageal cancer. https://seer.cancer.gov/statfacts/html/esoph.html. Accessed January 3, 2018.

37. Runge TM, Abrams JA, Shaheen NJ. Epidemiology of Barrett's esophagus and esophageal adenocarcinoma. *Gastroenterol Clin North Am*. 2015;44(2):203-231. doi:10.1016/j.gtc.2015.02.001.

38. Thrift AP. The epidemic of oesophageal carcinoma: where are we now? *Cancer Epidemiol*. 2016;41:88-95. doi:10.1016/j.canep.2016.01.013.

39. 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. doi:10.1007/s10654-014-9895-2.

40. Chen Y, Yu C, Li Y. Physical activity and risks of esophageal and gastric cancers: a meta-analysis. *PLoS One*. 2014;9(2):e88082. doi:10.1371/journal.pone.0088082.

41. Singh S, Devanna S, Edakkanambeth Varayil J, Murad MH, Iyer PG. Physical activity is associated with reduced risk of esophageal cancer, particularly esophageal adenocarcinoma: a systematic review and meta-analysis. *BMC Gastroenterol*. 2014;14:101. doi:10.1186/1471-230X-14-101.

42. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: stomach cancer. https://seer.cancer.gov/statfacts/html/stomach.html. Accessed January 3, 2018.

43. Abioye AI, Odesanya MO, Abioye AI, Ibrahim NA. Physical activity and risk of gastric cancer: a meta-analysis of observational studies. *Br J Sports Med*. 2015;49(4):224-229. doi:10.1136/bjsports-2013-092778.

44. Psaltopoulou T, Ntanasis-Stathopoulos I, Tzanninis IG, Kantzanou M, Georgiadou D, Sergentanis TN. Physical activity and gastric cancer risk: a systematic review and meta-analysis. *Clin J Sport Med*. 2016;26(6):445-464.

45. Singh S, Edakkanambeth Varayil J, Devanna S, Murad MH, Iyer PG. Physical activity is associated with reduced risk of gastric cancer: a systematic review and meta-analysis. *Cancer Prev Res (Phila)*. 2014;7(1):12-22. doi:10.1158/1940-6207.CAPR-13-0282.

46. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: kidney and renal pelvis cancer. https://seer.cancer.gov/statfacts/html/kidrp.html. Accessed January 3, 2018.

47. American Cancer Society. Risk factors for kidney cancer. https://www.cancer.org/cancer/kidney-cancer/causes-risks-prevention/risk-factors.html. Accessed January 3, 2018.

48. 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. doi:10.1038/bjc.2013.37.

49. World Cancer Research Fund International, American Institute for Cancer Research. *Continuous Update Project Report: Diet, Nutrition, Physical Activity and Kidney Cancer*; 2015. http://www.wcrf.org/kidney-cancer-2015. Accessed January 16, 2018.

50. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: lung and bronchus cancer. https://seer.cancer.gov/statfacts/html/lungb.html. Accessed January 3, 2018.

51. Sun JY, Shi L, Gao XD, Xu SF. Physical activity and risk of lung cancer: a meta-analysis of prospective cohort studies. *Asian Pac J Cancer Prev*. 2012;13(7):3143-3147.

52. Buffart LM, Singh AS, van Loon EC, Vermeulen HI, Brug J, Chinapaw MJ. Physical activity and the risk of developing lung cancer among smokers: a meta-analysis. *J Sci Med Sport*. 2014;17(1):67-71. doi:10.1016/j.jsams.2013.02.015.

53. Schmid D, Ricci C, Behrens G, Leitzmann MF. Does smoking influence the physical activity and lung cancer relation? A systematic review and meta-analysis. *Eur J Epidemiol*. 2016;31(12):1173-1190. doi:10.1007/s10654-016-0186-y.

54. Zhong S, Ma T, Chen L, et al. Physical activity and risk of lung cancer: a meta-analysis. *Clin J Sport Med*. 2016;26(3):173-181. doi:10.1097/JSM.0000000000000219.

55. Brenner DR, Yannitsos DH, Farris MS, Johansson M, Friedenreich CM. Leisure-time physical activity and lung cancer risk: a systematic review and meta-analysis. *Lung Cancer*. 2016;95:17-27. doi:10.1016/j.lungcan.2016.01.021.

56. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: leukemia. *https://seer*. https://seer.cancer.gov/statfacts/html/leuks.html. Accessed January 3, 2018.

57. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: non-Hodgkin lymphoma. https://seer.cancer.gov/statfacts/html/nhl.html. Accessed January 3, 2018.

58. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: Hodgkin lymphoma. https://seer.cancer.gov/statfacts/html/hodg.html. Accessed January 3, 2018.

59. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: myeloma. https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed January 3, 2018.

60. 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. doi:10.1158/1055-9965.EPI-13-0699.

61. Vermaete NV, Wolter P, Verhoef GE, et al. Physical activity and risk of lymphoma: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2013;22(7):1173-1184. doi:10.1158/1055-9965.EPI-13-0182.

62. Aschebrook-Kilfoy B, Cocco P, La Vecchia C, et al. Medical history, lifestyle, family history, and occupational risk factors for mycosis fungoides and Sézary syndrome: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr*. 2014;2014(48):98-105. doi:10.1093/jncimonographs/lgu008.

63. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: oral cavity and pharynx cancer. https://seer.cancer.gov/statfacts/html/oralcav.html. Accessed January 3, 2018.

64. National Cancer Institute. Head and neck cancers. https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet. Accessed January 3, 2018.

65. Nicolotti N, Chuang SC, Cadoni G, et al. Recreational physical activity and risk of head and neck cancer: a pooled analysis within the international head and neck cancer epidemiology (INHANCE) Consortium. *Eur J Epidemiol*. 2011;26(8):619-628. doi:10.1007/s10654-011-9612-3.

66. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: ovarian cancer. https://seer.cancer.gov/statfacts/html/ovary.html. Accessed January 3, 2018.

67. American Cancer Society. What are the risk factors for ovarian cancer? https://www.cancer.org/cancer/ovarian-cancer/causes-risks-prevention/risk-factors.html. Accessed January 3, 2018.

68. Zhong S, Chen L, Lv M, Ma T, Zhang X, Zhao J. Nonoccupational physical activity and risk of ovarian cancer: a meta-analysis. *Tumour Biol*. 2014;35(11):11065-11073. doi:10.1007/s13277-014-2385-z.

69. Cannioto R, LaMonte MJ, Risch HA, et al. Chronic recreational physical inactivity and epithelial ovarian cancer risk: evidence from the Ovarian Cancer Association Consortium. *Cancer Epidemiol Biomarkers Prev*. 2016;25(7):1114-1124. doi:10.1158/1055-9965.EPI-15-1330.

70. American Cancer Society. Cancer Facts & Figures 2017. Atlanta, GA: American Cancer Society; 2017.

71. Genkinger JM, Spiegelman D, Anderson KE, et al. A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. *Int J Cancer*. 2011;129(7):1708-1717. doi:10.1002/ijc.25794.

72. Elena JW, Steplowski E, Yu K, et al. Diabetes and risk of pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. *Cancer Causes Control*. 2013;24(1):13-25. doi:10.1007/s10552-012-0078-8.

73. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: pancreatic cancer. https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed January 3, 2018.

74. Bao Y, Michaud DS. Physical activity and pancreatic cancer risk: a systematic review. *Cancer Epidemiol Biomarkers Prev*. 2008;17(10):2671-2682. doi:10.1158/1055-9965.EPI-08-0488.

75. Farris MS, Mosli MH, McFadden AA, Friedenreich CM, Brenner DR. The association between leisure time physical activity and pancreatic cancer risk in adults: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2015;24(10):1462-1473. doi:10.1158/1055-9965.EPI-15-0301.

76. Behrens G, Jochem C, Schmid D, Keimling M, Ricci C, Leitzmann MF. Physical activity and risk of pancreatic cancer: a systematic review and meta-analysis. *Eur J Epidemiol*. 2015;30(4):279-298. doi:10.1007/s10654-015-0014-9.

77. O'Rorke MA, Cantwell MM, Cardwell CR, Mulholland HG, Murray LJ. Can physical activity modulate pancreatic cancer risk? A systematic review and meta-analysis. *Int J Cancer*. 2010;126(12):2957-2968. doi:10.1002/ijc.24997.

78. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: prostate cancer. https://seer.cancer.gov/statfacts/html/prost.html. Accessed January 3, 2018.

79. National Cancer Institute. Prostate Cancer Prevention (PDQ®)–Health Professional Version. https://www.cancer.gov/types/prostate/hp/prostate-prevention-pdq#section/_17. Updated March 17, 2017. Accessed January 3, 2018.

80. Liu Y, Hu F, Li D, et al. Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. *Eur Urol*. 2011;60(5):1029-1044. doi:10.1016/j.eururo.2011.07.007.

81. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: brain and other nervous system cancer. https://seer.cancer.gov/statfacts/html/brain.html. Accessed January 3, 2018.

82. Niedermaier T, Behrens G, Schmid D, Schlecht I, Fischer B, Leitzmann MF. Body mass index, physical activity, and risk of adult meningioma and glioma: a meta-analysis. *Neurology*. 2015;85(15):1342-1350. doi:10.1212/WNL.0000000000002020.

83. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer stat facts: thyroid cancer. https://seer.cancer.gov/statfacts/html/thyro.html. Accessed January 3, 2018.

84. American Cancer Society. Thyroid cancer risk factors. https://www.cancer.org/cancer/thyroid-cancer/causes-risks-prevention/risk-factors.html. Accessed January 3, 2018.

85. Schmid D, Ricci C, Behrens G, Leitzmann MF. Adiposity and risk of thyroid cancer: a systematic review and meta-analysis. *Obes Rev*. 2015;16(12):1042-1054. doi:10.1111/obr.12321.

86. Schmid D, Behrens G, Jochem C, Keimling M, Leitzmann M. Physical activity, diabetes, and risk of thyroid cancer: a systematic review and meta-analysis. *Eur J Epidemiol*. 2013;28(12):945-958. doi:10.1007/s10654-013-9865-0.

87. Kitahara CM, Platz EA, Beane Freeman LE, et al. Physical activity, diabetes, and thyroid cancer risk: a pooled analysis of five prospective studies. *Cancer Causes Control*. 2012;23(3):463-471. doi:10.1007/s10552-012-9896-y.

88. Cheng J, Chen Y, Wang X, et al. Meta-analysis of prospective cohort studies of cigarette smoking and the incidence of colon and rectal cancers. *Eur J Cancer Prev*. 2015;24(1):6-15. doi: 10.1097/CEJ.0000000000000011.

89. Kuipers EJ, Grady WM, Lieberman D, et al. *Nat Rev Dis Primers*. 2015;1:15065. doi:10.1038/nrdp.2015.65.

90. Shen D, Mao W, Liu T, et al. Sedentary behavior and incident cancer: a meta-analysis of prospective studies. *PLoS One*. 2014;9(8):e105709. doi:10.1371/journal.pone.0105709.

91. Biswas A, Oh PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med*. 2015;162(2):123-132. doi:10.7326/M14-1651.

92. Schmid D, Leitzmann MF. Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis. *J Natl Cancer Inst*. 2014;106(7). doi:10.1093/jnci/dju098. Print 2014 Jul.