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Epidemiologic Studies of Physical Activity and Primary Prevention of Cancer

Epidemiologische Studien zur körperlichen Aktivität und Primärprävention von Krebs

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SUMMARY

Evidence for a protective role of physical activity in cancer prevention is rapidly accumulating. The most convincing epidemiologic data in support of a beneficial effect of physical activity on cancer risk exists for colon, breast, and endometrial cancers. Evidence is weaker for cancers of the lung, pancreas, stomach, prostate, and ovary. Inconsistent findings for a physical activity and cancer relation in the literature may reflect methodologic constraints of available studies, including the use of inaccurate physical activity measurement instruments, failure to assess physical activity performed at etiologically relevant time periods of carcinogenesis, inadequate assessment of the dose of physical activity (frequency, duration, and intensity), incomplete control for potential confounding, and lack of consideration of subgroup findings. These methodologic issues require heightened attention in future studies. Several biologic mechanisms mediate the relation between physical activity and cancer but most etiologic pathways remain poorly understood. Most research on physical activity and primary cancer prevention has been conducted in observational settings, which are not designed to provide evidence of causal associations. Controlled physical activity intervention studies of cancer risk are needed to solidify existing mechanistic evidence and to further develop biologic models relating increased physical activity to decreased cancer risk.

Key Words: Physical activity, cancer prevention, epidemiology, methodologic considerations

ZUSAMMENFASSUNG

Die Evidenz bezüglich einer krebspräventiven Wirkung körperlicher Aktivität hat in den letzten Jahren erheblich zugenommen. Die überzeugendsten epidemiologischen Daten eines protektiven Effekts körperlicher Aktivität auf das Krebsrisiko betreffen Karzinome des Kolons, der Mamma und des Endometriums. Hingegen bestehen geringere bzw. zum Teil inkonsistente Evidenzen eines möglichen protektiven Effekts körperlicher Aktivität auf die Entwicklung von Karzinomen des Bronchialtraktes, des Pankreas, des Magens, der Prostata und der Ovarien. Als mögliche Ursache dieser Inkonsistenzen in der Literatur kommen methodologische Limitationen der verfügbaren Studien in Betracht. Dazu gehören inakkurate Erhebungen der körperlichen Aktivität, fehlende Berücksichtigung der innerhalb bestimmter ätiologisch relevanter Zeiträume der Karzinogenese stattgefundenen körperlichen Aktivität, unzureichende Bestimmung des Aktivitätsausmaßes (Häufigkeit, Dauer und Intensität der körperlichen Aktivität), inadäquate Adjustierung für potenzielle Störvariablen sowie unzureichende Betrachtung möglicher Subgruppen-Effekte. Diese methodologischen Aspekte sollten in künftigen Studien verstärkt Berücksichtigung finden. Es gibt eine Reihe physiologischer Wirkmechanismen, die den krebsprotektiven Effekt körperlicher Aktivität erklären, jedoch bleiben für viele Karzinome die zugrunde liegenden Mechanismen ungeklärt. Die meisten vorliegenden Erkenntnisse zur potenziell krebspräventiven Wirkung körperlicher Aktivität basieren auf Beobachtungsstudien, die keine konkrete Aussage über einen kausalen Zusammenhang zulassen. Kontrollierte Interventionsstudien sollen daher den Zusammenhang zwischen der körperlichen Aktivität und dem Krebsrisiko analysieren, um die vorhandenen Evidenzen zu sichern und einen Erkenntnisgewinn der zugrunde liegenden biologischen Mechanismen zu ermöglichen.

Schlüsselwörter: körperliche Aktivität, Krebsprävention, Epidemiologie, methodologische Überlegungen

INTRODUCTION

In recent years, epidemiologic studies on physical activity and cancer have rapidly accumulated. The etiologic role of physical activity in the primary prevention of cancer is now becoming increasingly convincing. According to the 2007 report by the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) on food, nutrition, physical activity, and cancer prevention (32) and a number of recent reviews (1,5,9,26), the epidemiologic evidence for an inverse association between physical activity and cancer is now convincing for cancers of the colon and

breast, it is probable for endometrial cancer, it is possible for cancers of the lung, pancreas, and stomach, and it is insufficient for cancers of the prostate and ovary (Tab. 1).

Physical activity may exert a protective role on carcinogenesis by increasing insulin sensitivity, decreasing levels of pro-inflamm-

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atory C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor (TNF)- α , modulating adipokines (e.g., leptin and adiponectin), growth factors (e.g., insulin-like growth factor (IGF)-1 and insulin-like growth factor-binding protein (IGFBP)-3), sex steroids (e.g., estrogens and androgens), and improving immune function by influencing components of the immune system (e.g., natural killer cells, neutrophils, monocytes, eosinophils, and lymphocytes) (20,24). Further potential mechanisms include improved capacity of DNA repair and antioxidant enzyme systems (Fig.1). Physical activity may act directly upon those biologic pathways or indirectly by reducing obesity and preventing weight gain. For example, physical activity may exert favorable effects on risks of breast and endometrial cancers by reducing body weight and lowering insulin levels, thereby increasing sex hormone binding globulin (SHBG), which reduces the bioavailability of cancer-promoting sex hormones.

The aims of the current review are to a) provide a brief update on recent progress that has been made in epidemiologic research of physical activity and the primary prevention of cancer as well as on potential direct and indirect biologic pathways; b) discuss methodologic issues related to epidemiologic studies of physical activity and cancer; and c) highlight areas of future research in the field of physical activity and cancer risk.

PHYSICAL ACTIVITY AND COLON CANCER

The most convincing epidemiologic evidence for an apparent protective effect of physical activity exists for colon cancer. Wolin and Tuchman summarized the findings of 24 case-control studies and 28 cohort studies and reported that high versus low levels of physical activity were associated with an average 25% reduction in co-

Table 1: Epidemiologic evidence on the association between physical activity and cancer risk (adapted from (9) and (26)).

Cancer site	Average risk reduction	Level of epidemiologic evidence
Colon	25%	Convincing
Breast	25%	Convincing
Endometrial	20-30%	Probable
Lung	20-50%	Possible
Pancreatic	25%	Possible
Gastric	30%	Possible
Prostate	10%	Insufficient
Ovarian	<10%	Insufficient

lon cancer risk (30). A recent meta-analysis on proximal and distal colon cancers reported average cancer risk reductions of 26% to 27%, indicating that the strength of the physical activity and colon cancer relation did not appear to vary by anatomic subsite (2). A beneficial effect of physical activity was apparent for recreational, occupational, and household activity. Accumulated data suggest that being active across the lifespan is related to a lower colon cancer risk than being active only in recent years. The association between physical activity and colon cancer does not appear to be meaningfully confounded by dietary intake, body mass index (BMI), or other risk factors for colon cancer. There is general agreement that physical activity is not related to rectal cancer. Physical activity may exert a beneficial effect on colon carcinogenesis by increasing insulin sensitivity, decreasing chronic inflammation, and improving immune function (20,31). Moreover, physical activity may inhibit the tumor-stimulating effect of prostaglandin E2 (PGE2), re-

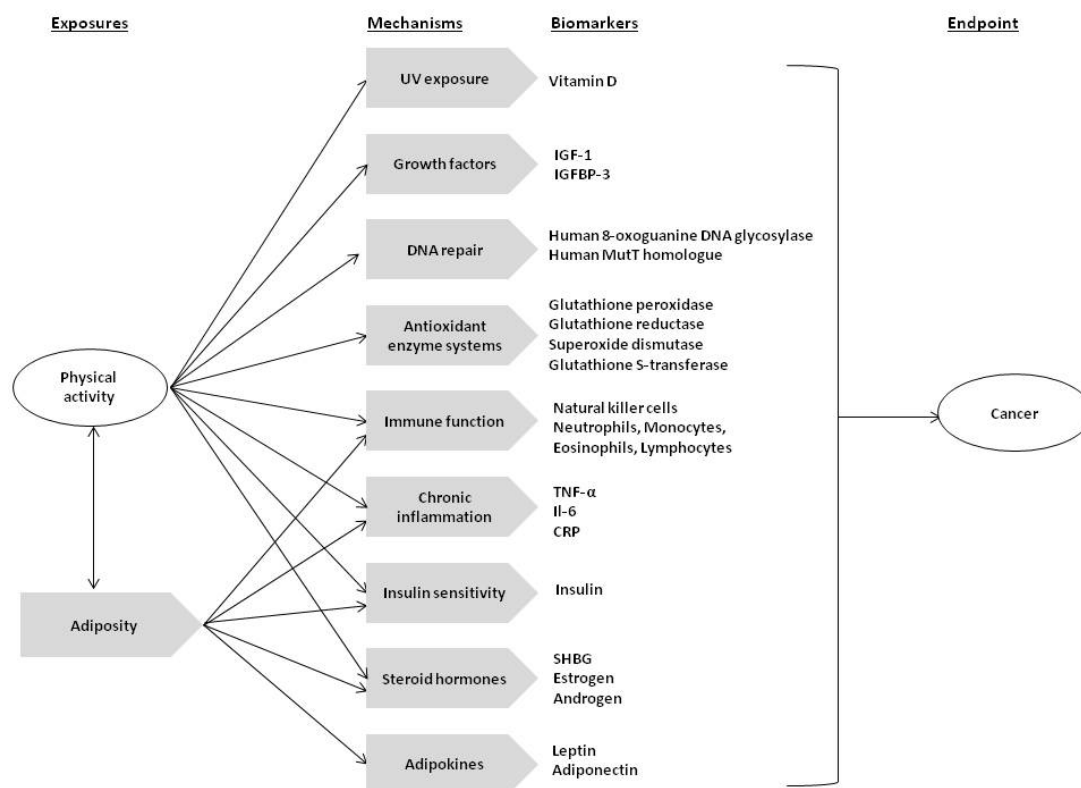


Figure 1: Hypothesized biologic mechanisms of physical activity on cancer risk (modified from (12)); IGF-1, insulin-like growth factor, IGFBP-3, insulin-like growth factor-binding protein-3; TNF- α , tumor necrosis factor- α ; IL-6, interleukin-6; CRP, C-reactive protein, SHBG, sex hormone binding globulin.

duce intestinal transit time, and increase vitamin D levels resulting from enhanced UV exposure while engaging in outdoor exercise (11, 13, 19) (Fig. 1).

PHYSICAL ACTIVITY AND BREAST CANCER

There is compelling epidemiologic evidence for an inverse association between physical activity and breast cancer. Lynch et al. reviewed 73 observational studies on physical activity and breast cancer and found a 25% breast cancer risk reduction with high versus low physical activity (18). An apparent protective effect was seen for physical activity over the lifespan and particularly for physical activity performed after menopause. The decrease in risk was more evident among postmenopausal than premenopausal women (14, 27). Moreover, the apparent beneficial effect of physical activity was greater among those who were normal-weight, non-Caucasian, parous, or those who had no family history of breast cancer (18). Wu et al. reviewed 31 prospective studies on physical activity and risk of breast cancer and reported a significant risk reduction for both occupational and non-occupational activity, and for physical activity of moderate and vigorous intensity (34). Whether risk reductions differ for hormone-receptor positive and negative breast cancer subtypes remains controversial (27). Several biologic pathways have been proposed to mediate the physical activity and breast cancer relation, including alterations in adiposity, sex steroid hormones, insulin sensitivity, chronic inflammation, and immune function (21) (Fig. 1).

PHYSICAL ACTIVITY AND ENDOMETRIAL CANCER

Abundant epidemiologic evidence suggests a preventive role of physical activity for endometrial cancer. A recent review reported a 20% to 30% risk reduction in endometrial cancer risk for women with the highest compared to the lowest physical activity levels (6). Most studies showed evidence for a dose-response relationship. Light and moderate physical activity appears to be sufficient for endometrial cancer risk reduction. The majority of available studies examined recreational or occupational activity and only few studies measured transportation or household activity. No meaningful difference in the association between physical activity and endometrial cancer risk among these different domains was evident. The association appeared to be stronger with recent and lifetime activity than activity performed in the distant past. The physical activity and endometrial cancer relation was not modified by BMI, menopausal status, or hormone replacement therapy. Potential biologic mechanisms linking physical activity to endometrial cancer risk involve sex steroid hormone levels, adiposity, and insulin-mediated pathways (7, 29) (Fig. 1).

PHYSICAL ACTIVITY AND CANCERS OF OTHER SITES

The evidence for a role of physical activity in reducing the risk of cancers of other sites is less clear than that seen for cancers of the colon, breast, and endometrium. In a recent meta-analysis, Sun et al. quantitatively summarized 14 prospective studies on physical activity and lung cancer and found risk reduction with higher levels

of physical activity (28). Emaus and Thune compiled the available evidence from 27 studies and reported a 20% to 30% lung cancer risk reduction for women and a 20% to 50% risk reduction for men with high versus low physical activity levels (8). Risk reduction was predominantly seen for total and recreational activity. The biologic mechanisms by which physical activity may protect against lung cancer include improved immune function, reduced levels of chronic inflammation, enhanced DNA repair capacity, and decreases in IGF-1 levels (3, 24) (Fig. 1). Further, physical activity may decrease lung cancer risk by increasing pulmonary ventilation and perfusion, which may reduce the amount of carcinogens in the lung (4, 15, 25).

O'Rourke et al. addressed the relationship between physical activity and pancreatic cancer in a meta-analysis of 28 studies. The highest versus lowest physical activity levels were associated with a 25% to 30% decrease in pancreatic cancer risk (22). A reduction in pancreatic cancer risk was found for total and occupational activity, whereas no significant relationship was observed with recreational and transportation activity. The authors suggested that one possible biologic mechanism linking increased physical activity to decreased pancreatic cancer risk is a physical activity-mediated reduction in abdominal fat depots leading to enhanced insulin sensitivity (Fig. 1).

Wolin et al. reviewed 16 studies investigating physical activity and gastric cancer (30). Of these, four studies observed a statistically significant risk reduction with higher levels of physical activity. Most studies did not investigate individual domains of physical activity. The average risk reduction in studies that reported an inverse association between physical activity and gastric cancer was approximately 30%.

In a meta-analysis of 19 cohort and 24 case-control studies, Liu et al. found that high versus low total physical activity decreased prostate cancer risk by 10% (17). The apparent protective effect was stronger for occupational than recreational activity. Analyses that were stratified by the timing in life of physical activity showed that physical activity performed during the ages of 20 to 45 years and between the ages of 45 to 60 years was related to a decreased risk of prostate cancer, whereas physical activity performed before age 20 or after age 65 was not. Studies that examined localized and advanced prostate cancers separately found comparable relative risk estimates. Proposed biologic mechanisms that may explain the inverse association between physical activity and prostate cancer include alterations in levels of hormones including insulin, IGF-1, IGFBP-3, and androgens; and improvements in immune function and antioxidant enzyme systems (16, 24) (Fig. 1).

There is only limited evidence for a protective effect of physical activity on ovarian cancer. Cust et al. reported that about half of the 21 available studies suggested a reduction in the risk of ovarian cancer with increased physical activity, whereas the other half showed no association, and one study observed an increased risk (6). The average risk reduction seen in those investigations was less than 10%. Studies regarding different activity intensity levels also showed inconsistent results. Most studies examined recreational activity and only a few studies investigated other physical activity domains, and no consistency in the results have emerged. Investigations that reported on subgroup effects revealed no evidence for effect modification of the physical activity and ovarian cancer relation by BMI, parity, family history of ovarian cancer, or menopausal status.

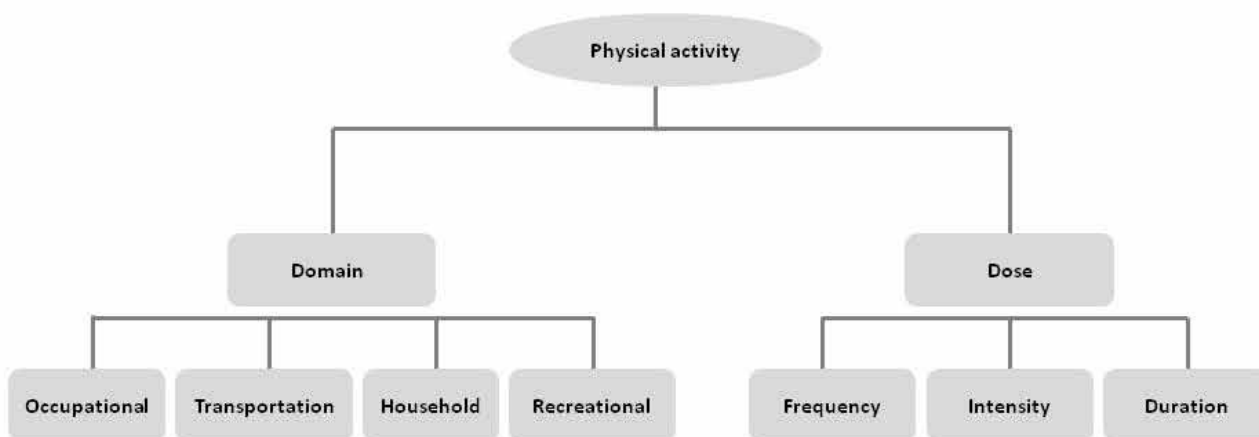


Figure 2: Components of physical activity.

METHODOLOGIC CONSIDERATIONS IN PHYSICAL ACTIVITY AND CANCER RESEARCH

Type of study design

Appropriately conducted case-control studies represent an efficient study design to investigate the relation of physical activity to cancer, but findings from case-control studies must be interpreted in light of the possibility of selection and recall biases. Cohort studies avoid recall bias because physical activity is assessed before the occurrence of the cancer outcome, and they minimize selection bias if follow-up is complete. Intervention studies provide an appropriate study design for investigating causality and underlying biologic mechanisms.

Method of physical activity assessment

In previous cancer investigations, the methods for physical activity measurement have not always been comprehensive and they have varied substantially across studies. In order to provide a complete assessment of physical activity, studies should query the frequency, duration, and intensity of physical activity in different domains including occupation, household, transportation, and recreation (Fig.2). Only a few epidemiologic cancer studies have assessed physical activity using objective measures, such as accelerometers, which bear the potential for providing more precise measurements of physical activity than self-report methods.

Timing in life of physical activity

A limited number of observational cancer studies have attempted to assess physical activity across the lifespan. Thus, for most cancer sites it remains unknown whether physical activity needs to be sustained throughout the life course for cancer risk reduction, or whether physical activity performed at specific time periods in life is most relevant for cancer prevention. Studies that examined physical activity across different time periods in life found that increased recent past physical activity was related to a reduced postmenopausal breast cancer risk, whereas physical activity during adolescence and mid-adulthood was unassociated with risk (23). Hormonal changes during the life course may have distinct effects on carcinogenesis that may differentially affect the association between physical activity and risk of hormone-sensitive cancers.

Confounding

Appropriate control for potential confounding is necessary to validly estimate the independent relation of physical activity to cancer. Dietary and alcohol intakes, BMI, smoking habits, and other health behaviors may confound the association between physical activity and cancer. A poorly measured covariate or inappropriate statistical modeling of a covariate may cause residual confounding, even after adjustment for the confounding variable. Confounding may also exist by different components of physical activity. For example, individuals who participate in vigorous exercise may also likely walk as a means of commuting, the latter of which may represent a confounding effect in an analysis of vigorous physical activity. Thus, appropriate adjustment should be made for the intensities of the activities performed.

Mediation

In studies of physical activity and cancer, mediators are variables that are affected by physical activity and lie on the causal pathway linking physical activity with cancer. Identifying mediators and appropriately interpreting their influence on the physical activity and cancer relation may help unravel the underlying biologic mechanisms. Mediators may also provide answers about which biomarkers are the most predictive of cancer risk and may help clarify direct or indirect consequences of physical activity on cancer development.

Effect modification

An association between physical activity and cancer may be distorted by effect modification, which occurs when a third factor modifies that association. For example, a more pronounced inverse association between physical activity and breast cancer risk was found among postmenopausal than premenopausal women (10). That finding supports the proposed biologic mechanism that hormonal status contributes to breast cancer risk. Thus, detecting and reporting differences in physical activity effects across population subgroups is important to disentangle potential biologic mechanisms.

Reverse causation

Observational studies investigating the association between phy-

sical activity and cancer can be prone to reverse causation, which may occur when preclinical cancer causes reduced physical activity rather than vice versa. Because cancer has a long latency period, the disease itself may cause long-term changes in physical activity, leading to potentially spurious results. Conducting sensitivity analyses by excluding subjects with early diagnosis of cancer during follow-up in a cohort study or excluding individuals with early deaths after diagnosis of cancer in a case-control study may help minimize the potential for reverse causation.

PHYSICAL ACTIVITY RECOMMENDATIONS

Based on the evidence available (Tab.1), enhanced physical activity pursuits should be encouraged for the primary prevention of cancer and should be incorporated in public health intervention programs. In addition, physicians should discuss the potential benefits of increased physical activity for cancer prevention with their patients and encourage them to engage in regular physical activity. According to the current World Health Organization (WHO) guidelines (33), adults should spend at least 150 minutes per week performing moderate intensity aerobic physical activity or engage in at least 75 minutes of vigorous intensity activity per week, or should combine moderate and vigorous intensity activities in an equivalent manner. In addition, muscle-strengthening activities should be performed on at least two days per week and this type of exercise should involve major muscle groups.

FUTURE RESEARCH ISSUES

Physical activity research represents a dynamic process continuously building new knowledge. The following research gaps on physical activity and cancer should be addressed in future studies:

1. The use of objective physical activity assessment tools should be encouraged as those instruments allow more valid and precise assessments of physical activity than self-report instruments.
2. More detailed knowledge is needed regarding which types, intensities, frequencies, and durations of physical activity are necessary to reduce cancer risk.
3. Future cancer studies should collect information on physical activity at different periods in life or throughout the entire life course in order to identify the etiologically relevant time periods of exposure to physical activity that potentially affect cancer risk.
4. Randomized controlled trials that address biologic mechanisms of physical activity and carcinogenesis are needed in order to more clearly define the etiologic pathways underlying the association between physical activity and cancer.
5. Enhanced research on physical fitness and sedentary behavior is required, which may provide additional information about the effects of physical activity on cancer risk.
6. More data on the population attributable risks of physical inactivity within and across societies is essential for health planning with respect to cancer prevention.

Conflicts of interests: *The authors declare that they have no conflict of interest.*

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