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PHYSICAL ACTIVITY AND TYPES OF CANCER

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Abstract – *Objective:* *To investigate the association between physical activity and common cancers.*

Patients and Methods: *This study was conducted in English by June 2018 to include studies reporting physical activity related cancer risks through a search in database of the PubMed, Scopus and Web of Science. The search strategy included the keywords: "cancer", "physical activity" or "mobility" or "inactivity" or "immobility". Articles that looked at the relationship between each type of cancer and PA were entered in to the study and summarized in review.*

Results: *Physical activity is associated with a decreased risk of some types of cancers including: colorectal, breast, esophagus, lung, liver, cervical, endometrial, kidney, brain, and blood cancers. However, further studies are required to confirm the association between PA and prostate, head and neck, stomach, bladder, pancreas, and skin cancer risks.*

Conclusions: *Given that inactivity plays a role in most cancers, it is necessary to develop sports programs through educational strategies and provide programs to increase the community awareness of the benefits of physical activity and participation in regular weekly exercise programs in order to prevent the incidence of various cancers.*

KEYWORDS: *Cancer, Physical activity, Mobility, Inactivity, Immobility.*

INTRODUCTION

Cancer is one of the leading burdens of disease worldwide, with rates of morbidity and mortality that keep rising in the world[1,2]. It is estimated that 12.7 million cases of CA and 6.7 million CA deaths have been occurred in 2008[3]. Cancer is a multifactorial disorder and about 90% of cancers are caused by environmental factors and lifestyle[4-6]. Physical activity (PA) is one of the most important factors associated with lifestyle that can affect the risk of cancer incidence[7]. Physical activity (PA) refers to any movement produced by skeletal muscles that requires more energy than a resting position. PA is divided into four major categories: occupational activity (physical activity at work),

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household (physical activity at home), transportation (activity performed during the journey to work) and recreational or leisure-time physical activities (activities conducted during entertainment or recreation)[8]. PA can vary in intensity, including light, moderate, and vigorous physical activity[9]. Examples of light, moderate and vigorous activities include housework, brisking, and running, respectively[9]. According to the World Health Organization (WHO) report, adults with lower PA levels are exposed to increased risk of all-cause mortality, heart disease, blood pressure [10], stroke, type 2 diabetes, metabolic syndrome, breast cancer and depression. PA also reduces the risk of colon, chest and endometrial cancers[11]. Less known, PA is associated with reduced risk of other cancers, accounting for 75% of cancers in the United States and 61% of the world's cancers[12]. Therefore, the WHO recommended at least 2.5 hours of moderate-intensity PA, 1.25 hours of vigorous-intensity PA, or a combination of moderate and vigorous- intensity aerobic physical activities during the week to reduce the risk of chronic non-communicable diseases (NCDs)[13]. Physical inactivity is a common concern; an estimated 51% of people in the United States and 31% of people in the world are physically inactive [14]. PA is associated with general health and any action in this regard is important to prevent cancer (15). So far, large prospective studies have examined the association between PA and the risk of cancer[16-19]. However, due to the low number of cases, no definitive findings have been reported in most types of cancers. Regarding the fact that there is few epidemiological evidence that has been systematically addressed this issue, we aimed to investigate the association between PA and common cancers of various organs of the body, taking into account the possible confounding variables for each organ based on available evidence and review of the literature.

MATERIALS AND METHODS

This study was conducted in English by June 2018 to include epidemiological evidence from all available randomized control trials, case-control and cohort studies reporting PA related cancer risks through a search in data bases of the PubMed, Scopus and Web of Science. The search strategy included the keywords: "cancer", "physical activity" or "mobility" or "inactivity" or "immobility". In addition, the reference lists of relevant articles were manually searched to find any other potentially eligible articles. Articles about PA intensity and types of PA are also included in the present study. We excluded reviews, commentaries, articles from overlapping samples, conference abstracts, and articles printed in languages other than English. Articles that looked at the relationship between each type of cancer and PA were entered into the study and summarized in review.

RESULTS

Study characteristics

In the initial electronic literature search, 2345 articles were obtained from database and 35 articles were obtained using manual search. After removing duplicates using Endnote X7 (n =1310), the title and abstract of the remaining 1070 articles were reviewed. After this stage, 184 articles were included in the study and 886 of these articles were removed because of scientific reasons and lack of eligible criteria or unrelated to our aim, in all, 170 full papers were reviewed. The most important cancers related to PA are summarized in Table I.

Types of cancer associated with PA

Colorectal cancer (CRC)

The findings of a case-control study in Northern California indicated that PA reduction accompanied by an increased body mass index (BMI) resulted in a significant increased risk for CRC[20]. Results of (CPS-II) also showed that there is a meaningful association between decreased level of physical activity and increased risk of CRC[21]. Findings of another study[22] showed that the risk of CRC in inactive workers was significantly higher than workers with light or vigorous physical activity. Results of a me-

TABLE 1. Relationship between physical activity and Cancer Types.

Cancer Types	*Protective*	*Controversial*
Colorectal cancer	*	
Breast cancer	*	
Endometrial cancer	*	
Prostate cancer		*
Lung Cancer	*	
Head and neck cancer		*
Esophageal adenocarcinoma	*	
Stomach cancer		*
Liver cancer	*	
Bladder cancer		*
Cervical Cancer	*	
Kidney cancer	*	
Pancreatic cancer		*
Brain cancer	*	
Lymphoma	*	
Skin cancer		*

ta-analysis on 52 epidemiological studies indicated that PA reduces 24% of CRC risk in physically active individuals compared to those with lower physical activity[23]. The POOL analysis, which was conducted on study data on recreational PA of 12 cohort studies in Europe and the United States, showed that the risk of CRC is reduced to 16% in those who have the highest levels of PA compared to those who have the lowest levels of PA[24]. Findings from two other studies also indicated that the incidence of distal and proximal colon cancers is lower in those who are physically more active than others[25,26]. PA is also associated with lower risk of colon (polyp) adenoma, a type of colon polyps that can progress to CRC[27]. Physical inactivity can increase the prevalence of obesity, and obesity is another risk factor for CRC[28]. The precise mechanism of PA's protective effect is unclear, but it seems that increased PA is associated with the lower risk of CRC due to reducing BMI, decreasing colonic transit time, and lowering insulin levels[29,30]. In addition, obesity increases serum leptin levels and leptin increases the growth and proliferation of colon cancer cells[25]. The findings of a study showed that men with the highest serum leptin levels are more likely to develop CRC than men with the lowest serum leptin levels[31].

Breast cancer (BC)

Several studies have found that the risk of developing BC in physically active women is lower than inactive women. The findings of a meta-analysis on 31 prospective studies showed that the risk of developing BC in physically active women is 12% lower than other women[32]. PA is associated with a reduction in the risk of BC in both premenopausal and postmenopausal women; nevertheless, this association is stronger in postmenopausal women[33-35]. Findings from two other studies showed that women who received physical activity after menopause had a lower risk of developing BC than those who were inactive[33,35]. Several studies have shown the correlation between PA and the outcomes for patients after BC diagnosis[36,37]. In this regard, cohort study findings indicated that recurrence and mortality rates in women who received a moderate exercise (3-4 hours of walking per week) after BC diagnosis was around 50-40 % less than inactive women[38]. Other cohort studies also found that breast cancer mortality risk was 35-49% lower in women with BC who were engaged in recreational PAs at pace of 2 to 2.9 mph for one hour per week compared to women with BC who had lower PA[39]. Wu et al[40] meta-analysis revealed that breast cancer risk for every 25 MET-hour/week increments in non-occupational activity reduces the risk of BC up to 2% and for every 10 MET-hour/week increments in recreational activities reduces the risk of BC up to 3%[40].

Endometrial cancer (EC)

Several studies have examined the association between PA and EC risk. The findings of a meta-analysis study on 33 studies showed that the risk of EC in women with a high PA level is 20% lower than those with low PA levels[41]. Findings from another meta-analysis of observational studies conducted by Keum et al[42] showed that an increase in PA by 3 MET-hours/week reduces the risk of EC up to 2% and an increase in PA by 1 hour per week reduces the risk of EC up to 5%[42]. There is evidence that the relationship between PA and EC can indicate the effect of PA on obesity, as one of the main risk factors for EC[43-45].

Prostate cancer (PC)

A wide range of older men is affected by prostate cancer and there are few effective preventive measures against this cancer[46]. Findings from a study conducted on males with non-metallic PCs showed that the death risk from PC in patients with vigorous activity is 61% lower than those who exercise less than an hour per week[46].

Findings of another study also indicated that a higher level of physical activity in men with localized PC was associated with a reduction in prostate cancer mortality rate and the overall mortality rate[47]. Based on the results of a systematic study in 2017, PA was one of the key measures in relapsing disease and improving survivors after the diagnosis and treatment of prostate cancer[46]. Potential mechanisms associated with benefits of regular exercise are: preventing obesity, boosting the immune system by increasing natural killer cells and, lowering testosterone levels[48,49]. A systematic review conducted by Friedenreich et al[50] on 24 studies found that in 14 studies there was an inverse association between PA and prostate cancer risk; however, according to 6 studies, PA has no effect on the risk of prostate cancer, and in four studies, there is a direct association between PA and prostate cancer risk. Other systematic findings from 13 cohort studies and 11 case-control studies reported controversial findings[51]. Therefore, further studies are required in this regard.

Lung Cancer (LC)

The findings of a meta-analysis of 28 studies showed that there is an inverse relationship between recreational PA and LC (RR, 0.76; 95% Confidence Interval (CI), 0.69-0.90)[52]. Findings of another meta-analysis study also indicated that higher levels of physical activity are linked to lower risks of LC[53]. The findings of the cohort study on older women showed that, after matching confounding variables, women with high PA levels were less likely to be affected by LC than women with low PA levels.

The hazard ratio was 0.77; 95% confidence intervals (CI), 0.64-0.94][54]. Several possible mechanisms have been used to explain reducing the risk of LC due to PA[55-57]. For example, PA improves pulmonary function, which can reduce the air concentration of carcinogenic agents, reduce the duration of the interaction of carcinogenic with the airways, and reduce the amount of deposited carcinogenic particles in the airways [54,57,58]. The effect of smoking on lung cancer is unavoidable, smoking causes chronic cough, increased sputum production, bronchitis and ultimately reduced lung function, which can lead to a decrease in person's desire for physical activity, and this way, it increases the chance of lung cancer[59,60]. On the other hand, the heart rate of smokers is two to three times higher than that of non-smokers; therefore, during exercise, smokers should be harder to work than non-smokers, which reduces smokers' tendency for physical activity[61,62].

Upper aerodigestive tract (UADT)

UADT cancers are including: oral, thoracic, hypopharyngeal, laryngeal, esophagus, nasal cavity, nasal sinus, pharyngeal and adenocarcinoma of the esophagus [63,64].

Head and neck cancer

Prospective study findings on 487732 U.S. men and women over the past 8 years showed that, PA inevitably plays an important role in preventing head and neck cancers[65]. The findings of a clinical trial showed that maintaining physical activity during chemotherapy treatment in patients with head and neck cancer, in the intervention group compared to the control group, has significantly improved the mobility, diet, function, and quality of life of the patient[66]. However, findings of other studies[67] showed no association between PA protective effect on the incidence of head and neck cancer. Therefore, further studies are needed.

Esophageal adenocarcinoma (EAC)

Findings of a meta-analysis of 9 case-control and cohort studies showed that the risk of EAC in physically active subjects was 29% lower compared to least physically active subjects (OR, 0.71, 95% CI: 0.57-0.89)[68]. Findings of several studies[69,70] showed that there is a significant inverse association between PA and EAC. Researches also reported a reverse and significant correlation between PA and Esophageal squamous cell carcinoma (ESCC). One of the potential mechanisms for the association between PA and EAC is obesity due to immobility. The first reports[71,72] about the possible relationship between obesity and EAC were published in the 1990s. This finding was confirmed in studies of large populations, case studies in the United States, Europe and Australia, which indicate a strong association between elevated BMI and increased risk of EAC [73,74]. Findings from epidemiological studies indicate that obesity is one of the main causes of EAC[75,76]. One of the major risk factors for EAC is gastro-esophageal reflux (GER), and obese people experience GER symptoms repeatedly[75]. Two main mechanisms for the development of AC in obese patients are proposed. First, the physical mechanism involves an increase in the incidence of GERD, and the second is the hormone dependent mechanism, mainly due to inflammatory markers secreted by moderated adipocytes[77]. Other possible mechanisms that can explain the role of PA in reducing UADT are metabolic syndrome and insulin resistance, which are associated with an increased risk of CA, especially EAC[59,78]. Exercise is effective in reducing visceral fat, reducing the level of carcinogenic adipocytokines, improving insulin sensitivity, lowering blood sugar levels in the morning and C-peptide levels, and decreasing insulin-like growth factor-1[79]. PA also reduces chronic inflammation and IL-6 and TNFα factor independent of weight loss in clinical trials[80]. PA also affects the immune system and enhances acquired and inherent immune responses[79,81]. Studies have shown that aerobic exercise reduces oxidative stress, enhances DNA repair mechanisms, and reduces carcinogenesis[8]. Individuals who exercise will be exposed to more sunlight, which can increase the level of vitamin D. Vitamin D causes to replenish cell proliferation cascades[82].

Stomach cancer (SC)

The findings of a case-control study that evaluated the association between PA and the incidence of SC showed that Strenuous PA increase during the life-cycle was associated with a decrease in SC incidence[38]. Findings of another study indicated that physical inactivity at work was associated with increased risk of SC in men (OR: 1.4; 95% CI: 0.9-2.2)[83]. According to another study[84], the average work physical activity index was related to cardia (OR: 0.76; 95% CI: 0.49-1.18) and non-cardia stomach cancer (OR: 0.77; 95% CI: 0.52-1.14). Another study reported that there was no association between Career PA and SC risk[85], and previous evidence of association between PA and SC is inconsistent. The findings of the cohort study on British men also showed that despite the association between PA and SC, this relationship was not significant[86]. The findings of a meta-analysis of 7 cohort and 4 case-control studies showed that a very small correlation was observed between adequate PA and stomach cancer (SC) risk (relative risk: 0.81 (95% CI 0.69 to 0.96) in cohort studies and (relative risk: 0.78 (95% CI 0.66 to 0.91); I2 = 0%) in case-control studies[87]. Therefore, PA cannot be considered as a definitive protective factor against SC risk.

Liver cancer (LC)

The findings of a meta-analysis study that investigated the association between PA in leisure-time and the incidence of various cancers showed that high PA levels lead to reduced LC compared to low PA levels (HR = 0.73, CI: 0.55-0.98). Cohort study findings in Japan also reported a significant relationship between the level of physical activity in daily life and LC in both genders[88]. Results of another cohort study on 444963 men, older than 40 years, indicated that PA has a protective effect on liver cancer[89]. The 10-year cohort study also found that PA has a potentially preventative effect on LC risk[90].

Bladder cancer

Findings of a meta-analysis and systematic study of 15 studies with 5402369 subjects and 27784 bladder cancer cases showed that high levels of PA compared with low levels of PA reduced the risk of bladder cancer (Relative Risk (RR) = 0.85, 95% confidence interval CI = 0.74-0.98). PA can indirectly contribute to bladder cancer by reducing obesity and helping to maintain body weight[91]. In this regard, Qin et al[92] also showed that obesity is one of the risk factors for BC, and vice versa, PA is a protective agent against bladder cancer[92]. Potential mechanisms for linking PA and reducing BC increased immune function, reduced chronic inflammation, increased detoxification of carcinogens and apoptosis[93]. The findings of the systematic review on 11 studies (8 cohort studies and 3 case-control studies) showed that in one of the positive relationship studies, seven studies reported non-association and three studies reported a reverse relationship between PA and bladder cancer[94]. So there is a need for further research in this regard.

Cervical Cancer (CC)

Few studies have investigated the relationship between PA and CC. Cohort study findings of 1979 American Indian women showed that 60% of women who had physical activity participated in Pap smear screening tests, which can lead to early detection and prevention of CC proliferation[95]. The findings of a case-control study that investigated the effect of immobility on the risk of CC showed that physically inactive women were two-and-a-half times more likely to develop CC compared to physically active women[96].

Kidney cancer (KC)

Based on the findings of the systematic and meta-analysis study performed by Behrens et al[97], the increase in PA level leads to a decrease in KC in comparison with the low PA level (REL) = 0.88 confidence interval (CI) = 0.79-0.97)[97]. Behrens et al[97] also reported that PA has a protective effect on the prevention of KC due to contributing to reduce the obesity. PA can also be effective through other mechanisms, including the reduction in lipid peroxidation[98]. In total, a few studies have reported an inverse association between PA and kidney cancer[99]. The findings of a descriptive study on the baseline data from the U.S. National Institutes of Health from 1998 to 2006 showed that mortality rates from KC in individuals, who had physical activity, were 50% less than physical inactive individuals (adjusted hazard ratio (adjusted HR) 0.50, 95% CI 0.27-0.93, p = 0.028))[100]. Findings from several prospective studies also showed that the incidence of kidney cancer and obesity are directly associated with each other, and any factor that leads to weight loss acts as a protective agent against KC[101-103].

Pancreatic cancer (PC)

The findings of a meta-analysis study indicated that PA has been associated with a lower risk of PC[104]. Findings of another research[105] showed that there was no correlation between PA and PC in individuals with normal weight, but an inverse relationship was observed in obese individuals. Findings of a systematic review of 19 studies in 2008 showed that there is no significant relationship between total physical activity and risk of PC. The risk of PC is reduced by increasing PA at work, but it is not associated with PA at leisure-time. No clear association was identified between having a light, moderate or vigorous PA and pancreatic cancer development. Also, Behrens et al[97] in a meta-analysis and systematic study in 2014, showed that PA has no strong relationship with the risk of PC. Therefore, the need for further studies with a stronger methodology is felt in this regard.

Brain cancer (BC)

Few studies have been conducted to investigate the effect of PA on health-related outcomes in Brain cancer patients. The findings of a systematic study showed that there are strong causes of the effect that sport exercises are effective interventions in the management of symptoms and the treatment of side effects in patients with brain cancer[106]. The clinical trial findings for children with brain tumors also showed that exercise improves physical performance and fitness in children with brain tumors[107]. Exercise increases the production of testosterone in men and women; testosterone is a strong anabolic hormone with significant non-genomic effects on the nervous system, including depression and anxiety[108-110]. Findings from multiple studies showed that PA exercises relieve psychological distress by maintaining physical abilities and functional autonomy and improving self-efficacy[106,111]. Exercise improves the function and structure of the brain by stimulating neurogenesis neural plasticity and up-regulating growth factors including brain-derived neurotropic factor, reducing the level of endogenous corticosteroids and pro-inflammatory cytokines, reducing oxidative stress, maintaining brain volume, improving blood flow, increasing blood circulation in the entire central nervous system, and increasing the level of hormones affect the function and structure of the brain [112-114].

Lymphoma

Hematopoietic lymphoma is a type of malignant lymphoid tissue that varies in clinical and biological characteristics[115]. Lymphoma consists of two major types of Hodgkin's Lymphoma (HL) and non-Hodgkin's lymphoma (NHL)[116]. Findings of a case-control study among women aged 19 to 79 years showed that a strenuous PA and membership in sports teams caused a significant decrease in HL in young adults[117]. Findings of a cohort study on college graduates also revealed that varsity sports last for more than 5 hours per week in college during the follow-up period reduces the risk of HL (age- and sex-adjusted risk ratio, 0.73; $p = 0.34$). However, this study was unable to investigate the potential social class confounding characteristics or the level of physical activity in later life that could be associated with the risk of HL[118]. One of the potential mechanisms associated with reducing HL in individuals with PA is the increase in the activity of natural killer cells (TNFα)[50,119,120] or decreased inflammation[121]. PA also reduces bioavailability of insulin and insulin-like growth factors[122,123], which stimulates cellular turnover in most tissues of the body and inhibits cell death or endogenous sex hormone levels, which may affect the pathogenesis of HL indirectly and through influence on immune function[79]. A few studies have examined the relationship between PA and NHL risk. Results from a case-control study between 2004 and 2005 in Canada indicated that vigorous PA during the life course was negatively correlated with NHL risk. Participants who had vigorous-intensity physical activity in their second, third and fourth decade of their life were approximately 25-30% less likely to be at risk of NHL than others [adjusted odds ratios, 0.69 (95% confidence interval [CI], 0.52-0.93); 0.68 (95% CI, 0.50-0.92); and 0.75 (95% CI, 0.55-1.01), respectively][124]. The findings of two meta-analysis studies showed that individuals with the highest levels of PA had a much lower risk of developing NHL than those with the lowest levels of PA[125,126]. Among the possible mechanisms for explaining this relationship, we can point out the effect of PA on weight loss and increased immune function, both cases assume to play an important role in the development of NHL[125]. PA also affects the risk of NHL by reducing inflammation, improving insulin sensitivity, and improving antioxidant defense system[127]. Researchers have shown that PA intensity and time can also affect cancer[128-130], but few studies have examined this issue in relation to NHL risk[125,126]. Etter et al[131] investigated the relationship between physical inactivity during the life and the risk of HL and NHL in a case-control study. The findings of this study showed a significant positive correlation between physical inactivity during the life course and the risk of HL (OR = 1.90, 95% CI: 1.15-3.15) and NHL (OR = 1.35; 95% CI: 1.01- 1.82)[131].

Skin cancer

Study findings on animal models showed that PA reduces the incidence of skin tumors and reduces the formation of skin tumors[132]. One of the biological mechanisms for reducing this risk is the induction of epidermal induced apoptosis tumors through UBV. Fat cells can secrete substances that prevent apoptosis, thus reducing the amount of fat through diet or exercise can also prevent carcinogenesis[133]. However, retrospective cohort study findings in patients undergoing kidney, liver, and pancreas transplantation showed that PA had no significant effect on the risk of Non Melanoma Skin Cancer (NMSC) in these patients. Based on the literature, limited studies have been conducted in this issue, so clinical trials and population-based studies to determine the impact of exercise on reducing the risk of NMSC in the general population are needed. This finding can be due to other factors such as the type of skin (which is a strong predictor of cancer) and the level of immunosuppression, which is the most important factor affecting the risk of skin cancer in this group. But skin cancer may have more effects on the risk of skin cancer is in the general population[134]. Prospective study findings on 1171 adults showed that 98 men and 90 women suffered from newly diagnosed SCCs during a 16-year follow-up period. In this study, there was a significant inverse correlation between PA at work and SCC expansion in women. In total, the findings of this study showed that, after controlling potential confounding factors including exposure to sunlight, there was no significant correlation between recreational activities and the incidence of SCC in men and women[135]. The findings of a prospective study in Denmark also showed that there was a significant positive correlation between leisure-time physical activity and keratinocytic skin cancers in most men, but, no correlation was observed in women[136]. Schnohr et al[136] concluded that gender differences in the incidence of this cancer can result from men's more outdoor exercises, less wear, and less use of sunscreens than women[136]. Findings from two other studies investigating the incidence of melanoma or keratinocytic cancer in women with high physical activity over the life course showed a similar rate in both groups. In one of the studies conducted on graduate students in America, a significant difference was observed between the incidence of keratinocyte cancers and melanoma among former college athletes and non-athletes[137]. Another study in Finland, investigating the association between physical activity during the life course and the risk of cancer in female teachers during the follow-up period 1967-91, indicated that physical education teachers had a 2-fold higher standardized incidence ratio of melanoma compared to the language teachers[138]. Both of these studies mentioned the lack of adjustment in terms of exposure to sunlight or other potential confounders. Therefore, further studies are needed in this regard after controlling the confounding variables.

CONCLUSIONS

The purpose of this review study was to investigate the association between PA and common cancers. Based on the results, PA is associated with a decreased risk of some types of cancers including: colorectal, breast, esophagus, lung, liver, cervical, endometrial, kidney, brain, and blood cancers. However, further studies are required to confirm the association between PA and prostate, head and neck, stomach, bladder, pancreas, and skin cancer risks. Given that inactivity plays a role in most of cancers, it is necessary to develop sports programs through educational strategies and provide programs to increase the community awareness of the benefits of physical activity and participation in regular weekly exercise programs in order to prevent the incidence of various cancers. Global recommendations on physical activity for health in different age grope provided by WHO available at https://www.who.int/dietphysicalactivity/factsheet_recommendations/en/

Conflict of Interest:

The authors declare no conflict of interest.

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