REVIEW

Physical Activity and its Relation to Cancer Risk: Updating the Evidence

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Abstract

Abstract: Scientific evidence for the primary prevention of cancer caused by physical activity of regular moderate-intensity or greater is rapidly accumulating in this field. About 300 epidemiologic studies on the association between physical activity and cancer risk have been conducted worldwide. The objectives of this paper were three-fold: (*i*) to describe briefly the components of physical activity and its quantification; (*ii*) to summarize the most important conclusions available from comprehensive reports, and reviews of the epidemiologic individual and intervention studies on a role physical activity in cancer prevention; (*iii*) to present proposed biological mechanisms accounting for effects of activity on cancer risk. The evidence of causal linked physical activity and cancer risk is found to be strong for colon cancer - convincing; weaker for postmenopausal breast and endometrium cancers - probable; and limited suggestive for premenopausal breast, lung, prostate, ovary, gastric and pancreatic cancers. The average risk reductions were reported to be 20-30%. The protective effects of physical activity on cancer risk are hypothesized to be through multiple interrelated pathways: decrease in adiposity, decrease in sexual and metabolic hormones, changes in biomarkers and insulin resistance, improvement of immune function, and reduction of inflammation. As there are several gaps in the literature for associations between activity and cancer risk, additional studies are needed. Future research should include studies dealing with limitations in precise estimates of physical activity and of a lack of consensus on what defines sedentary behavior of individuals and those linked with the proposed biomarkers to cancer risk and controlled exercise intervention trials.

Keywords: Cancer - physical activity - prevention - epidemiology - review

Asian Pac J Cancer Prev, **14 (7)**, 3993-4003

Introduction

The past two decades of the epidemiological studies have produced a large amount of evidence on the benefits of moderate to vigorous physical activity in relation to risk of cancer at several organs and other chronic diseases. It is assessed that over one third of cancers deaths and about 80% of heart diseases, stroke and type-2 diabetes could be prevented by elimination of behavioural risk factors such as physical inactivity, unhealthy diet, tobacco smoking and alcohol use (WHO, 2002; 2008). Only 5-10% of cancer is described to genetic susceptibility (IARC, 2002), the remaining are due to environmental (Kruk and Aboul-Enein, 2006) and lifestyle factors (Czene et al., 2002, Kruk and Aboul-Enein, 2007; Moore and Sobue, 2010). Cancer is a leading cause of disease worldwide. According to the International Agency for Research on Cancer GLOBOCAN database, 12.7 million new cancer causes occurred in 2008, excluding non-melanoma skin cancer, was estimated (Ferlay et al., 2010). Cancer was also estimated to account for 7.6 million deaths worldwide in 2008, i.e. around 14% of all deaths. According to WHO estimates the percentage of all deaths due to cancer varied 4-fold across the regions of the world: 5% in Africa, 9% in South-Eastern Asia, 20% in Americas and Europe, and 21% in Western Pacific. It is undoubtedly that physical activity, health and quality of life are strongly correlated. The cancer statistics data for an individual developing cancer in the United States for 2009 estimates that the likelihood is 44% for men and 37% for women (Jemal et al., 2009) though these data may be overestimated. Therefore, from a public health perspective, there is a need to estimate the cancer burden attributable to physical inactivity. Physical inactivity is a seriously groving among individuals worldwide. Stevens et al. (2009) maintains that "physical inactivity is one of the most important public health problem of the 21st century, and may even the most important". To date, findings of the preventive action of

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physical activity against cancer development are most conclusive for colon and postmenopausal breast cancers. Despite that interest in an impact of physical activity on cancer risk began in the early 1980s and a large number of the literature data has been provided, there is still several uncertainties and open questions. Among them are: the consistency, the strength and dose-response of physical activity-cancer relations, duration and frequency of activity, intensity of activity, how different types of activity influence the risk, and timing of activity over lifetime. This paper describes briefly the components of physical activity and its quantification, and summarizes the most important conclusions available from comprehensive reports, reviews of the epidemiologic individual studies, as well as intervention studies on a role of physical activity in cancer prevention. We also briefly present the possible biological mechanisms accounting for effects of physical activity on the carcinogenesis process.

Types and Determinants of Physical Activity

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure by Caspersen et al. (1985). A commonly used the simplest categorization of physical activity, considered in epidemiological studies, identifies the activities at leisure-time (recreational physical activity); household activity, transport activity (traveling to and from work), and occupational activity. Recreational physical activity includes sports, conditioning exercise and other activities. For a complete analysis how different types of physical activity influences cancer risk all its components: i.e. duration, frequency, and intensity in all domains need to be determined. A combination of the duration and intensity of physical activity is a measure of the total amount of energy that individual uses engaging in a particular activity (WCRF/AICR, 2007). A quantitative measures of physical activity energy expenditure dose is the most frequently measured using metabolic equivalent scoring (MET) (Ainsworth et al., 1993; 2000) of the Compendium of Physical Activities that groups physical activities by purpose. The kilojoules (kcalories) energy cost of an activity is calculated by multiplication of the kJ (kcal) expended during rest by the MET values listed in the Compendium (Ainsworth et al., 2000). A MET score is defined as the ratio of associated metabolic rate for the specific activity compared to a standard resting metabolic rate of 1.0. The MET score of 1.0, considered as the reference, is equivalent to quiet sitting which for the average adult is approximately equals to 4.184kJ•kg^{-1} body weight•h^{-1} (1kcal•kg^{-1} body weight•h^{-1}). One MET is equal to approximately 3.5ml of oxygen•kg body weight^{-1}•min^{-1}. All other physical activities are multiples of the resting MET level. For example, a 3METs activity requires three times the metabolic energy expenditure of quiet sitting. Physical activities listed in the Compendium range from 0.9MET for sleeping to 18METs for running at 10.9miles per hour. For example, an individual who shows home activities at a 3.5MET value (walking-shopping) for 1 hour, 2 days per weeks and stands at work MET=2.5 (store clerk) for 2.5 hours, 5 days per week would accumulate a total of 38.25MET-hrs per week (3.5METs•1 hour•2 days/week+2.5METs•2.5 hours•5 days/week). By multiplying the body weight by this METs we may calculate a kJ energy expenditure specific to an individuals body weight. For example, a 60 kg individual walking at a 2.5MET score for 30 min expends the following 2.5METs×60kg ×30 min/60min=75kcal (313.5kJ), whereas for an 70kg individual an energy expenditure is 87.5kcal (365.7kJ). The estimates of energy expenditure when weight was included strongly reflect body weight. It is noteworthy that absolute energy costs of any particular activity depend on an individual basal energy expenditure, age, sex, size, skill and level of fitness (WCRF/AICR, 2007). The MET scores in the Compendium were calculated considering of healthy 40 year old males with the average body mass of 70 kg, and may not correspond to absolute energy expenditure for females (Byrne et al., 2005). However, MET-scores are valid and useful when the relative energy expenditure is compared within populations (Ainsworth et al., 1993; Friedenreich et al., 1998).

The energy requirements of healthy adults are determined by their habitual physical activity levels (PALs). PAL is defined as a person's total energy expenditure (TEE) in a 24-hour period to his or her basal metabolic rate (BMR) (FAO, 2003; FAO/WHO/UNU, 2004). PAL is defined for a non-pregnant, non-lactating adult. TEE is the average amount of energy spent in a 24-hour period by an individual or a group of individuals. BMR is the minimal rate of energy expenditure compatible with life. This term is estimated in the supine position under standard conditions of rest, fasting, immobility, thermoneutrality and mental relaxation (James and Schofield, 1990; FAO, 2003). A PAL of <1.40 corresponds to extremely inactive persons (e.g. Cerebral Palsy patients); PAL 1.40-1.69 - to the sedentary lifestyle (e.g. office worker engaging in little or no exercise); PAL 1.70-1.99 - to moderately active persons (e.g. person running one hour daily), PAL 2.00-2.40- to vigorously active (e.g. person swimming two hours daily), and PAL >2.40 - to extremely active (e.g. competitive cyclist). A desirable PAL for health is advocated to be 1.7, but in the high-income countries the average is accounted for about 20-30% of TEE in the first decade of 21st century (e.g. 1.4 in UK) (FAO/WHO/UNU, 2004; WCRF/AICR, 2007). Using MET-scores, the intensity of physical activity is often stratified into four levels (Norton et al., 2010): *i*) *Sedentary* (MET score 1.0-<1.6) (or inactivity) involves sitting or lying and no noticeable effort: heart and breathing are not raised perceptibly above resting level (requires <40% maximum heart rate). *ii*) *Light* (MET score 1.6-<3.0) – physical activity has only minor effects on breathing and heart rate, requires from 40 to <55% maximum heart rate, and its intensity may last for at least 60 minutes. *iii*) *Moderate* (MET score 3.0-<6.0) – physical activity that increases maximum heart rate from 55-<70% and its intensity may last between 30 and 60 minutes. *iv*) *Vigorous* (MET score ≥6.0): physical activity which increases heart and breathing rates up to 70-<90% of their maximum (i.e. the point at which anaerobic metabolism is needed to provide energy) (WCRF/AICR, 2007); its intensity may last up to about 30 min.

Recommended Dose of Physical Activity for Health Benefits and the Prevention Against Cancer

It is obvious that physical activity is essential in the prevention of civilization diseases. Clear estimates of the optimal frequency, intensity and duration of exercise are important for public health strategies. According to the Second Expert Report (WCRF/AICR, 2007) the scientific evidence shows that for adults "engage in at least 30 minutes of moderate to vigorous physical activity, in addition to usual activities, on 5 or more days of the week" by adults may reduce not only the risk of certain cancers, heart diseases and diabetes, but also provides other important health benefits (ACS, 2008). Forty five to 60 minutes of intentional physical activity is preferable. For breast cancer risk the greatest reduction was observed among women who engaged in 7 or more hours of moderate to vigorous activity weekly. In addition, physical activity improves survival of patients with cancer; the preventive effect was seen among survivors who performed walking 1 or more hours weekly being the greatest among those who performed exercise for 3-5 hours weekly (Warburton et al., 2006). It is also important to note that there is a dose response relation between physical activity and cardiovascular – related morbidity and mortality and premature death (death before the age of 75) from any cause [for review and the extensive discussion the review by Warburton et al. (2007) is illustrative].

Current review of the evidence for Canada's physical activity guidelines for adults (Warburton et al., 2010) supports the evidence that 30 min or more daily of moderate to vigorous exercise on most days of the week is associated with a reduced risk of colon and breast cancer. Given that an energy expenditure can be generated by performing, e.g. moderate-intensity activity for a long duration or vigorous physical activity for a shorter duration, it seems appropriate to consider the current recommendations for general health and those for protective effect on cancer risk, separately. The recently published guidelines dealing with the amount and intensity of physical activity needed for good health recommends at least 30 min a week of moderate-intensity on 5 or more days weekly or at least 25 min vigorous-intensity aerobic physical activity on 5 or more days weekly (Miles, 2008; Bull and Groups, 2010; WHO, 2010). Examples of exercise and leisure activity are: leisurely bicycling, canoeing (moderate-intensity activities); fast bicycling, jogging, jumping rope (vigorous-intensity activities). Examples of sports are: downhill skiing, badminton (moderate intensity); single tennis, cross-country skiing (vigorous intensity). Scientific evidence indicates that these three types of physical activity may have different physiological effects (Janssen and Ross, 2012). The general recommendations for the primary prevention cancer risk advice moderate, vigorous or moderate-vigorous intensity as appropriate to prevent cancer. Light-intensity requires further studies to determine if can also protect against cancer (Kushi et al., 2006). It is important to underline that recommendations of the international fight against cancer for individual, beside adoption of a physically active lifestyle, include maintaining a healthy weight, throughout life by balance caloric intake with energy expenditure (metabolism, physical activity) and avoidance of weight gain during lifetime. A healthy diet with an emphasis on plant products (e.g. intake of vegetables and fruits for 5 or more times daily, limitation of consumption of processed and red meats), and limitation of consumption of alcoholic beverages by people who drink alcohol to no more than 2 drinks daily (men) and 1 drink per day (women) are recommended (Kushi et al., 2006; ACS, 2008).

Evidence for the Protective Effect of Physical Activity on Different Types of Cancer

Among men, cancers of prostate (241740, 29%), lung and bronchus (116470, 14%), colon and rectum (73420, 9%) and pancreas (22090, 3%) accounted about half of the estimated new cancer cases in USA in 2012. Among women, the most commonly diagnosed types of cancer in 2012 breast (226870, 29%); lung and bronchus (109690, 14%); colon and rectum (70040, 9%); ovary (22280, 3%), and pancreas (21830, 3%) will account for about half of all newly diagnosed cancers (Siegel et al., 2012). Extensive research has been carried out in the area of physical activity - cancer relation. Numerous reviews of epidemiological and randomized controlled trials have confirmed an inverse relationship between physical activity and the incidence of cancer. The supporting evidence of the protective effect of physical activity in the primary prevention of cancer at specific cancer sites are summarized in Table 1. The level of scientific evidence for the relationship between physical activity and cancer, developed and used in the World Cancer Research Fund and American Institute for Cancer Research report on diet and cancer prevention, according to the Second Panel judgments (WCRF/AICR, 2007) was categorized in 5 – degree scale: *convincing*, *probable*, *limited suggestive*, *limited – not conclusion*, *substantial effect on risk unlikely*. The evidence that physical activity protects against colon and colorectal cancers at all ages is *convincing*, physical activity probably protect against breast cancer diagnosed postmenopause and endometrium. There is *limited*

Table 1. Summary of Evidence for the Prevention of Cancer by Physical Activity

Cancer Site	Average Risk Reduction	Level of Scientific Evidence**	No. of Studies
Colon	20-25%	*Convincing*	>60
Breast (postmenopause)	20-30%	*Probably*	>76
Endometrium	20-30%	*Probably*	>20
Breast (postmenopause)	27%	*Limited suggestive*	>33
Prostate	10-20%	*Limited suggestive*	>20
Lung	20-40%	*Limited suggestive*	>20
Ovary	10-20%	*Limited suggestive*	>20
Pancreatic	40-50%	*Limited suggestive*	>20
Gastric	30%	*Limited suggestive*	>15

*Sources: Data summarized from: Friedenreich et al. (2004); Tardon et al. (2005); Miles, 2007; Olsen et al. (2007); Voskuil et al. (2007); WCRF/AICR (2007)**; Gierach et al. (2009); Harriss et al. (2009); Leitzmann et al. (2009b); Wolin et al. (2009); Bernstein et al. (2010); Friedenreich et al. (2010a); Lynch et al. (2011); Speck et al. (2011); Loprinzi et al. (2012)

evidence showing that physical activity protects against breast cancer diagnosed premenopause. The evidence that physical activity protects against prostate, lung, ovary, gastric and pancreas cancers is *limited suggestive*. According to the Panel judgments, there is the strongest evidence (*convincing* and *probable*) that all types of physical activity protect against cancers of the colon, and also of the breast (postmenopause) and endometrium.

Colon cancer

Colon and rectum cancer is the 3rd common cancer occurred worldwide in 2008 (1.2 million, 9.7% of the total for men and women) and the 4th cause of death (0.61 million, 8.1% of all sites for men and women) (Ferlay et al., 2010). Observational findings from cohort and case-control studies showed that both men and women engaging in aerobic physical activity of moderate or vigorous intensity for 3-4 hours per week have on average a 30% reduction in colon cancer risk compared with those who exercised no more than 30 minutes per week, however relationship is stronger in men than women (Speck et al., 2011). The risk reductions were observed among individuals who undertook recreational or occupational physical activity of moderate-vigorous level. For higher levels of activity evidence for a dose-response effect was detected (Harriss et al., 2009; Wolin et al., 2009). Trends of decreasing colon cancer risk have been observed with both increasing amounts and increasing intensities of activity. It is worthy to add that physical activity is effective in reduction of colon cancer risk even in the individuals who intake high levels of energy, have a high body mass index, or a high glycaemic index (Miles, 2007). In addition, the association between physical activity and the risk of colon cancer may vary across population sub-groups, race/ethnicity, tumour type, dietary intake, and hormone replacement therapy use (HRT) (Friedenreich et al., 2010a). For example, the California Teachers Study (Mai et al., 2007) found that premenopausal women who exercised at least 4 hours weekly had lowered risk of colon by 25% versus those who exercised 30 minutes weekly. In turn, postmenopausal women who had never used HRT and had averaged at least 4 hours exercise weekly had the risk 45% lower. Mai et al. (2007) also reported that women who had used HRT had no benefit from exercise, but, they experienced benefit comparable to 4 hours of activity weekly from having used HRT. Much of the evidence summarized colon and rectal cancer together as *colorectal* cancer. The Second Panel judged that the evidence for the prevention is weaker for rectum than for colon cancer (WCRF/AICR, 2007). More than 50% of the studies on the physical activity – rectal cancer risk have found no significant relationships (Spence et al., 2009; Speck et al., 2011).

Overall, the evidence for a role for physical activity in colon cancer prevention in populations in USA, Asia and Europe is consistent, although the amount of physical activity needed to reduce risk is not determined, due to the variety of methods applied to determine physical activity. It is obvious that higher intensity of activity or physical activity performed over a long period of time provided the strongest decrease in colon cancer risk. In contrast, sedentary behavior may be considered as independent predictor of colon cancer risk (Howard et al., 2008). The authors published results from the NIH-AARP Diet and Health Study cohort that shows that men who spend at least 9 hours daily watching television had 56% greater risk of colon cancer compared with those who spent less than 3 hours daily.

Breast cancer

Breast cancer is the most frequently diagnosed cancer among women worldwide, accounting for 1383500 of the total new cancer cases and 458400 of the total cancer deaths in 2008 (Jemal et al., 2011). Fifty percentage of the cases and 27.4% deaths occurred in developed countries. For example, in 2011, 230480 new cases of invasive breast cancer and 57650 cases of in situ breast cancer among women were expected. In addition, about 2140 cases among men, i.e. about 1% of all breast cancers. Breast cancer known as a hormone-related cancer is associated with a greater lifetime exposure to estrogens (Miles, 2007). However, the development of breast cancer is considered as a multifactorial process. Epidemiologic finding, laboratory animal and clinical studies have recognized risk factors that increase the likelihood of breast cancer developing, such as older age, biopsy – confirmed atypical hyperplasia, genetic mutations for breast cancer (BRCA1 and/or BRCA2), personal history of breast cancer, high levels of estrogen and testosterone, early menarche (<12 years), late age at first full-term pregnancy (>30 years), late menopause (>55 years), never breastfed a child, obesity, recent oral contraceptive use, recent long-term use of HRT and sedentary lifestyle (ACS, 2011; Jemal et al., 2011). There is a strong evidence that breast cancer risk is statistically significant decreased among physically active individuals. The average risk reduction for breast cancer is thought to be 25% (an average risk reduction of 30% in the case-control studies and a 20% reduction in the cohort studies). A dose-response dependence of this relationship was examined in 41 studies of the 51 studies that found a decreased breast cancer risk with increased levels of physical activity. Of the 41 studies, 33 found evidence for a dose-response association between decreased breast cancer risk and increased levels of activity. The risk reductions were observed for recreational, household and occupational activity, however, the association was the strongest for moderate-vigorous recreational activity, sustained regularly over lifetime or at least after menopause, ranging 23-65% in findings from case-control studies and 21-39% from cohort studies (Monninkhof et al., 2007). The risk reductions were observed among women with each BMI category except those with BMI ≥30 kg/m^2, but were stronger in postmenopausal women, normal weight women, parous women, and women without a family history of breast cancer. In addition, physical activity was associated with a lower risk of breast cancer among women of different racial/ethnic groups, and a slightly greater risk reduction was detected for vigorous intensity of activity, compared with moderate intensity. Also, greater duration of moderate-vigorous activity results in a greater risk reduction (Lynch et al., 2011). The preventive role of exercise was observed independently

on menopausal status, although the average risk reduction was somewhat smaller in premenopausal women than postmenopausal women (26% versus 30%) (Lynch et al., 2011; Loprinzi et al., 2012). Another potential effect modifier, hormone receptor status, was investigated in 11 studies. Greater risk reduction was observed for women with estrogen receptor negative/progesterone receptor negative (ER-/PR-) tumors (27%), than for women with estrogen receptor positive/progesterone receptor positive (ER+/PR+), (14%) (Monninkhof et al., 2009; Lynch et al., 2011; Steindorf et al., 2012).

Endometrial cancer

Overweight and obesity, low parity, and HRT use, have been found to increase the risk of endometrium (Key et al., 2004). In a review of cohort and case-control studies, Lee and Oguma (2006) calculated that physically active women were at a 30% lower endometrial cancer risk than those in lowest categorized level of activity. The recent reviews by Voskuil et al. (2007) of 20 studies and that carried out by Cust and co-workers (2007) estimated about 20-30% significant and consistent risk reduction among physically active women, and *convincing* or *probable* level of evidence. Another noteworthy finding of the investigators was the benefit of household physical activity and walking or cycling to work (transportation activity); further, they suggested that long-term of activity and higher intensity result in a higher protective effect against endometrial cancer than shorter duration and lower intensity of activities. These investigators concluded that about 1 hour daily of moderate-intensity can reduce endometrial cancer risk. Due to some inconsistency in dose-response association as well as the effect of physical activity on the risk among women of different sub-groups (BMI categories, menopausal status, differences in activity type, race) and activity performed in different life periods, continuation of investigation is needed.

Prostate cancer

Prostate cancer is the most frequently diagnosed cancer in men, with an estimate 186320 new cases and 28660 deaths in the USA during 2008. Incidence rates are significantly higher in African American men than in white men (ACS, 2008). The well-recognized risk factors for the disease are: age, ethnicity, and familiar predisposition. The last factor may be responsible for 5-10% of prostate cancers. There is also suggestion that a diet reach in saturated fat and obesity may also increase the risk of this cancer.

International studies have suggested that higher levels of physical activity are linked to lower risk of the advanced and aggressive prostate cancer. There is common recommendation that blood test detecting a protein produced by prostate PSA (prostate-specific antigen) should be offered to men aged 50 years and more, and also the digital rectal examination as early cancer detection in order to save live and to increase treatment efficiency.

More than 20 studies have been conducted on physical activity and prostate cancer risk, the majority of them have suggested a risk reduction, ranging from 10% to 20% with increasing level of activity (Friedenreich and Orenstein, 2002; Friedenreich et al., 2004; Miles, 2007; Moore et al., 2008). In addition, the studies found that increased level of physical activity indicates on lower risk for benign prostatic hyperplasia (Lagiou et al., 2008). It is important mention of some studies that have reported reduced risk for advanced prostate cancer and for fatal prostate cancer among individuals engaged in regular vigorous activity (Giovannucci et al., 2005; Nilsen et al., 2006). Due to limited number of studies regarding the physical activity-prostate cancer and some methodological issues, such as selection bias resulting from slow grow of tumour and its long latency period, investigators may have difficulties in a measure of a difference in physical activity levels between the prostate cancer cases and the healthy control populations. In addition, it is unknown if relationship between physical activity and prostate cancer risk is not influenced by other risk factors, therefore more comprehensive study of the activity effects on prostate cancer risk within population sub-groups is needed. This suggestion is supported by the American prospective cohort study (Littman et al., 2006). The investigators found that physical activity was not associated with the risk of prostate, except in normal weight men (BMI≤25 kg/m^2) or in men with non-aggressive prostate cancer aged about 65 years. There is now *probable* evidence for a beneficial effect of physical activity on the risk of prostate cancer (Table 1).

Lung cancer and bronchus cancer

Lung cancer and bronchus cancer is the second the most frequently diagnosed cancer in men and women; 116470 new cases in men and 109690 in women were estimated in Americans in 2008. With an estimated 90810 and 71030 deaths in 2008, lung and bronchus cancer is a leading cause of cancer death in men and women (31% and 26%), respectively (ACS, 2008). Smoking and occupational exposure to nickel are established risk factors for certain histologic types of lung cancer (Miles, 2007). Over 20 studies have been carried out on the relationship between physical activity and lung cancer and their results demonstrate a risk reduction ranging from 20-40%, considering the studies that controlled for the effect of smoking or they examined the risk among non-smokers (Tardon et al., 2005; Subramanian and Govindan, 2007; Leitzmann et al., 2009a; Friedenreich et al., 2010a).

The effect of recreational activity for the risk was found to be stronger than occupational activity. The inconsistencies seen in studies may be attributable mainly to small sample sizes, errors in assessment of physical activity (lack of precision and evaluation of all types of activity), and incomplete assessment of association between physical activity and lung cancer risk on well-established and probable risk factors. Therefore, a more accurate assessment of lung cancer risks is needed.

Ovarian cancer

According to recent estimates of total women cancer cases and death about 3% (21650) of women will develop ovarian cancer and 6% (15520) will die in USA during 2008. More than 20 studies have been conducted on physical activity and ovarian cancer demonstrating

inconsistent findings (Olsen et al., 2007; WCRF/AICR, 2007; Friedenreich et al., 2010a; Speck et al., 2011). The reviews concluded that there was a modest inverse relationship between physical activity and ovarian cancer development with about 10-20% reduction of the risk. It also should be noted that only half of studies that had published data observed a benefit. In addition, one study found an increased risk (Friedenreich et al., 2010a). Estimation of a dose-response trend showed inconsistency for all types of activity, i.e. the beneficial effect of physical activity was somewhat stronger for recreational activity than occupational activity (Olsen et al., 2007). It is worthwhile to add that two studies (Zhang et al., 2004, Patel et al., 2006) reported about 50% increase in ovarian cancer risk among women sitting ≥6 hours daily. There are inconsistencies in previous studies dealing with the intensity level. Some studies found increased risk for vigorous-intensity activity (Anderson et al., 2004; Carnide et al., 2009), in turn, other reported decreased risk for this level of activity (Leitzmann et al., 2009b; Rossing et al., 2010). The investigators found no difference in sub-groups of analyses, considering BMI, menopausal status, HRT use, smoking habits, parity, and family history.

Pancreatic cancer

An estimated 18,770 (3%) new pancreatic cancer cases will occur in the American men. In the review of 18 studies by Bao and Michaud (2008) the relative risk of pancreatic cancer ranged from 0.42 to 1.24. Three later published papers (Inoue et al., 2008; Jiao et al. 2009; Stevens et al., 2009) suggested benefits from physical activity. In spite of some methodological limitations and inconsistency of the evidence, the Panel judges that the evidence for beneficial effect of physical activity on pancreatic cancer is *limited-suggestive* (WCRF/AICR, 2007).

Gastric cancer

The relationship between physical activity and gastric cancer risk has been estimated in over 15 studies (Friedenreich et al., 2010a). Of the 15 studies only four reported a decreased risk linked to increased physical activity levels. The results of the studies show that the relationship may vary according to histological sub-type which has not been investigated in most carried out studies (Leitzmann et al., 2009c).

The relation between physical activity and risk for other cancers, for example stomach, kidney, bladder has been evaluated in a few studies. In addition, the number of identified cases was small. Therefore more evidences is needed to highlight the association between physical activity and risk of these cancer site.

Hypothesized Biological Mechanisms Relating Physical Activity to Cancer Risk

To date, biologic mechanisms by which physical activity can influence cancer have not been established; however several mechanisms through which physical activity exerts effects have been proposed (Feig et al., 1994; Toyokuni et al., 1995; Hoffman-Goetz et al., 1998; Shephard and Shek, 1998; Rundle, 2005; Garofalo and Surmacz, 2006; Kay and Sing, 2006; Kruk and Aboul-Enein, 2006; 2007; Szlosarek et al., 2006; Wetmore and Ulrich, 2006; Tworoger et al., 2007a; WCRF/AICR, 2007; Coyle, 2008; Renehan et al., 2008; Neilson et al., 2009; Thompson et al., 2009; Verna and Montgomery, 2009; Friedenreich et al., 2010a; 2011; Kruk, 2011; Lynch et al., 2011; Heikkila et al., 2013) and examined in randomized controlled trials (McTiernan et al., 2005; Abrahamson et al., 2007; Tworoger et al., 2007b; Hawkins et al., 2008; Balducci et al., 2010; Campbell et al., 2010; Friedenreich et al., 2010b; 2010c; 2011; Reding et al., 2011).

Physical activity appears to impact all the stages of carcinogenesis (initiation, promotion and progression). It is highly likely that multiple mechanisms act cooperatively to reduce cancer risk, and some of them may predominate and be dependent on specific types or doses of physical activity. A strength of mechanism action may be different in certain subgroups (Lynch et al., 2011). The biological mechanisms include the following responsive pathways of physical activity: *i*) Decreased weight/obesity and central adiposity; *ii*) Changes in endogenous sexual (estrogens, androgens) and metabolic hormones levels (insulin and glucose); *iii*) decrease of growth factors levels; *iv*) Reduction of endogenous oxidative stress; *v*) Detoxification of chemical carcinogens and reactive oxygen species; *vi*) Reduction of systemic inflammation; *vii*) Improvement of immune function; *viii*) DNA repair.

Weight control may be particularly important pathway of the biological mechanisms altering an association between physical activity and cancer prevention. Energy balance between consumption of energy and expenditure has become an important factor in etiology of a number of chronic diseases, including cancer. In particular, abdominal fat is metabolically active in cancerogenesis (Friedenreich and Orenstein, 2002; Kaaks et al., 2002; Rodriguez et al., 2007). Recommendation for the maintains of body mass are 45-60 min daily of physical activity, and 60-90 min daily to sustain long-term weight loss (Warburton et al., 2007). Weight and weight gain in adulthood are associated with increased risk of colon, postmenopausal breast cancer, endometrium and ovaries cancers. For premenopausal breast cancer the mechanisms are less well recognized. Exercise has been reported to be associated with delayed menarche and menstrual dysfunction. This leads to a decrease of circulating estrogens and progesterone hormones, known as powerful mitogens in the breast. For prostate cancer, reported mechanisms include the effect of physical activity on level of testosterone and alterations in insulin level and its sensitivity, and circulating insulin-like growth factor (IGF-1) levels (Rodriguez et al., 2007). IGF-1 may act as a mitogen increasing cell proliferation and decrease apoptosis in breast tissue (Lynch et al., 2011). Adipose tissue is the primary source of endogenous estrogens and testosterone. Sex hormones are considered as important determinants of endometrial, breast and prostate cancers (McTiernan et al., 2006; McTiernan, 2008; Bernstein et al., 2010). Estrogen – induced carcinogenesis is thought to result from a combination of genotoxic and endocrine processes which can participate in DNA damage and in all stages of carcinogenesis (Lichr and Jones, 2001). The

formation of catecholestrogens and their metabolic redox-cycling between catechol and quinone forms leads to the formation of free radicals such as semiquinone. The radical reacts with molecular oxygen to produce superoxide radical ($O_2^{\cdot-}$). Superoxide radical may be reduced to hydrogen peoxide and further to hydroxyl radical ($HO^{\cdot}$) in the presence of transition metal ions, e.g. iron, copper. These oxygen species are highly reactive ($HO^{\cdot}$ especially), and have the potential to alter nucleotide residues under oxidative stress. Oxidative stress has been reported to be implicated in apoptosis and the pathogenesis of cancer (Mates and Sanchez-Jimenez, 2000). The chemical changes in DNA exerted by reactive oxygen species can be mutagenic lesions occurring in the cancer etiology. There is evidence that regular moderate physical activity can enhance antioxidant defense system (Gomez-Cabrera et al., 2008), reduce of basal formation of antioxidants (e.g. SOD, glutathione) and increase resistance of tissues against oxidative stress (for review see Kruk, 2011). The quinone products of estrogen oxidation can form with DNA highly reactive quinone and semiquinone adducts. Thus, the hormone can stimulate cell proliferation and enhance tumor development or inhibit apoptosis. Physical activity may also increase concentration of sex hormone binding globulin (SHBG), which can bind reversible to estrogens and limit their availability (Kaaks et al., 2002). Another potential mechanism through physical activity may have effect on carcinogenesis, through the obesity decrease, are changes in blood insulin level and insulin resistance. Insulin resistance and hyperinsulin are strongly linked to obesity, intraabdominal fat, circulating adipokines, and inflammatory factors (Lynch et al., 2011). Physical activity improves insulin sensitivity, lowers the hormone concentration in plasma, increases glucose transport into muscle, and decreases synthesis of fatty acids. In addition, exercise causing significant weight loss may result in an increase of adiponectin concentrations (Neilson et al., 2009). Adiponectin is known as anti-angiogenic, anti-mitogenic, and anti-inflammatory factor. This compound is recognized as a promoter of insulin sensitivity of which level is lowered with obesity (Kelesidis et al., 2006). Expression of adiponectin is inhibited by interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α). IL-6, TNF-α, leptin (produced by adipocytes or adipose tissue), and C-reactive protein (CRP) (produced in the liver in response to TNF-α and IL-6) are recognized as inflammatory markers. These markers are strongly positive correlated with obesity and negative correlated with physical activity (Garofalo and Surmacz, 2006). The relevance of the adiponectin/leptin ratio in breast cancer etiology is still under study. The decreased level of adiponectin have been linked with increased risk of cancers related to obesity (colon, postmenopausal breast cancer, endometrium, thyroid, renal) (McTiernan, 2008).

Physical activity is also suggested to enhance immune function, thus to have preventive action against cancer. It is hypothesized that regular moderate exercise can improve the number and function of natural killer cells (Shephard and Shek, 1998; Jakobisiak et al., 2003). Natural killer cells are able to attack most types of cancer and participate in tumor suppression. It has been reported that regular moderate exercise has a positive influence on a number of components of immune function, for example, monocytes, neutrophils, lymphocytes, and eosinophils. However, excessive physical activity may cause immunosuppression. Also, additional mechanisms in the association between physical activity and cancer, like carcinogen activation or detoxification, intracellular signaling pathways may also occur (Friedenreich et al., 2010a). Moreover, physical activity may inhibit synthesis of prostaglandin E_2 which promotes colon cancer, or increase gut motility and decrease gastrointestinal transit time, thus decrease colon cancer risk. Exercise improves pulmonary function and lowers concentration of chemical carcinogens in lung (Friedenreich et al., 2010a). The complexity of biological mechanisms involved in the pathways between physical activity and cancer, their interrelationship, additive oppositive or synergistic effects, the lack of standard definition of physical activity for sedentary behaviour, different methods used in measurement of physical activity determinants across studies cause that the mechanisms remain still poorly understood. Considering the multiple biological pathways, the difficulty in assessing physical activity in epidemiological studies and the fact that cancer is multifactorial process, it is not surprising that the epidemiologic evidence from case-control and cohort studies is still not confirmed or is even conflicting in several cancer site. It should be noted that the observational studies provide only etiological insight but are not able to determine a direct causal relationship between physical activity and cancer (Lynch et al., 2011). Randomized controlled trials (RCTs) are recognized as the strongest type of research, providing valuable information on the causal pathway between physical activity and cancer occurrence. They are, unfortunately, the most labor-consuming and costly of all studies to conduct. RCTs have tested the direct influence of exercise on potential biomarkers of cancer, through potential exercise responsive pathways. For example, for sex hormones and binding proteins, concentrations of estradiol, estrone, testosterone and SHBG may be biomarkers detected; for antioxidant enzyme systems – glutathione, SOD, catalase, and glutathione S-transferase; for growth factors and growth factor binding proteins – IGF-1, IGF-binding protein I and III; for oxidative stress – thiobarbituric acid reactive compounds, 8-hydroxydeoxyguanosine; for DNA repair – 8-oxyquanine DNA glycosylase; for immune function – number and activity of natural killers, lymphocyte activity (Rundle, 2005) are recognized as markers. Intervention studies have designed exercise programs that are the most relevant to particular cancer-side, and provide information on the appropriate type, dose, and timing of physical activity that link to cancer risk reduction. For example, three RCTs were specifically designed for the mechanisms through exercise effects postmenopausal breast cancer: Physical Activity for Total Health (PATH) (McTiernan et al., 2004); Alberta Physical Activity and Breast Cancer Prevention (ALPHA) (Friedenreich et al., 2010b), and sex Hormones and Physical Exercise (SHAPE) (Monninkhof et al., 2009). These RCT studies found the impact of exercise on a variety of proposed breast cancer biomarkers, like

significantly decreased concentration of estrogen and androgen in blood after 12 months of exercise (SHAPE and PATH studies) and significantly decreased adiposity and increased SHBG (ALPHA). Similarly, other RCT (Campbell et al., 2008) reported a reduction of CRP and IL-6 for 12 months of a moderate-intensity exercise. Also, the second-arm of ALPHA study (Friedenreich et al., 2011) demonstrated the significant improvements in insulin resistance indicators, leptin, and adiponectin/leptin ratio: for 12 months of moderate to vigorous aerobic exercise in previously inactive postmenopausal women. Another RCT study by Campbell et al. (2010) of overweight or obese sedentary women supported the important role of 12 months of moderate intensity exercise in modulation of inflammatory processes; the investigators observed reduced concentration of CRP among obese women (BMI≥30). In contrast, the most recent RCT study did not confirm significant changes in colon mucosal prostaglandin concentrations under the influence of 12 months moderate-to-vigorous intensity aerobic exercise (Abrahamson et al., 2007). According to American Institute for Cancer Research estimation (AICR, 2010), percentage of cases of the most common cancers that could be prevented annually through healthy diet, regular physical activity and a BMI≤25 kg/m^2 is estimated as follows: endometrial cancer 70%, colorectal cancer 45%, breast cancer 38%, lung cancer 36%, prostate cancer 11%, pancreatic cancer 39%, and stomach cancer 47%.

In conclusions, the evidence for a protective effect of regular moderate-to-vigorous physical activity against cancer incidence is classified as *convincing* for colon cancer, *probable* for postmenopausal breast and endometrial cancers, and *limited suggestive* for premenopausal breast, prostate, lung, ovary, pancreatic and gastric cancers. The basic biological mechanisms underlying the effect of physical activity on cancer are hypothesized. They involve decrease in adiposity, decrease in sex and metabolic hormones, changes in markers and insulin resistance, improvement of immune function, and reduction of inflammation. Although all types of physical activity were reported to reduce cancer, stronger risk reductions were observed for recreational activity. Research findings demonstrate that the benefits from physical activity occur when activity is at least of moderate intensity and performed regularly, and is sustained over lifetime or at least for a long term. Biological markers of DNA damage and metabolism of biogenic hormones, improvements in objective determination of dose and timing activity over lifetime are essential for understanding how physical activity influences on multiple cancer stages. Therefore, there is a need to continue cohort studies linked with the proposed biomarkers to cancer risk and controlled exercise intervention trials to compare change in biomarker concentrations from baseline to the several follow-up time points in the exercising individuals versus the control group. These studies can give answers for many basic questions, like what determinants of physical activity (intensity, frequency, timing) are optimal, whether impact of physical activity depends on cancer subtype, at what age exercise is the most beneficial, and what type of activity and its dose provide the strongest risk reduction for specific cancer sites.

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