

REVIEW

Physical activity and cancer prevention: a review of current evidence and biological mechanisms

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Key words

Physical activity • Rats • Mice • Cancer prevention

Summary

Objective. The main aim of this paper is to review the evidence available from the date of PubMed's inception to May 2011 for a link between cancer and physical activity (PA) in both animal models and humans.

Methods. We decided to select studies that comply with the scheme proposed by the American College of Sports Medicine/American Heart Association (ACSM/AHA) that distinguish occupational physical activity (OPA) and leisure-time physical activity (LT-PA), further classified in three levels of intensity (low, moderate and heavy) based on the Metabolic Equivalent of Task (MET) index.

Results. Considering animal models, there was strong evidence for an inverse association between voluntary wheel exercise and the risk of colon and breast cancer. Regarding human studies, we identified the following main results: 1) colorectum: LT-PA

provided an overall colon risk reduction of 13-14%; 2) breast: significant reduction in the frequency of post-menopausal (PMP) cancers in women that practiced heavy and moderate LT-PA; 3) prostate: heavy OPA and LT-PA seemed to reduce the risk of advanced prostate cancers; 4) endometrium: strong protective effect of heavy/moderate LT-PA among overweight/obese women; 5) lung: inverse relationship between heavy LT-PA and lung cancer in former or current smokers across all histologies.

Conclusion. Increased LT-PA is associated with cancer prevention in several organs, but strong biases, such as body mass index (BMI), gender and age, make it difficult to assess which aspects of PA contribute most strongly to the reduced risk. Furthermore, we found few studies that indicated a protective role for OPA in cancer prevention when compared with LT-PA.

Introduction

The most critical modifiable risk factor for cancer is smoking, followed by weight, diet and physical activity (PA) [1]. Several biological mechanisms are involved in the preventive effects mediated by PA, involving not only reduction of the intra-abdominal fat store (a metabolically active site that releases carcinogens in overweight individuals) [2], but also the increase in anti-tumour immune defence [3] and reductions in the levels of insulin and insulin-like growth factor-1 (IGF-1), mainly through the increased production of its binding protein (IGFBP-3). [4]. Unfortunately, the extreme variability of subjects included in trials and the heterogeneity in PA estimation make it difficult to establish the "highest" and "lowest" necessary levels, especially when we focus on specific target organs. The quantitative index used most commonly is the metabolic equivalent of task (MET), which expresses the energy cost as multiples of resting metabolic rate. Based on the MET concept, PA can be classified as either an occupational physical activity (OPA) or a leisure-time physical activity (LT-PA). We decided to analyse all presented data using the scheme proposed by the American College of Sports Medicine/American Heart Association (ACSM/AHA) [5]:

- OPA: low for sitting work (e.g., sitting office work, secretary), moderate for standing and walking

work (e.g., store assistant, light industrial worker), heavy for manual work (e.g., forestry work, heavy farm work, heavy building and industrial work that lasted ≥ 20 minutes per day and caused increases in breathing, heart rate or sweating).

- LT-PA: low for < 3 MET activities (e.g., reading, watching television), moderate for 3–6 MET activities (e.g., walking, hunting, gardening more than 4 h/week), heavy for > 6 MET activities (e.g., aerobics, jogging, running, skiing, swimming, bicycling more than 3 h/week or activities that lasted ≥ 20 minutes per day and caused increases in breathing, heart rate or sweating).

Even though there were several articles that contained questionnaires with more LT-PA/OPA categories, we decided to follow the aforementioned classification scheme because more detailed subdivisions do not appear to improve meta-analysis-related interpretations [6]. It is also well established that approximately 3 hours/week of heavy PA or 4 hours/week of moderate LT-PA are necessary to reduce the incidence of cancer among the middle-aged population [7].

The aim of this study is to provide an update on the experimental and epidemiological evidence for PA and the related reduction in cancer risk through the selection of articles that satisfy our quality assessment and selection criteria.

Materials and methods

STUDY SELECTION

We systematically searched PubMed (from the date of its inception to May 2011) for original articles, systematic reviews and meta-analyses about experimental studies on animal models and epidemiological studies in humans describing the association between PA and cancer incidence in the following organs: colorectum, breast, prostate, endometrium, lung, ovary, kidney, thyroid gland, testicle, and pancreas. We limited the search to publications in English. We used terms related to PA ('physical activity', 'energy expenditure' and 'metabolic equivalent') and combined these with site-specific terms. We designed separate data extraction forms for case-control and cohort studies, and when data from a study was reported in more than one article, we included only the most recent publication.

From the results section of the selected articles, we extracted the reported relative risk (RR), odds ratio (OR) and 95% confidence limits (IC) for site-specific cancers in relation to PA exposure variables (total, occupational and leisure-time), gender difference and type of statistical data analysis performed. We considered an RR and an OR < 0.80 to indicate a significant risk reduction, a

risk estimate between 0.80 and 1.25 to indicate no association and a risk estimate higher than 1.25 to indicate an increased risk.

DATA EXTRACTION AND QUALITY ASSESSMENT

Because cancer is a multifactor outcome, we selected articles that adopted "exclusion criteria" regarding the main confounding biases (age, gender, cigarette smoke, alcohol consumption, BMI, daily diet) [8] and that used the aforementioned LT-PA/OPA categories.

Taking cues from similar reviews in the literature [2], we divided the epidemiological studies into six site-specific subgroups: colorectum, breast, prostate, endometrium, lung and others. Our methodology was similar to that used in the "World Cancer Research Fund (WCRF) first report" [9], which utilised four different and descending categories to indicate the strength of the effects of PA:

1. "convincing" (colorectum and breast);
2. "probable" (prostate);
3. "possible" (endometrium, lung);
4. "insufficient" (others).

Given the high level of heterogeneity in the study design, no attempt was made to estimate the overall quantitative synthesis of data across selected studies. We chose to present the meta-analysis data in Tables I and II.

Tab I. Colorectum.

Authors	Year	No. of studies	Type of analysis	Site	Type of exercise	Sex	RR	95%IC	OR	95% IC		
Samad et al.	2005	47	Fixed meta-analysis	Colon	OPA	M	0.79	(0.72-0.87)	0.70	(0.64-0.77)		
						F	1.11	(0.84-1.46)	0.49	(0.37-0.65)		
					Rectum	Any	M	0.78	(0.68-0.91)	0.58	(0.47-0.72)	
							F	0.71	(0.57-0.88)	0.61	(0.45-0.83)	
						Any	M	1.00	(0.78-1.29)	0.94	(0.83-1.07)	
							F	1.00	(0.53-1.88)	0.87	(0.51-1.47)	
Wolin et al.	2009	52	Random meta-analysis	Colon	OPA	BG	0.85	(0.77-0.93)	0.73	(0.67-0.79)		
						BG	0.82	(0.75-0.87)	0.69	(0.62-0.78)		
						M	0.81	(0.73-0.89)	0.68	(0.64-0.72)		
Wolin et al.	2011	20	Random meta-analysis	Colon	Any	F	0.89	(0.81-0.99)	0.72	(0.66-0.79)		
						M	0.81	(0.67-0.98)	-	-		
Harris et al.	2009	14	Random meta-analysis	Colon	LT-PA	M	0.80	(0.67-0.96)	-	-		
						F	0.86	(0.76-0.98)	-	-		
						Rectum	LT-PA	M	1.02	(0.83-1.26)	-	-
								F	1.29	(0.82-2.01)	-	-

BG: both genders; OPA: occupational physical activity; LT-PA: leisure-time physical activity.

Tab II. Breast, endometrium and lung.

Authors	Year	No. of studies	Type of analysis	Site	Type of exercise	Sex	RR	95%IC	OR	95% IC
Monnikhof et al.	2007	48	Arithmetic media of high quality studies (> 70%)	Breast	TPA (AMP)	F	-	-	0.94	(0.24)*
						F	1.14	(0.36)*	0.42	(0.26)*
						F	1.60	(0.54)*	-	-
						F	0.64	(0.33)*	0.71	(0.40)*
Voskuil et al.	2005	11	Fixed meta-analysis	Endometrium	Any	F	0.77	(0.70-0.85)	0.71	(0.63-0.80)
Tardon et al.	2007	13	Random meta-analysis	Lung	High PA	M	-	-	0.75	(0.66-0.86)
						F	-	-	0.62	(0.48-0.79)
						M	-	-	0.93	(0.85-1.00)
					Moderate/mild PA	F	-	-	0.77	(0.66-0.89)

TPA: total physical activity, AMP: ante-menopause; PMP: post-menopause; * standard deviation.

Results

EXPERIMENTAL STUDIES ON ANIMAL MODELS

PA is defined as the full set of factors able to activate skeletal muscles and to involve energy consumption [10]. In such models, rodents run on wheels and treadmills so that the slope and velocity can be controlled in order to assure that all animals experience the same amount of PA. Voluntary wheel exercise must be preferred to forced treadmill exercise because the latter, in nocturnal animals such as rats and mice, causes sleep deprivation, which is known to be stressful [11], and stress plays a major role in the initiation and progression of cancers through oxidative stress and DNA damage (especially in the colorectum) [12]. The main confounder was “food intake” because administration of a high-fat diet [13] or regulated energy intake [14] influenced both the incidence and the anatomical distribution of tumours.

Colorectum

Basterfield et al. [13] collected eight studies that induced cancer through the administration of colic carcinogens (azoxymethane and 1,2-dimethylhydrazine) in male Fisher and Sprague-Dawley rats or by genetic mutations of the Apc gene (the gatekeeper gene for bowel cancer) in monitored mice to induce spontaneous intestinal neoplasms. Rats benefited more from PA than mice; a possible explanation is not only the different primary endpoints (colon cancer for rats versus bowel adenomas for mice) but also the different behavioural responses to the exercise intervention. In particular, mice spontaneously reduced non-exercise physical activity (NEPA) so that they maintained a similar energy balance despite their greater energy expenditure during daily forced running [13].

Moreover, the original articles underlined the synergistic effect of PA when administered in combination with a high concentration of colonic butyrate and increased sleep duration [15] as well as the inverse correlation between daily wheel running distance and total polyp number [16]. Baltgalvis et al. found that treadmill exercise decreased the number of macrophages and down-regulated pre-carcinogenic markers in intestinal polyps (e.g., ↓ TUNEL positive cells, ↓ bax protein expression, ↑ catenin phosphorylation) [17].

Breast

Three articles reported that wheel exercise reduced both the incidence and multiplicity of breast cancer in 1-methyl-nitrosourea-treated mice through the reduction of proteins involved in cell proliferation (e.g., cyclin D1), the elevation of those involved in apoptosis via the mitochondrial pathway (e.g., caspase-3 activity) [14, 18] and blood marker variations (i.e., ↑ plasma corticosterone, ↓ IGF-1, ↓ insulin, ↓ leptin) [19]. The involvement of citrate synthase is controversial because free-wheel running increased the level of enzyme activity and reduced the average number of cancers per rat, but regression analyses failed to provide evidence of a significant association [20].

Other sites

Esser et al. [21] found that exercise decreased prostate cancer progression in predisposed transgenic C3Tag mice, while Michna et al. [22] determined that running wheel exercise decreased the number and size of non-malignant tumours and squamous cell carcinomas of the skin in UVB-induced carcinogenesis.

EPIDEMIOLOGICAL STUDIES

Colorectum

For the colorectum, we selected four meta-analyses [6, 23-25] and three original articles [26-28]. No association was consistently found for LT-PA and rectal cancer [6, 23]; the consensus is that one is unlikely to exist [24]. LT-PA provides a colon cancer risk reduction of 13% and 14% from the 20th to 95th percentile for men and women, respectively [6]. One recent meta-analysis found a decreased risk, especially for large/advanced polyps [25]. The magnitude of risk reduction reported in case-control studies was stronger than reported in cohort studies; this difference may be explained by greater recall biases and a stronger PA assessment in case-control studies [24] (Tab. I). The PA effect was independent of other factors; there was no statistical alteration after adjustment for confounders such as BMI, smoking and alcohol. Moreover, recent studies showed that PA also influenced mortality in patients diagnosed with colon cancer [26].

In terms of biological patterns, several mechanisms and response pathways have been hypothesised to explain the protective effect of PA. The mechanisms supported by the strongest evidence involve a lower faecal bile acid concentration [27], increased gastrointestinal transit [28], decreased levels of insulin and IGF-1, and a decreased IGF-1:IGF-BP3 (binding protein 3) ratio [24]. The latter is the most probable because hyperinsulinemia and insulin resistance provide a unifying mechanism through which PA, dietary and other lifestyle factors have a causal effect on colorectal cancer.

Breast

For the breast, we selected one meta-analysis [29], three reviews [30-32] and three original articles [33-35]. The lack of a consistent PA versus breast cancer association is mainly due to population heterogeneity because breast cancer is influenced by non-modifiable factors such as early age at menarche, nulliparity, older age at first childbirth and menopause. For that reason, Monninkhof et al. [29] presented a quality scoring system of selected studies without a random or fixed meta-analysis calculation. According to our review design, we calculated the OR and RR arithmetic mean of high-quality studies (> 70%) [29]. We found a significant reduction of post-menopausal (PMP) cancers in women that practiced LT-PA (Tab. II). Among post-menopausal women, the breast seemed to be more sensitive to reductions in BMI and oestrogen levels induced by LT-PA [30, 31].

Regarding hormone receptor status, Adams et al. reported a protective effect mediated by LT-PA in both receptor(+) and receptor(-) cancers. In particular, premenopausal women who reported LT-PA during both adolescence and the last 10 years showed a significant decrease in the risk for receptor(+) and receptor(-) cancer (decreases of 66% and 49%, respectively) [33]. In addition, West-Wright et al. demonstrated that women with heavy or moderate levels of LT-PA had lower risk, regardless of hormone receptor status, but this applied only to overweight women [34]. In conclusion, the idea that LT-PA is associated with a decreased risk of breast cancer, partly through the activation of hormone-related mechanisms, is controversial because complete information regarding receptor status is not always available for the studied subjects [35], and we know little about the differential response of oestrogenic and progesterone receptors [32].

Moreover, BMI level did not appear to exert a dramatic influence on the preventive effect mediated by LT-PA [29], even if the greatest benefits were observed among lean women with a BMI < 22 [32]. This result is easily explicable if we consider that adipose tissue is the major source of endogenous oestrogen, especially in post-menopausal women [32].

Prostate

For the prostate, we selected one review [36] and eight original articles [37-44]. The lack of meta-analyses is due to strong confounders such as large geographical variations in incidence, end-point choice (localised or advanced cancers) and PA type. In addition, early detection remains of uncertain benefit, and controversy exists regarding the most appropriate treatment for early-stage prostate cancer [36]. Heavy OPA seemed to reduce the risk of advanced prostate cancers [37]. Subjects with moderate OPA (standing and walking work) experienced a 20% lower risk than those with low OPA (sitting work), and heavy LT-PA (bicycling) decreased the risk of all types of prostate cancer (especially advanced cases) [38]. Moreover, moderate LT-PA minimised the side effects related to androgen deprivation therapy (ADT) in prostate cancer patients [39, 40], and all levels of LT-PA reduced the risk of aggressive prostate cancers [41] and benign prostatic hyperplasia (BPH) [42].

PA could reduce the incidence of prostate cancer by lowering basal testosterone levels, suppressing 5- α reductase activity, improving immune system function (e.g., the number and capacity of NK cells) and enhancing antioxidant activity (e.g., scavenger enzymes such as superoxide dismutase and glutathione peroxidase and levels of antioxidants such as glutathione and tocopherols) [36]. Moreover, PA increased the cellular p53 protein content, leading to reduced p21-mediated cellular growth, the induction of apoptosis through the mitochondrial pathway [43], and a reduced IGFI:IGFBP3 ratio (a high ratio was associated with increased BPH risk) [44].

Endometrium

For the endometrium, we selected one meta-analysis [45], one review [46] and five original articles [47-

51]. Voskuil et al. [45] highlighted the confounding effect of BMI, which nonetheless appeared to be an independent factor, because the incidence was decreased in both normal-weight and obese women (Tab. II). In contrast with Voskuil et al., recent cohorts displayed stronger effects of heavy [46] and moderate [47] LT-PA among overweight/obese women and no correlation with OPA [46]. However, Conroy et al. pointed out that overweight women (BMI \geq 25) have a higher endometrial cancer risk, regardless of LT-PA level [48]; it therefore remains difficult to assess the influence of BMI versus LT-PA. Moreover, recent case-control studies underlined the importance of distinguishing OPA from LT-PA to fully understand the effect of PA [49], in particular the protective effect of heavy LT-PA, especially between menarche and full-term pregnancy and after menopause [50].

Cust et al. [51] summarised the biological mechanisms hypothesised to underlie the LT-PA-mediated improvement in insulin sensitivity, the increase in the levels of sex hormone-binding globulin (SHBG) and IGFBP-1, and the influence on the balance of oestrogen and progesterone levels. The 'unopposed oestrogen hypothesis' states that prolonged exposure to oestrogen, insufficiently counterbalanced by progesterone, is a major aetiological determinant of endometrial cancer. LT-PA was associated with menstrual cycle irregularities, which decrease the cumulative number of ovulatory cycles and reduce exposure to oestrogens [51].

Lung

For the lung, we selected one meta-analysis [52] and five original articles [53-57]. Tardon et al. [52] included only trials that provided a smoking adjustment. They found a greater reduction for heavy LT-PA than for moderate LT-PA (Tab. II), with a significant dose-response relationship. Recent studies have shown quite similar LT-PA effects across all histologies in former or current smokers, but only effects unrelated to LT-PA among those who have never smoked [53], a stronger effect of LT-PA on major cell cancer [54], as well as a synergistic effect of LT-PA and diet on lung cancer in smokers [55]. In contrast, Staindorf et al. found an augmented lung cancer risk for moderate OPA and unemployed men, but these data were probably influenced by occupational exposures [56].

The IGFI:IGFBP3 ratio seems to be a crucial part of the mechanism underlying the protective effect of LT-PA [57]. In particular, high levels of circulating IGF-1 were associated with an increased risk of lung cancer, while high levels of IGFBP-3 were associated with a decreased risk [57]. However, it is difficult to assess all the effects of PA because the lung is affected by several independent confounders (smoke, air pollution and food intake) that influence both histology and gender differences in incidence [52]. The effect of smoking could be investigated using cohorts of individuals that have never smoked as controls. However, the low rates of lung cancer in this population make such studies difficult.

Other sites

- Ovary: Although Olsen et al. found a modest inverse association between the level of LT-PA and the risk of ovarian cancer [58], Rossini et al. [59] showed a stronger reduction in the risk of invasive epithelial ovarian cancer in subjects that practice heavy LT-PA compared with those that practice moderate LT-PA.
- Kidney: one review [60] underlined that moderate LT-PA during adolescence and heavy LT-PA in adults could protect against renal cell carcinoma through a reduction in body weight, blood pressure, chronic inflammation, oxidative stress and an improvement of insulin sensitivity.
- Thyroid gland: one original article [61] provided a possible inverse relation between papillary thyroid cancer incidence and heavy LT-PA during the two years before diagnosis with cancer.
- Testicle and pancreas: no studies predicted a preventive effect mediated by PA.

Discussion

The effect of PA on cancer incidence is perceived to be large, but quantification measures and the implied

biological mechanisms remain elusive. A possible dose-response pattern [23, 52] compelled the “World Cancer Research Fund (WRCF) second report” [62] to report “more PA is better”, but drove researchers to three unexplained questions: how much PA is enough, what type is best (LT-PA versus OPA) and when during the life cycle is it important? It is possible that PA non-standardised available measures contributed to inconsistency in some results. Hence, we mainly focused on meta-analysis reports because their selection criteria allow one to exclude major heterogeneities that cannot be controlled in single trials. However, few studies found a protective role for OPA compared with LT-PA in cancer prevention and the explanation could be that occupational activities are known to be stressful and stress can partially counteract the beneficial effect of OPA through oxidative stress and DNA damage [12].

In order to remove all confounding factors and the prominent role played by genetic predisposition, cancer outcomes may not represent primary end points. There is a need for more “intermediate end-points” to assess PA biological effects through the measure of pre-carcinogenic biomarkers (e.g., apoptosis-related proteins, IGFs and immune markers) so that they can be introduced in community intervention studies [62, 63].

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