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-analisys	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)
					LT-PA	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)
				Rectum	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-analisys	Colon	OPA	BG	0.85	(0.77-0.93)	0.73	(0.67-0.79)
					LT-PA	BG	0.82	(0.75-0.87)	0.69	(0.62-0.78)
					Any	M	0.81	(0.73-0.89)	0.68	(0.64-0.72)
						F	0.89	(0.81-0.99)	0.72	(0.66-0.79)
Wolin et al.	2011	20	Random meta-analisys	Colon	Any	M	0.81	(0.67-0.98)	-	
						F	0.87	(0.74-1.02)	-	
Harris et al.	2009	14	Random	Colon	LT-PA	M	0.80	(0.67-0.96)	-	
						F	0.86	(0.76-0.98)	-	
			Meta-analisys	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)*
					LT-PA (AMP)	F	1.14	(0.36)*	0.42	(0.26)*
					TPA (PMP)	F	1.60	(0.54)*	-	
					LT-PA (PMP)	F	0.64	(0.33)*	0.71	(0.40)*
Voskuil et al.	2005	11	Fixed meta-analisys	Endometrium	Any	F	0.77	(0.70-0.85)	0.71	(0.63-0.80)
Tardon et al.	2007	13	Random meta-analisys	Lung	High PA	M	-		0.75	(0.66-0.86)
						F	-		0.62	(0.48-0.79)
					Moderate/ mild PA	M	-		0.93	(0.85-1.00)
						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 20^{th} to 95^{th} 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 progesteronic 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 ≥ 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 aetiologic 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].

References

[1] Demark-Wahnefried W, Rock CL, Patrick K, et al. *Lifestyle interventions to reduce cancer risk and improve outcomes*. Am Fam Physician 2008;77:1573-8.

[2] Friedenreich CM, Orenstein MR. *Physical activity and cancer prevention: etiologic evidence and biological mechanisms*. J Nutr 2002;132(Suppl):3456S-64.

[3] Shephard RJ, Rhind S, Shek PN. *The impact of exercise on the immune system: NK cells, interleukins 1 and 2, and related responses*. Exerc Sport Sci Rev 1995;23:215-41.

[4] Yu H, Rohan T. *Role of the insulin-like growth factor family in cancer development and progression*. J Natl Cancer Inst 2000;92:1472-89.

[5] Haskell WL, Lee IM, Pate RR, et al. *Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association*. Med Sci Sports Exerc 2007;39:1423-34.

[6] Harriss DJ, Atkinson G, Batterham A, et al. *Colorectal Cancer, Lifestyle, Exercise And Research Group. Lifestyle factors and colorectal cancer risk (2): a systematic review and meta-analysis of associations with leisure-time physical activity*. Colorectal Dis 2009;11:689-701.

[7] Laukkanen JA, Rauramaa R, Makikallio TH, et al. *Intensity of leisure-time physical activity and Cancer mortality in men*. Br J Sports Med 2011;45:125-9.

[8] Pan SY, DesMeules M. *Energy intake, physical activity, energy balance, and cancer: epidemiologic evidence*. Methods Mol Biol 2009;472:191-215.

[9] World Cancer Research Fund and the American Institute for Cancer Research. *Food, nutrition, physical activity and the prevention of cancer: a global perspective*. First edition. Washington DC: American Institute for Cancer Research 1997.

[10] International Agency for Research on Cancer. *Weight control and physical activity*. Vol 6. IARC Handbooks of cancer prevention: Lyon 2002.

[11] Penalva RG, Lancel M, Flachskamm C, et al. *Effect of sleep and sleep deprivation on serotonergic neurotransmission in the hippocampus: a combined in vivo microdialysis/EEG study in rats*. Eur J Neurosci.2003;17:1896-906.

[12] Seril DN, Liao J, Yang G-Y, et al. *Oxidative stress and ulcerative colitis-associated carcinogenesis: studies in humans and animal models*. Carcinogenesis 2003;24:353-62.

[13] Basterfield L, Reul JM, Mathers JC. *Impact of physical activity on intestinal cancer development in mice*. J Nutr 2005;135(Suppl):3002S-8.

[14] Zhu Z, Jiang W, McGinley JN, et al. *Energetics and mammarycarcinogenesis: effects of moderate-intensity running and energy intake oncellular processes and molecular mechanisms in rats*. J Appl Physiol 2009;106:911-8.

[15] Basterfield L, Mathers JC. *Intestinal tumours, colonic butyrate and sleep in exercised Min mice*. Br J Nutr 2010;104:355-63.

[16] Colbert LH, Mai V, Tooze JA, et al. *Negative energy balance induced by voluntary wheel running inhibits polyp development in APCMin mice*. Carcinogenesis 2006;27:2103-7.

[17] Baltgalvis KA, Berger FG, Peña MM, et al. *Effect of exercise on biological pathways in ApcMin/+ mouse intestinal polyps*. J Appl Physiol 2008;104:1137-43.

[18] Zhu Z, Jiang W, Sells JL, et al. *Effect of non motorized wheel running on mammary carcinogenesis: circulating biomarkers, cellular processes, and molecular mechanisms in rats*. Cancer Epidemiol Biomarkers Prev 2008;17:1920-9.

[19] Jiang W, Zhu Z, Thompson HJ. *Effects of physical activity and restricted energy intake on chemically induced mammary carcinogenesis*. Cancer Prev Res (Phila) 2009;2:338-44.

[20] Mann PB, Jiang W, Zhu Z, et al. *Wheel running, skeletal muscle aerobic capacity and 1-methyl-1-nitrosourea induced mammary carcinogenesis in the rat.* Carcinogenesis 2010;31:1279-83.

[21] Esser KA, Harpole CE, Prins GS, et al. *Physical activity reduces prostate carcinogenesis in a transgenic model*. Prostate 2009;69:1372-7.

[22] Michna L, Wagner GC, Lou YR, et al. *Inhibitory effects of voluntary running wheel exercise on UVB-induced skin carcinogenesis in SKH-1 mice*. Carcinogenesis 2006;27:2108-15.

[23] Samad AK, Taylor RS, Marshall T, et al. *A meta-analysis of the association of physical activity with reduced risk of colorectal cancer.* Colorectal Dis 2005;7:204-13.

[24] Wolin KY, Yan Y, Colditz GA, et al. *Physical activity and colon cancer prevention: a meta-analysis*. Br J Cancer 2009;100:611-6.

[25] Wolin KY, Yan Y, Colditz GA. *Physical activity and risk of colon adenoma: a meta-analysis.* Br J Cancer 2011;104:882-5.

[26] Meyerhardt JA, Ogino S, Kirkner GJ, et al. *Interaction of molecular markers and physical activity on mortality in patients with colon cancer*. Clin Cancer Res 2009;15:5931-6.

[27] Wertheim BC, Martínez ME, Ashbeck EL, et al. *Physical activity as a determinant of fecal bile acid levels*. Cancer Epidemiol Biomarkers Prev 2009;18:1591-8.

[28] Harriss DJ, Cable NT, George K, et al. *Physical activity before and after diagnosis of colorectal cancer: disease risk, clinical outcomes, response pathways and biomarkers*. Sports Med 2007;37:947-60.

[29] Monninkhof EM, Elias SG, Vlems FA, et al. *Physical activity and breast cancer: a systematic review*. Epidemiology 2007;18:137-57.

[30] Neilson HK, Friedenreich CM, Brockton NT, et al. *Physical activity and postmenopausal breast cancer: proposed biologic mechanisms and areas for future research*. Cancer Epidemiol Biomarkers Prev 2009;18:11-27.

[31] Friedenreich CM, Cust AE. *Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects*. Br J Sports Med 2008;42:636-47.

[32] Friedenreich CM. *The role of physical activity in breast cancer etiology*. Semin Oncol 2010 Jun;37:297-302.

[33] Adams SA, Matthews CE, Hebert JR, et al. *Association of physical activity with hormone receptor status: the Shanghai Breast Cancer Study*. Cancer Epidemiol Biomarkers Prev 2006;15:1170-8.

[34] West-Wright CN, Henderson KD, Sullivan-Halley J, et al. *Long-term and recent recreational physical activity and survival after breast cancer: the California Teachers Study*. Cancer Epidemiol Biomarkers Prev 2009;18:2851-9.

[35] Suzuki R, Iwasaki M, Yamamoto S, Iet al.; Japan Public Health Center-based Prospective Study Group. *Leisure-time physical activity and breast cancer risk defined by estrogen and progesterone receptor status--the Japan Public Health Center-based Prospective Study*. Prev Med 2011;52:227-33.

[36] Friedenreich CM, Thune I. *A review of physical activity and prostate cancer risk*. Cancer Causes Control 2001;12:461-75.

[37] Johnsen NF, Tjønneland A, Thomsen BL, et al. *Physical activity and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.* Int J Cancer 2009;125:902-8.

[38] Orsini N, Bellocco R, Bottai M, et al. *A prospective study of lifetime physical activity and prostate cancer incidence and mortality.* Br J Cancer 2009;101:1932-8.

[39] Haseen F, Murray LJ, O'Neill RF, et al. *A randomised controlled trial to evaluate the efficacy of a 6 month dietary and physical activity intervention for prostate cancer patients receiving androgen deprivation therapy*. Trials 2010;11:86.

[40] Culos-Reed SN, Robinson JW, Lau H, et al. *Physical activity for men receiving androgen deprivation therapy for prostate cancer: benefits from a 16-week intervention*. Support Care Cancer 2010;18:591-9.

[41] Patel AV, Rodriguez C, Jacobs EJ, et al. *Recreational physical activity and risk of prostate cancer in a large cohort of U.S. men*. Cancer Epidemiol Biomarkers Prev 2005;14:275-9.

[42] Sea J, Poon KS, McVary KT. *Review of exercise and the risk of benign prostatic hyperplasia*. Phys Sportsmed 2009;37:75-83.

[43] Barnard RJ, Leung PS, Aronson WJ, et al. *A mechanism to explain how regular exercise might reduce the risk for clinical prostate cancer*. Eur J Cancer Prev 2007;16:415-21.

[44] Neuhouser ML, Schenk J, Song YJ, et al. *Insulin-like growth factor-I, insulin-like growth factor binding protein-3 and risk of benign prostate hyperplasia in the prostate cancer prevention trial.* Prostate 2008;68:1477-86.

[45] Voskuil DW, Monninkhof EM, Elias SG, et al. *Task Force Physical Activity and Cancer. Physical activity and endometrial cancer risk, a systematic review of current evidence*. Cancer Epidemiol Biomarkers Prev 2007;16:639-48.

[46] Gierach GL, Chang SC, Brinton LA, et al. *Physical activity, sedentary behavior, and endometrial cancer risk in the NIH-AARP Diet and Health Study*. Int J Cancer 2009;124:2139-47.

[47] Patel AV, Feigelson HS, Talbot JT, et al. *The role of body weight in the relationship between physical activity and endometrial cancer: results from a large cohort of US women*. Int J Cancer 2008;123:1877-82.

[48] Conroy MB, Sattelmair JR, Cook NR, et al. *Physical activity, adiposity, and risk of endometrial cancer*. Cancer Causes Control 2009;20:1107-15.

[49] John EM, Koo J, Horn-Ross PL. *Lifetime physical activity and risk of endometrial cancer*. Cancer Epidemiol Biomarkers Prev 2010;19:1276-83.

[50] Friedenreich CM, Cook LS, Magliocco AM, et al. *Case-control study of lifetime total physical activity and endometrial cancer risk*. Cancer Causes Control 2010;21:1105-16.

[51] Cust AE, Armstrong BK, Friedenreich CM, et al. *Physical activity and endometrial cancer risk: a review of the current evidence, biologic mechanisms and the quality of physical activity assessment methods*. Cancer Causes Control 2007;18:243-58.

[52] Tardon A, Lee WJ, Delgado-Rodriguez M, et al. *Leisure-time physical activity and lung cancer: a meta-analysis*. Cancer Causes Control 2005;16:389-97.

[53] Leitzmann MF, Koebnick C, Abnet CC, et al. *Prospective study of physical activity and lung cancer by histologic type in current, former, and never smokers*. Am J Epidemiol 2009;169:542-53.

[54] Kubik A, Zatloukal P, Tomasek L, et al. *A case-control study of lifestyle and lung cancer associations by histological types*. Neoplasma 2008;55:192-9.

[55] Kubík A, Zatloukal P, Tomásek L, et al. *Interactions between smoking and other exposures associated with lung cancer risk in women: diet and physical activity.* Neoplasma 2007;54:83-8.

[56] Steindorf K, Friedenreich C, Linseisen J, et al. *Physical activity and lung cancer risk in the European Prospective Investigation into Cancer and Nutrition Cohort.* Int J Cancer 2006;119:2389-97.

[57] Mao Y, Pan S, Wen SW, et al. The Canadian Cancer. *Physical activity and the risk of lung cancer in Canada.* Am J Epidemiol 2003;158:564-575.

[58] Olsen CM, Bain CJ, Jordan SJ, et al. *Australian Ovarian Cancer Study Group. Recreational physical activity and epi-*

thelial ovarian cancer: a case-control study, systematic review, and meta-analysis. Cancer Epidemiol Biomarkers Prev 2007;16:2321-30.

[59] Rossing MA, Cushing-Haugen KL, Wicklund KG, et al. *Recreational physical activity and risk of epithelial ovarian cancer*. Cancer Causes Control 2010;21:485-91.

[60] Chow WH, Dong LM, Devesa SS. *Epidemiology and risk factors for kidney cancer*. Nat Rev Urol 2010;7:245-57.

[61] Rossing MA, Remler R, Voigt LF, et al. *Recreational physical activity and risk of papillary thyroid cancer (United States)*. Cancer Causes Control 2001;12:881-5.

[62] World Cancer Research Fund and the American Institute for Cancer Research. *Food, nutrition, physical activity and the prevention of cancer: a global perspective*. Second edition. Washington, DC: American Institute for Cancer Research 2007.

[63] McTiernan A, Schwartz RS, Potter J, et al. *Exercise clinical trials in cancer prevention research: a call to action*. Cancer Epidemiol Biomarkers Prev 1999;8:201-7.

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