Endometrial cancer and physical activity

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A- Conception and study design; **B -** Collection of data; **C -** Data analysis; **D -** Writing the paper; **E**- Review article; **F** - Approval of the final version of the article; **G** - Other (please specify)

ABSTRACT

Physical activity (PA) is an important modifiable risk factor for endometrial cancer (EC). PA has been studied using diverse measures including metabolic equivalent of task MET, duration, frequency and subjective levels, but for practical reasons most of epidemiological studies use questionnaires rather than objective measures to document PA. Moderate-intense daily PA has a protective effect and have a 20-40% reduced risk of EC. In this review complex and variable behaviour, and the ability of epidemiological studies to determine the relationship between PA and EC has been discussed.
Keywords: Endometrial cancer, physical activity

DOI: 10.5604/01.3001.0012.1330

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Received: 06.05.2018
Accepted: 20.06.2018
Progress in Health Sciences
Vol. 8(1) 2018 pp 203-207

INTRODUCTION

Endometrial cancer (EC) is the sixth most common malignancy among females worldwide with an estimated incidence of about 320,000 new cases in the year 2012. In developed countries, EC is the fourth most common cancer in women. Every year about 88,000 new cases are registered in the European Union. The highest incidence of EC was in North America (the age-standardized rate is 19.1). In Europe the age-standardized rate is 13.9 whereas in Poland, the age-adjusted incidence was 13.7 per 100 000 women per year. Incidence of EC is on the rise with a lifetime risk of approximately 3%. Most strikingly, 5-year survival is currently significantly worse than 30 years ago, making EC only one of two cancers with increased mortality [1]. Both endogenous and exogenous estrogen and insulin promote endometrial carcinogenesis. Established risk factors include use of unopposed estrogen therapy, early menarche, late menopause, nulliparity, obesity and diabetes mellitus, with excess body weight accounting for about 40% of incident EC cases [2].

Physical activity and endometrial cancer

More than 100 scientific review papers based on PubMed database have examined the association between EC and PA, and many of these have found that adults, who increase their PA, in intensity, duration, or frequency, can reduce the risk of EC regardless of their body mass index (BMI). In addition, the greatest reduction in risk was in more active individuals. The protective effect also appears to be higher in those who perform high-intensity activities, although the exact level of training has not been established [3, 4].

Physical activity's biological link with EC has been hypothesized to be mediated through three hormonal systems: sex steroids, insulin and insulin-like growth factors, and leptin, and adiponectin levels [5]. Among other evidence for a link between PA and these hormonal systems, randomized exercise trials show that randomization to a one year PA intervention reduces levels of estrone and estradiol [6, 7] and insulin [8] in postmenopausal women, with effects mediated, at least in part, through reduced adiposity.

Physical activity can also modify a number of inflammatory and immune factors that are involved in this process. However, the role of the timing, duration, and intensity of PA is unclear. According to some authors, 30-60 min. of moderate-intense daily PA has a protective effect and have a 20-40% reduced risk of EC. This risk does not seem to be vary by age. Change in the BMI, level of sex hormones and metabolism appears to be the main biological mechanisms that connect PA and EC [9-11].

In The Endometrial Cancer 2013 Report from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), PA of all types (occupational, household, transport and recreational) was classified as a probable protective factor of EC [12]. Published case-control and cohort studies utilize a variety of PA measurements, and only some reported on intensity of activity and risk. Sitting time is also emerging in the literature as a possible independent risk factor for EC [13].

As the adipose tissue is the major producer of estrogen for postmenopausal women [14] and obesity is a major determinant of hyperinsulinemia [15, 16], reduction in adiposity may be a possible pathway through which PA reduces EC risk. Yet, even in the absence of weight reduction, PA has been shown to suppress estrogen and enhance insulin sensitivity [11,17], which suggests the presence of a direct effect of PA on EC risk, independent of adiposity.

As mentioned above high insulin level does so directly by facilitating endometrial proliferation or indirectly by increasing the levels of other EC facilitators (e.g., estrogen and IGF-1) by means of decreasing the levels of their binding proteins (e.g., SHBG and IFGBP) that lower the bioavailability of estrogen and IGF-1 [2,18,19].

Increased PA levels are related to lower insulin levels and improved insulin sensitivity [20], which lowers exposure to hormones and growth factors available in the blood. Increased PA has also been shown to improve free radical defenses by upregulating free scavenger enzymes and antioxidant levels [21]. Exercise is also linked with an increase in antitumor immune defenses and improvements in antioxidant defense systems, increasing the number and activity of macrophages, lymphokine-activated killer cells and regulating cytokines [22]. Friedenreich and Orenstein in an article from 2002 [23] on the role of PA in reducing the risk of EC indicate an important role of decreasing the percentage of adipose tissue. Voskuil et al. [24] pooled diverse types of PA including total, occupational and leisure-time PA, suggesting a benefit associated with being generally active, their analysis specifically focused on leisure-time PA, which is relatively more modifiable and, thus, a better target for public health intervention.

Moore et al. [25] found that PA was clearly associated with reduced risk of EC, with active women having an approximately 30% lower risk than inactive women. These researchers put a hypothesis that sitting time is independently associated with endometrial cancer and to refine estimates of the proportion of endometrial cancers that could be prevented by increasing participation in moderate–vigorous physical activity and reducing sitting time. Given that obesity is an established risk factor for EC [2,18], obesity could be an intermediate or confounder. To the extent that

PA helps control body weight, [26], BMI may be an intermediate. Yet, as obesity may limit PA making overweight and obese people less likely to engage in PA, or PA could be correlated with other behaviors (e.g., diet) that can independently influence body weight, BMI could be a confounder.

Despite consistent evidence on the directionality of the relationship, important questions remain to be elucidated. First, to see whether the benefit of PA on EC risk continues or plateaus at a high level of PA, the shape of dose-response needs to be identified. Second, as PA has been studied using diverse measures including metabolic equivalent of task (MET)-hour/week, duration (e.g., hour/week), frequency (e.g., times/week) and subjective levels (e.g., inactive, moderately inactive, moderately active and active), it is critical to investigate the relationship by measures and to examine consistency across different measures. In particular, two measures are of interest. MET-hour/week is a comprehensive measure as it incorporates intensity, duration and frequency of PA [27,28]. Hour/week, though lacking information on intensity, is a useful measure as most PA guidelines are made in terms of hour/week owing to its interpretability. Given the interrelationship that MET-hour/week is the product of MET and hour/week, results from respective measures could be compared based on reasonable assumptions on the types of PA [4].

One MET, defined as the ratio of work metabolic rate to a standard resting metabolic rate of 1.0 (4.184 kJ kg^{-1} h^{-1}), is considered a resting metabolic rate achieved during quiet sitting. MET levels were calculated as hours per week from self-report of various forms of activity (average times per week, average minutes per time, and number of months per year) performed in the two to five years before interview [29].

Leisure-time PA are activities done at an individual's discretion to improve or maintain fitness or health. Many analysis includes leisure-time activities of moderate intensity, defined as an intensity of three or more METs, or vigorous intensity, defined as six or more METs; these are the intensity levels recommended by PA guidelines [30]. Analytical models should include: age, sex, smoking, alcohol, race/ethnicity, education, BMI, hormone replacement therapy, use of oral contraceptives, age during menarche, age at menopause and parity as well as diet as a potential variable, adding variables accompanying the adoption of kilocalories, vitamins, supplements and consumption of fruits, vegetables and red meat. Women who had hysterectomy should be excluded from the study.

The impact of physical activity on the risk of EC can be also assessed using various questionnaires. Their examples are included in Table I. Although available questionnaires can properly classify participants according to the level of PA, there is still a significant level of measurement error when assessing the PA of a given person. It has been shown that PA questionnaires with similar measurement characteristics lead to a significant weakening of the estimates of the relative risk of links between PA and the risk of EC.

Table 1. Selected questionnaires designed to assess the physical activity of adults [31-34]

Name of the questionnaire	The type of motor activity being assessed	Analyzed period; way of collecting data	Repeatability of the questionnaire (test-retest)	Correlation coefficient with VO_2max
Minesota Leisure-Time Physical Activity Questionnaire (MLTPAQ)	during free time from work	last 12 months; questionnaire completed by the interviewer	r=0,79*-0,88* (after one month)	r=0,47*
Paffenbarger Physical Activity Questionnaire (PPAQ)	during free time from work	last 7 days or 12 months; questionnaire completed by the respondent or pollster	r=0,72* (after one month)	r=0,60*
Stanford Usual Activity Questionnaire (SUAQ)	during free time from work	typical activity or last 3 months; questionnaire completed by the interviewer	r= 0,67*-0,77* (after one month)	r=0,27*-0,38*
Seven-Day Physical Activity Recall (SDPAR)	whole	last 7 days; questionnaire completed by the interviewer	r=0,99 (after two weeks)	r=0,33*

*p<0,05

CONCLUSIONS

In conclusion, further studies are needed in the future to understand the positive biological effects of PA on EC, especially the type 1 (endometrioid) that mostly benefit from exercise, and the frequency and intensity of training that can improve quality of life and survival of EC patients because any decrease in risk of cancer associated with PA may therefore be public health relevant, and important for cancer prevention efforts.

Conflicts of interest

The authors declare no conflicts of interest.

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