Physical activity and risk of endometrial cancer in the Norwegian Women and Cancer (NOWAC) Study

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Complete List of Authors:	Borch, Kristin; UiT The Arctic University of Norway, Department of Community Medicine Weiderpass, Elisabete ; UiT The Arctic University of Norway, Department of Community Medicine; Karolinska Institutet, Department of Medical Epidemiology and biostatistics; Kreftregisteret, Institute of Population-Based Cancer Research; Samfundet Folkhalsan, Genetic Epidemiology Group Braaten, Tonje; Department of Community Medicine Tromsø, Norway, ISM Jareid, Mie; UiT - The Arctic University of Norway, Department of Community Medicine Gavrilyuk, Oxana; University of Tromsø, Institute of Community Meidicine Licaj, Idlir; Department of Community Medicine,
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Physical activity and risk of endometrial cancer in the Norwegian Women and Cancer (NOWAC) Study

Kristin B Borch[1*], Elisabete Weiderpass[1, 2, 3, 4], Tonje Braaten[1], Mie Jareid[1], Oxana A Gavrilyuk[1], Idlir Licaj[1]

*Cooresponding author: Kristin Benjaminsen Borch, email: Kristin.benjaminsen.borch@uit.no

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Novelty and impact statements:

We found evidence of a dose-response association between physical activity and overall endometrial cancer.The novelty include use of repeated measurements for physical activity and confounders combined with multiple imputation to address attrition, which is a particular problem in observational epidemiology. As a nationally representative cohort our study gave us an unique opportunity to calculate robust population attributable fractions. 22% of endometrial cancer could be avoided if women increase their physical activity level.

Abbreviations:

BMI – body mass index
CI – confidence interval
CUP - Continous Update Project
PA – physical activity
PAF – population attributable fractions
HR – hazard ratio
RR – relative risk
NOWAC – The Norwegian Women and Cancer Study
WCRF/AICR - World Cancer Research Fund/American Institute for Cancer Research

Affiliations:

1. Department of Community Medicine, Faculty of Health Sciences, UiT, The Arctic University of Norway, Tromsø, Norway
2. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
3. Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway
4. Genetic Epidemiology Group, Folkhälsan Research Centre, Samfundet Folkhälsan, Helsinki, Finland

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Author's contributions

KBB, EW and IL designed the study. IL and KBB preformed all statistical analyses, and drafted the manuscript. EW, MJ, and OG critically revised the manuscript. TB participated in the statistical analyses and revised the manuscript critically. All authors read and approved the final manuscript.

Abstract

Few studies have investigated the association between endometrial cancer and physical activity (PA) using repeated measures of PA and different subtypes of endometrial cancer.

We aimed to investigate the association between endometrial cancer and PA level at two points in time in women with different body mass index (BMI) profiles, and to calculate the population attributable fraction (PAF) of endometrial cancer for low PA levels.

We included 82,759 women with complete information on PA at baseline in the Norwegian Women and Cancer Study; 52,370 had follow-up information on PA. 687 endometrial cancer cases were identified. Multivariate cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). The PAF indicated the proportion of endometrial cancer that could be avoided in the population if these women had a higher PA level.

There was a statistically significant association between low PA levels at baseline and follow-up and endometrial cancer risk, with a dose-response trend (lowest PA level: HR=1.60, 95% CI 1.16-2.20; highest PA level: HR=0.73, 95% CI 0.45-1.16 compared to the median). Analyses that included follow-up measurements yielded similar results. 21.9% (95% CI 7.1-34.3) of endometrial cancers could be avoided if women with low PA levels (≤ 4 in a 1-10 degree self reported PA scale) increased their PA levels to 5-10.

We found an inverse dose-response association between PA and endometrial cancer, independent of BMI. In this nationally representative cohort, 21.9% of endometrial cancers could potentially be avoided if PA levels increased to higher PA levels.

Introduction

Endometrial cancer is the sixth most common cancer, and the most frequent gynecologic malignancy among women in Norway. In 2014, 727 new cases were diagnosed and 81 women died of the disease [1]. Established risk factors for endometrial cancer include use of exogenous estrogens unopposed by progestagens, early menarche (10-12 years of age), late menopause, nulliparity, diabetes mellitus, and obesity. Currently, the majority of endometrial cancer, and about half of the cases in postmenopausal women are attributable to being overweight or obese [2-4]. As the population ages and the prevalence of overweight, obesity, and sedentary lifestyle increase, the incidence of endometrial cancer is also expected to increase, especially in postmenopausal women [5, 6]. Thus primary prevention of endometrial cancer through modifiable lifestyle factors is of potential public health importance.

Physical activity (PA) is a modifiable lifestyle factor, which is important in the regulation of hormones and metabolic pathways. It is also associated with weight control, and thus may reduce endometrial cancer risk [7-9]. A pooled analysis of nine cohorts from Europe and the United States included 1.44 million participants and found a 21% reduced risk of endometrial cancer associated with recreational PA [10] . However, within individual studies, results are inconsistent [8]. For example, the Women's Health Study did not find any relationship between recreational PA and walking and endometrial cancer risk [11]. Similarly, there was no significant association between total PA – including occupational, recreational, and household-related PA – and endometrial cancer risk in the European Prospective Investigation into Nutrition and Cancer [12]. The 2007 evaluation by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concluded that there is a probable relationship between PA and endometrial cancer despite the variety of PA assessments not allowing for meta-analysis on dose-response [7]. This conclusion was supported in their Continous Update Project (CUP) report from 2013 [8]. Of four cohort

studies published after the 2013 CUP report [10, 13-15], three found an inverse association between recreational PA and endometrial cancer risk [10, 15, 14], and one did not [13].

Few studies have investigated the association between endometrial cancer and PA using a total and repeated measure of PA and different subtypes of endometrial cancer [12, 16, 17]. Endometrial cancer is classified as type I (estrogen dependent), which constitutes the majority of cases (about 80%), and type II (estrogen independent), based on clinical, endocrine, and epidemiological observations. The most common histological subtypes of endometrial cancer are endometrioid carcinoma, serous carcinoma, carcinosarcoma, and clear cell carcinoma [18]. While the association between body mass index (BMI) and endometrial cancer is well established, the relationship between PA and endometrial cancer in women with different body sizes remains unclear.

The present study aimed to investigate the association between endometrial cancer and PA level at two points in time in women with different BMI profiles in the Norwegian Women and Cancer (NOWAC) Study, and to calculate the population attributable fraction (PAF) of endometrial cancer for low PA levels.

Methods

The NOWAC Study

The NOWAC Study is a nationally representative cohort study that has been described in detail previously [19, 20]. Briefly, random samples of Norwegian women aged 30-70 years were invited to participate during three waves of data collection (1991/92, 1996/97, and 2003/04) [20]. More than 172,000 women completed a questionnaire with detailed questions regarding lifestyle, diet, and health, and were enrolled in the study (overall response rate: 52.7%). The NOWAC Study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate, and all particpants included in the study gave written informed consent.

In this analysis we used information from enrollment questionnaires completed in the period from 1996 to 2004 (baseline), and those with follow-up questionnaires completed 6-8 years after enrollment. In total 101,321 women completed questionnaires in these periods and were eligible for inclusion in this study. We excluded women with prevalent cancers other than non-melanoma skin cancer at baseline (n=4,454), those who emigrated or died before the start of follow-up (n=20), those with hysterectomy (n=5,426), and those who had missing information on PA level at baseline (n=8,662). Thus, the final analytical study sample consisted of 82,759 women. Follow-up information on PA level, smoking, weight, and height was available for for 52,370 (63.3%) of these women.

Assessment of PA level and covariates

PA level was assessed in the NOWAC questionnaires on a 10-point scale by the following question: *"By physical activity we mean activity both at work and outside work, at home, as well as training/exercise and other physical activity, such as walking, etc. Please mark the number that best describes your level of physical activity; 1 being very low and 10 being very*

high". This PA scale has been validated [21] and refers to the total amount of PA across different domains, including recreation, occupation, transportation, and household in one global score. Moderate, but significant Spearman's rank correlation coefficients were found (range: 0.36-0.46; $P<0.001$) between PA level at enrollment and concurrent outcomes from criterion measures of a combined sensor monitoring heart rate and movement. The PA scale appeared valid to rank PA level in Norwegian women, but not to quantify a definite dose of PA [21].

Information on the covariates height, weight, age at menarche, parity, oral contraceptive use, menopausal status, age at menopause, hormone therapy use, years of education, smoking status and alcohol consumption, were obtained from NOWAC questionnaires. The women were considered postmenopausal if they stated that the period had stopped or reported use of hormonal therapy if they were ≥53years. This cut-off point is based on the definition used in the the Million Women Study [22], and has been used by the NOWAC study earlier [23]. Information on height and weight was used to calculate BMI (kg/m^2).

Cancer incidence, death, and emigration

Women diagnosed with a primary, invasive, malignant neoplasm of the endometrium (International Statistical Classification of Diseases, Injuries and Causes of Death Revision 7 codes 172.0 [24]) were identified through linkage to the Cancer Registry of Norway, from which date of diagnosis and morphology (International Classification of Diseases for Oncology, 3rd edition) were also obtained. Based on the morphology, endometrial cancers were categorized into overall endometrial cancer (all subtypes), endometrioid carcinoma, type 1 endometrial cancer (adenocarcinoma NOS, endometrioid, and squamous carcinomas), and other subtypes (non-endometrioid or non-type 1).

Information on date of death or emigration was obtained through linkage to the Norwegian National Population Register.

Statistical methods

Analyses using baseline data only

We used Cox proportional hazard regression models to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) comparing five categories of PA level (1-2, 3-4, 5-6, 7-8, and 9-10). PA level 5-6 was set as the reference group. Follow-up time was defined as the interval between age at baseline and age at cancer diagnosis, death, emigration, or the end of follow-up (31 December 2013), whichever came first.

Departures from the proportional hazards assumption in the Cox models were tested through the inclusion of an interaction variable between categories of PA and underlying time (age). A preliminary analysis of baseline data only was used to select the covariates that were adjusted for in the final models. In the preliminary model, we adjusted for: height (in metres), BMI (normal weight: <25, overweight: 25–29.9, obese: ≥30 kg/m^2), age at menarche (<12, 13-14, 15+ years), parity (0, 1, 2, 3, 4+) , oral contraceptive use (ever/never), menopausal status (premenopausal, perimenopausal, postmenopausal, hormone therapy use ≥53 years), hormone therapy use (ever/never), years of education (≤9, >9-12, ≥13 years), smoking status (never, former, current), alcohol consumption (grams per day), and diabetes mellitus (yes/no). The removal of each covariate had to be associated with a change in the regression coefficients of at least 10% in any of the categories of PA level to be included in the final model. To test for linear trend, we used the original, 10-point PA scale, modelled as a continuous variable in the analyses. Interactions (log likelihood test) between PA and the above-mentioned categories of BMI, educational attainment and smoking status were tested. The Wald $\chi 2$ statistic was used to test for heterogeneity between normal weight and obese women.

Analyses using repeated PA measurements

We used the method proposed by Hu et al [25], i.e., baseline data was used until follow-up information became available, death, or emigration, whichever occurred first. Thereafter follow-up information was applied until death, emigration, or the end of the study period, which ever occurred first. In the analysis using repeated PA measurements, we also used follow-up information on BMI and smoking once it became available.

Complementary analysis - multiple imputation

Compared to women who did not drop out of the study, those who dropped out of the study at follow-up (n=30,389 (36.7%)), were more often overweight (31.4% vs 29.2%) or obese (10.3% vs 8.6%), more often reported oral contraceptive use (46.6% vs 43.5%) and hormone therapy use (36.7% vs 31.7%), more often had a history of diabetes mellitus (2.9% vs 1.7%), and had fewer years of education (24.3% vs 23.7%). They were also more often current smokers, but on average they had a similar PA level and alcohol consumption as women who did not drop out of the study. In order to deal with dropouts, we used multiple imputation models [26] and compared the results with those of complete-case analyses. Multiple imputation models were used under the assumption that data was missing at random. To reduce sampling variability, we created 20 replicate datasets from the imputation simulation [27]. We used the outcomes overall endometrial cancer, type 1 endometrial cancer, and endometrioid carcinoma. Nelson-Aalen cumulative hazard estimator was included as a predictor in the imputation models [28]. The estimates from the 20 imputed datasets were combined using Rubin's rules [29]. All the analyses and multiple imputations were done in STATA version 14.0 (Stata Corp, College Station, TX, USA).

PAF calculation

We calculated the PAF to estimate the proportion of endometrial cancer that could be avoided in the population if women had different PA levels, using the formula: *PAF= Pe*(RRe-1)/[Pe*RR+(1-Pe)],* where *Pe* is the proportion of PA level in the study population and *RRe* is the RR in the model adjusting for BMI (model 1) and the final baseline multivariable proportional hazards regression model (model 2), including all aforementioned confounders and BMI. We calculated two-sided 95% CIs for the PAFs using the PUNAF Stata module [30]. The PA levels were divided into two levels; levels 1 to 4 were classified as exposed to low PA levels and levels 5-10 as unexposed to low PA levels. The PAF was interpreted as the proportion of overall endometrial cancers that would not occur in the average population if PA levels were between 5 and 10 according to the scale.

Results

The median age at baseline was 51 years. During a mean follow-up time of nearly 13 years, 687 cases of endometrial cancer were identified, with type 1 endometrial cancer (adenocarcinoma not otherwise specified [NOS], endometrioid and squamous carcinoma) accounting for 83.8% of the cases. The age at diagnosis ranged between 42 and 86 years, with a mean of 62 years of age. Nearly half (43%) of the women reported a PA level between 5 and 6 (Table 1), and approximately 74% of the women reported a PA level between 5 and 10. Women with a PA level >5 had a lower BMI, used less hormone therapy, reported less diabetes mellitus, and were more often never smokers compared to women reporting low PA levels.

Multivariable models of the associations between baseline and one follow-up measurement of PA and endometrial cancer risk showes that compared to women with a PA level of 5-6, those with a PA level of 1-2 had a 60% higher risk of overall endometrial cancer (HR=1.60, 95% CI 1.16-2.20). For analyses using repeated PA measurements, the corresponding risks adjusted for BMI and smoking status were similar to those obtained when using baseline data only (HR=1.54, 95% CI 1.01-2.). In analyses using baseline data only and those using repeated PA measurments, BMI and smoking status were negatively associated with the risk of type 1 endometrial cancer and endometroid carcinomas. Compared to the age-adjusted models, the associations were attenuated in the multivariable adjusted models that included BMI (Table 2).

Interactions between PA and categories of BMI, educational attainment and smoking status were not significant. However, as BMI is a strong risk factor for endometrial cancer, we decided to investigate the association between PA and endometrial cancer risk in normal weight, overweight, and obese women, even though the interaction term was not significant (p=0.49).When analyses were stratified by BMI category the PA levels 7-10 were collapsed,

PA was not associated with overall endometrial cancer among normal-weight women in analyses using baseline data only ($HR_{PA(1-2)\ vs\ (5-6)}$=1.32, 95% CI 0.71-2.45). The corresponding association in obese participants was $HR_{PA(1-2)\ vs\ (5-6)}$=3.08 (95% CI 1.76-5.39) ($p_{heterogeneity}$=0.05) (Table 3).

Using multiple imputation, we found that the estimates at all levels of adjustment and for all endpoints (overall endometrial cancer, type 1 endometrial cancer, and endometrioid carcinoma) were consistent with those obtained from the complete-case analyses (Table 4). PAF calculations showed that if women with a PA level ≤4 increased to levels 5-10 in the scale, 21.9% (95% CI: 7.1-34.3) of endometrial cancers could be avoided (Table 5). PAF calculations based on the proportional hazards regression model including BMI yielded a lower proportion (17%, 95% CI: 2.3-29.5) (Table 5). The results did not differ substantially for subtypes of endometrial cancer (Supplemental table 1)

Discussion

In this large Norwegian cohort we found an inverse dose-response association between PA and endometrial cancer overall, type 1 endometrial cancer, and endometrioid carcinoma. The results were consistent when using baseline data on PA and when using repeated PA measurements, as well as when multiple imputation was used. Our findings further suggest that the association between PA and endometrial cancer is independent of BMI, as risk estimates were attenuated, but still significant, when BMI was incorporated in the statistical models. Stratification by BMI category indicated that the risk of low PA on endometrial cancer was statistically significant among obese women only (although the test for interaction was not statistically significant, p=0.49). Among women with PA levels ≤4, 21.9% of endometrial cancer could potentially be avoided if these women adopted a PA level between 5-10 in the scale.

Other cohort studies investigating the association between total PA levels – which include domains such as recreation, occupation, transportation, and household – and endometrial cancer are sparse; most studies measured recreational PA only and few studies use repeated measurements of PA. In contrast to our results, the European Prospective Investigation into nutrition and Cancer reported a non-significant trend (p-trend 0.36) for total PA (including the domains recreation, occupation, and household) when comparing active with inactive women (multivariable adjusted model including BMI: HR=0.88, 95% CI 0.61-1.27) [12]. This was similar for the Breast Cancer Detection Demonstration Project study, which measured the total intensity of PA and found no significant associations with endometrial cancer [31]. Findings from the Netherlands Cohort Study on Diet and Cancer showed that total baseline non-occupational PA was inversely associated with endometrial cancer, with a lower risk observed for a PA corresponding to >30 minutes per day [17, 32]. In a Swedish cohort the risk was decreased, although this decrease was not significant [16].

Several studies have reported on recreational PA and endometrial cancer. Nine prospective cohort studies on recreational PA were included in the WCRF/AICR CUP report up to 2012 [8], but due to different measures of PA, the meta-analysis of these studies only looked at the highest vs lowest PA level (RR=0.73, 95% CI 0.58-0.93), and these results were attenuated when the model was adjusted for BMI (RR=0.80, 95% CI 0.69-0.92). A limitation of this meta-analysis was the high heterogeneity (I^2=75.9%) of the individual studies [8]. Indeed, only three of these studies [33, 32, 34] found significant inverse associations, three found no significant association [35, 11, 36], and three [37, 12, 16] found an inverse, but insignificant association between endometrial cancer and recreational PA. Since the publication of the WCRF/AICR CUP report from 2012 we have identified four additional prospective cohort studies on recreational PA and endometrial cancer [10, 13-15]. The Nurses' Health study investigated recreational PA in the past year and found no association

between baseline recreational PA and endometrial cancer risk, however, brisk walking time ≥3 hours per week was inversely associated with endometrial cancer [15]. In the California Teachers Study cohort, moderate and vigorous recreational PA was associated with a 25% lower endometrial cancer risk [13]. The findings of Land et al [14] are in accordance with our findings, although they studied recreational PA and had a small number of cases in a population of women at high risk for breast cancer. A large pooled analysis of 12 cohorts was recently published and reported a HR of 0.79 (95% CI 0.68-0.92) in the association between recreational PA and endometrial cancer based on 5346 cases. However, the degree of heterogeneity between cohorts was high (I^2=69%)[10] .

Analysis of occupational PA measured twice during 1974 and 1981 in a Norwegian study showed a significant trend, with a reduced risk for women who were consistently moderately active; however, the association was attenuated in the multivariable model and the trend was no longer significant [36]. The WCRF/AICR CUP report [8] included four cohort studies [16, 38, 12, 39], none of which found a significant association between occupational PA and endometrial cancer. In a highest vs lowest occupational PA meta-analysis, the summary RR was 0.79 (95% CI 0.71-0.88), with a high degree of heterogeneity between studies (I^2= 75.9%) and concluded a probable inverse association between occupational PA and endometrial cancer [8].

Overweight and obesity are strong risk factors for endometrial cancer, and studies suggest that the association between PA and endometrial cancer is either mediated or confounded by body weight, which can affect hormone profiles. Therefore, it is important to model the association both with and without adjustment for BMI [15]. In our study, adjustment for BMI in the multivariable analyses attenuated the associations. However, a modest inverse association remained, suggesting that PA is independently associated with endometrial cancer. Simultanously, the analyses of the different BMI categories showed that the

association was more pronounced in obese than in normal-weight women. In our data, obesity may confound the association between PA and overall endometrial cancer. Our findings are in accordance with Friberg et al [16]. However, Moore et al adjusted for BMI in the association between recreational PA and endometrial cancer and showed an attenuation of the estimates from a significant towards a non-significant result compared to multivariable models unadjusted for BMI (HR=0.98, 95% CI 0.89-1.09 vs HR=0.79, 95% CI 0.68-0.92) . This was similar to several previous studies [14, 15, 33, 37]. Some studies have found a statistically significant increased endometrial cancer risk in both inactive and active overweight women [11], which correspond to our findings. Others have shown an effect modification, where the inverse relationship was only seen among overweight or obese women [10, 37]. As in our study, several other studies have reported no significant effect modification for BMI [33, 12, 16, 17, 31].

Heterogeneity in different study results may be explained by variations in the methods used to assess PA (self-adminstered questionnaires, interviews, or use of job titles); PA domains (recreation, occupation, transportation, household); frequency, duration, and intensity of PA; and time periods in life when PA was measured, as well as different statistical methods used in the data analysis [40]. Nevertheless, there is substantial biological evidence to support a potential protective role of PA on endometrial cancer. The mechanisms involved have been hypothesized as affecting endogenous sex hormone levels, insulin-mediated pathways, and maintenance of energy balance [41].

Physical inactivity is considered an important risk factor for different cancers [42-44]. The consistent associations between low PA levels and endometrial cancer risk in our study justify the estimation of PAFs. Our definition of low PA levels was based on self-reported PA using a validated 10-point scale [21]. Our PAF estimation represents the minimum move required from low to higher levels of PA to create a significant change in the incidence of

endometrial cancer (21.9%, 95% CI: 7.1-34.3). However, the definite dose cannot be quantified and our results must be interpreted with caution. In the UK, Parkin found a PAF for endometrial cancer of 3.8% attributable to exercising less than the minimum recommended amount [43]. The proportion related to inadequate PA in the UK in 2002 was 30% for endometrial cancer, however that compared the highest (≥60 minutes) and lowest (<30 minutes) PA levels, which gives a higher reference category than the recommendation of PA [45]. To quantify the PAF requires a realistic population distribution of the exposure of interest, which in our study is PA. We consider our cohort to be a nationally respresentative Norwegian cohort with a reliable population distribution of PA, and as such it should give a robust estimate. Furthermore, it is valuable to evaluate the impact of different factors in cancer prevention, which is helpful in prioritizing cancer prevention and intervention strategies.

A major strength of our study is its prospective, population-based design, and the use of a high-quality, national cancer registry to identify endometrial cancer cases [20]. The large sample size and representativeness of the Norwegian female population 30 to 70 years of age gives a unique opportunity to calculate robust PAF estimates. The PA scale has been validated [21] and correlated well with all-cause mortality rates [46]. Furthermore, PA level, BMI, and smoking were re-assessed at follow-up. Self-reported BMI has been validated for the NOWAC study, indicating that there was a substantial agreement between self-reported and measured BMI values [47]. There was, however, a small but statistically significant under-reporting of weight, which would affect self-reported BMI; this tendency was largest among overweight and obese women [20, 47] . A survey of the PA levels in the adult population in Norway showed that 34% of women reached the national guidelines for PA [48]. This proportion is higher than in our study. The relatively large number of cases made it possible to investigate subtypes of endometrial cancer, however the proportion of type 2 endometrial

cancer was too low to allow for separate analyses. Multiple imputation of missing data, in addition to complete-case analysis, confirmed our results. The PA assessment in our study comprised all areas of PA, not only recreational PA. However, the total self-reported measure of PA cannot differentiate intensity, duration, and frequency of PA, nor the type of PA in our study, and given the self report of PA, measurement errors cannot be ruled out. However, measurement errors would likely lead to a non-differential bias and a potential underestimation of the true effect. The PA assessment used in this study may not apply to women in other countries. Moreover, the potential for residual confounding, in particular by BMI, remains.

Conclusions

Overall, we found an inverse dose-response association between PA and endometrial cancer with similar findings for subtypes of endometrial cancer. This risk was higher in obese women. Also, 21.9% of the endometrial cancer cases could be attributable to low levels of PA, and could potentially be avoided if women attained a higher PA level.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Physical activity and risk of endometrial cancer in the Norwegian Women and Cancer (NOWAC) Study

Kristin B Borch[1*], Elisabete Weiderpass[1, 2, 3, 4], Tonje Braaten[1], Mie Jareid[1], Oxana A Gavrilyuk[1], Idlir Licaj[1]

*Cooresponding author: Kristin Benjaminsen Borch, email: Kristin.benjaminsen.borch@uit.no

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Novelty and impact statements:

We found evidence of a dose-response association between physical activity and overall endometrial cancer.The novelty include use of repeated measurements for physical activity and confounders combined with multiple imputation to address attrition, which is a particular problem in observational epidemiology. As a nationally representative cohort our study gave us an unique opportunity to calculate robust population attributable fractions. ~~3~~122% of endometrial cancer could be avoided if women increase their physical activity ~~to the recommended~~ level.

Abbreviations:

BMI – body mass index
CI – confidence interval
CUP - Continous Update Project
PA – physical activity
PAF – population attributable fractions
HR – hazard ratio
RR – relative risk
NOWAC – The Norwegian Women and Cancer Study
WCRF/AICR - World Cancer Research Fund/American Institute for Cancer Research

Affiliations:

1. Department of Community Medicine, Faculty of Health Sciences, UiT, The Arctic University of Norway, Tromsø, Norway
2. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
3. Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway
4. Genetic Epidemiology Group, Folkhälsan Research Centre, Samfundet Folkhälsan, Helsinki, Finland

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Author's contributions

KBB, EW and IL designed the study. IL and KBB preformed all statistical analyses, and drafted the manuscript. EW, MJ, and OG critically revised the manuscript. TB participated in the statistical analyses and revised the manuscript critically. All authors read and approved the final manuscript.

Abstract

Few studies have investigated the association between endometrial cancer and physical activity (PA) using repeated measures of PA and different subtypes of endometrial cancer. We aimed to investigate the association between endometrial cancer and PA level at two points in time in women with different body mass index (BMI) profiles, and to calculate the population attributable fraction (PAF) of endometrial cancer for low PA levels.

We included 82,759 women with complete information on PA at baseline in the Norwegian Women and Cancer Study; 52,370 had follow-up information on PA. 687 endometrial cancer cases were identified. Multivariate cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). The PAF indicated the proportion of endometrial cancer that could be avoided in the population if these women had a higher PA level~~ corresponding to ≥150 minutes of moderate/vigorous PA per week.~~

There was a statistically significant association between low PA levels at baseline and follow-up and endometrial cancer risk, with a dose-response trend (lowest PA level: HR=1.~~85~~60, 95% CI 1.16~~36~~-2.20~~53~~; highest PA level: HR=0.7~~1~~3, 95% CI 0.45-1.1~~2~~6 compared to the median). ~~The~~ Aanalyses that included~~including~~ follow-up measurements yielded similar results. ~~se associations were attenuated after adjustment for BMI, but remained significant.~~ 2~~3~~1.9~~1~~% (95% CI 7.1~~6~~--34.3~~49~~) of endometrial cancers could be avoided if women with low PA levels (≤ 4 in a 1-10 degree self reported PA scale) increased their PA levels to 5-10.~~at least 150 minutes/week .~~

We found an inverse dose-response association between PA and endometrial cancer, independent of BMI. In this nationally representative cohort, 21.9% ~~One~~ of ~~four~~ endometrial cancers could potentially be avoided if PA levels increased to higher PA levels (5-10 in the scale)~~150 minutes per week~~.

Introduction

Endometrial cancer is the sixth most common cancer, and the most frequent gynecologic malignancy among women in Norway. In 2014, 727 new cases were diagnosed and 81 women died of the disease [1]. Established risk factors for endometrial cancer include use of exogenous estrogens unopposed by progestagens, early menarche (10-12 years of age), late menopause, nulliparity, diabetes mellitus, and obesity. Currently, the majority of endometrial cancer, and about half of the cases in postmenopausal women are attributable to being overweight or obese [2-4]. As the population ages and the prevalence of overweight, obesity, and sedentary lifestyle increase, the incidence of endometrial cancer is also expected to increase, especially in postmenopausal women [5, 6]. Thus primary prevention of endometrial cancer through modifiable lifestyle factors is of potential public health importance.

Physical activity (PA) is a modifiable lifestyle factor, which is important in the regulation of hormones and metabolic pathways. It is also associated with weight control, and thus may reduce endometrial cancer risk [7-9]. A pooled analysis of nine cohorts from Europe and the United States included 1.44 million participants and found a 21% reduced risk of endometrial cancer associated with recreational PA [10] . However, within individual studies, results are inconsistent [8]. For example, the Women's Health Study did not find any relationship between recreational PA and walking and endometrial cancer risk [11]. Similarly, there was no significant association between total PA – including occupational, recreational, and household-related PA – and endometrial cancer risk in the European Prospective Investigation into Nutrition and Cancer [12]. The 2007 evaluation by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concluded that there is a probable relationship between PA and endometrial cancer despite the variety of PA assessments not allowing for meta-analysis on dose-response [7]. This conclusion was supported in their Continous Update Project (CUP) report from 2013 [8]. Of four cohort

studies published after the 2013 CUP report [10, 13-15], three found an inverse association between recreational PA and endometrial cancer risk [10, 15, 14], and one did not [13].

Few studies have investigated the association between endometrial cancer and PA using a total and repeated measure of PA and different subtypes of endometrial cancer [12, 16, 17]. Endometrial cancer is classified as type I (estrogen dependent), which constitutes the majority of cases (about 80%), and type II (estrogen independent), based on clinical, endocrine, and epidemiological observations. The most common histological subtypes of endometrial cancer are endometrioid carcinoma, serous carcinoma, carcinosarcoma, and clear cell carcinoma [18]. While the association between body mass index (BMI) and endometrial cancer is well established, the relationship between PA and endometrial cancer in women with different body sizes remains unclear.

The present study aimed to investigate the association between endometrial cancer and PA level at two points in time in women with different BMI profiles in the Norwegian Women and Cancer (NOWAC) Study, and to calculate the population attributable fraction (PAF) of endometrial cancer for low PA levels.

Methods

The NOWAC Study

The NOWAC Study is a nationally representative cohort study that has been described in detail previously [19, 20]. Briefly, random samples of Norwegian women aged 30-70 years were invited to participate during three waves of data collection (1991/92, 1996/97, and 2003/04) [20]. More than 172,000 women completed a questionnaire with detailed questions regarding lifestyle, diet, and health, and were enrolled in the study (overall response rate: 52.7%). The NOWAC Study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate, and all particpants included in the study gave written informed consent.

In this analysis we used information from enrollment questionnaires completed in the period from 1996 to 2004 (baseline), and those with follow-up questionnaires completed 6-8 years after enrollment. In total 101,321 women completed questionnaires in these periods and were eligible for inclusion in this study. We excluded women with prevalent cancers other than non-melanoma skin cancer at baseline (n=4,454), those who emigrated or died before the start of follow-up (n=20), those with hysterectomy (n=5,426), and those who had missing information on PA level at baseline (n=8,662). Thus, the final analytical study sample consisted of 82,759 women. Follow-up information on PA level, smoking, weight, and height was available for for 52,370 (63.3%) of these women.

Assessment of PA level and covariates

PA level was assessed in the NOWAC questionnaires on a 10-point scale by the following question: *"By physical activity we mean activity both at work and outside work, at home, as well as training/exercise and other physical activity, such as walking, etc. Please mark the number that best describes your level of physical activity; 1 being very low and 10 being very*

high". This PA scale has been validated [21] and refers to the total amount of PA across different domains, including recreation, occupation, transportation, and household in one global score. Moderate, but significant Spearman's rank correlation coefficients were found (range: 0.36-0.46; P<0.001) between PA level at enrollment and concurrent outcomes from criterion measures of a combined sensor monitoring heart rate and movement. ~~This corresponded to mean values of 0.8 (very low) and 3.4 hours per day (very high) of moderate/vigorous PA, respectively, with a linear increase (*P for trend* <0.001).~~ The PA scale appeared valid to rank PA level in Norwegian women, but not to quantify a definite dose of PA [21].

Information on the covariates height, weight, age at menarche, parity, oral contraceptive use, menopausal status, age at menopause, hormone therapy use, years of education, smoking status and~~,~~ alcohol consumption, were obtained from NOWAC questionnaires. The women were~~as~~ considered postmenopausal if they stated that the period had stopped or ~~had a hysterectomy (excluded from the study) or~~ reported use of hormonal therapy if they were ≥53years. This cut-off point is based on the definition used in the the Million Women Study [22], and has been used by the NOWAC study earlier [23]. Information on height and weight was used to calculate BMI (kg/m^2).

Cancer incidence, death, and emigration

Women diagnosed with a primary, invasive, malignant neoplasm of the endometrium (International Statistical Classification of Diseases, Injuries and Causes of Death Revision~~s~~ 7 ~~and 10~~ codes 172.0 ~~and C 54.1, respectively~~ [24]) were identified through linkage to the Cancer Registry of Norway, from which date of diagnosis and morphology (International Classification of Diseases for Oncology, 3rd edition) were also obtained. Based on the morphology, endometrial cancers were categorized into overall endometrial cancer (all

subtypes), endometrioid carcinoma, type 1 endometrial cancer (adenocarcinoma NOS, endometrioid, and squamous carcinomas), and other subtypes (non-endometrioid or non-type 1).

Information on date of death or emigration was obtained through linkage to the Norwegian National Population Register.

Statistical methods

Analyses using baseline data only

We used Cox proportional hazard regression models to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) comparing five categories of PA level (1-2, 3-4, 5-6, 7-8, and 9-10). PA level 5-6 was set as the reference group. Follow-up time was defined as the interval between age at baseline and age at cancer diagnosis, death, emigration, or the end of follow-up (31 December 2013), whichever came first.

Departures from the proportional hazards assumption in the Cox models were tested through the inclusion of an interaction variable between categories of PA and underlying time (age). A preliminary analysis of baseline data only was used to select the covariates that were adjusted for in the final models. In the preliminary model, we adjusted for: height (in metres), BMI (normal weight: <25, overweight: 25–29.9, obese: ≥30 kg/m^2), age at menarche (<12, 13-14, 15+ years), parity (0, 1, 2, 3, 4+) , oral contraceptive use (ever/never), menopausal status (premenopausal, perimenopausal, postmenopausal, hormone therapy use ≥~~<~~53 years), hormone therapy use (ever/never), years of education (≤9, >9-12, ≥13 years), smoking status (never, former, current), alcohol consumption (grams per day), and diabetes mellitus (yes/no). The removal of each covariate had to be associated with a change in the regression coefficients of at least 10% in any of the categories of PA level to be included in the final model. To test for linear trend, we used the original, 10-point PA scale, modelled as a

continuous variable in the analyses. Interactions (log likelihood test) between PA and the above-mentioned categories of BMI, educational attainment and smoking status were tested. The Wald $\chi 2$ statistic was used to test for heterogeneity between normal weight and obese women. ~~not significant.~~

~~As BMI is a strong risk factor for endometrial cancer, we decided to investigate the association between PA and endometrial cancer risk in normal weight, overweight, and obese women, even though the interaction term was not significant (p=0.49). The Wald $\chi 2$ statistic was used to test for heterogeneity between normal weight and obsese women.~~

Analyses using repeated PA measurements

We used the method proposed by Hu et al [25], i.e., baseline data was used until follow-up information became available, death, or emigration, whichever occurred first. Thereafter follow-up information was applied until death, emigration, or the end of the study period, which ever occurred first. In the analysis using repeated PA measurements, we also used follow-up information on BMI and smoking once it became available.

Complementary analysis - multiple imputation

Compared to women who did not drop out of the study, those who dropped out of the study at follow-up (n=30,389 (36.7%)), were more often overweight (31.4% vs 29.2%) or obese (10.3% vs 8.6%), more often reported oral contraceptive use (46.6% vs 43.5%) and hormone therapy use (36.7% vs 31.7%), more often had a history of diabetes mellitus (2.9% vs 1.7%), and had fewer years of education (24.3% vs 23.7%). They were also more often current smokers, but on average they had a similar PA level and alcohol consumption as women who did not drop out of the study. In order to deal with dropouts, we used multiple imputation models [26] and compared the results with those of complete-case analyses. Multiple

imputation models were used under the assumption that data was missing at random. To reduce sampling variability, we created 20 replicate datasets from the imputation simulation [27]. We used the outcomes overall endometrial cancer, type 1 endometrial cancer, and endometrioid carcinoma. Nelson-Aalen cumulative hazard estimator was included as a predictor in the imputation models [28]. The estimates from the 20 imputed datasets were combined using Rubin's rules [29]. All the analyses and multiple imputations were done in STATA version 14.0 (Stata Corp, College Station, TX, USA).

PAF calculation

We calculated the PAF to estimate the proportion of endometrial cancer that could be avoided in the population if women had different PA levels, using the formula: *PAF= Pe*(RRe-1)/[Pe*RR+(1-Pe)],* where *Pe* is the proportion of PA level in the study population and *RRe* is the RR in the model adjusting for BMI (model 1) and the final baseline multivariable proportional hazards regression model (model 2), including all aforementioned confounders and BMI. We calculated two-sided 95% CIs for the PAFs using the PUNAF Stata module [30]. The PA levels were divided into two levels; levels 1 to 4 were classified as exposed to low PA levels and levels 5-10 as unexposed to low PA levels. The PAF was interpreted as the proportion of overall endometrial cancers that would not occur in the average population if PA levels ~~was~~were between 5 and 10 according to the scale.≥ ~~8, corresponding to 150 minutes per week according to the validation of PA in NOWAC , assuming that the distribution of the adjustment variables remained unchanged.~~

Results

The median age at baseline was 51 years. During a mean follow-up time of nearly 13 years, 687 cases of endometrial cancer were identified, with type 1 endometrial cancer (adenocarcinoma not otherwise specified [NOS], endometrioid and squamous carcinoma) accounting for 83.8% of the cases. The age at diagnosis ranged between 42 and 86 years, with a mean of 62 years of age. Nearly half (43%) of the women reported a PA level between 5 and 6 (Table 1), and ~~collapsing the upper part of the scale showed that a~~Approximately 74% of the women reported a PA level between 5 and 10. ~~with level ≥8 comprised 15% of the participants.~~ Women with a PA level >5 had a lower BMI, used less hormone therapy, reported less diabetes mellitus, and were more often never smokers compared to women reporting low PA levels. ~~(Table 1).~~

Multivariable models of the associations between baseline and one follow-up measurement of PA and endometrial cancer risk showes that compared to women with a PA level of 5-6, those with a PA level of 1-2 had a 60% higher risk of overall endometrial cancer (HR=1.60, 95% CI 1.16-2.20). ~~Removing BMI from the models increased these estimates (HR=1.85, 95% CI 1.36-2.36).~~ For analyses using repeated PA measurements, the corresponding risks adjusted for BMI and smoking status were similar to those obtained when using baseline data only (HR ~~with BMI adjustment~~=1.54, 95% CI 1.01-2.~~17 and HR without BMI adjustment=1.80, 95% CI 1.19-2.72~~). In analyses using baseline data only and those using repeated PA measurments, BMI and smoking status were negatively associated with the risk of type 1 endometrial cancer and endometroid carcinomas~~ncers~~. Compared to the age-adjusted models, the associations were attenuated in the multivariable adjusted models that included BMI (Table 2).

Interactions between PA and categories of BMI, educational attainment and smoking status were not significant. However, a~~A~~s BMI is a strong risk factor for endometrial cancer,

we decided to investigate the association between PA and endometrial cancer risk in normal weight, overweight, and obese women, even though the interaction term was not significant (p=0.49).When analyses were stratified by BMI category the PA levels 7-10 were collapsed, PA was not associated with overall endometrial cancer among normal-weight women in analyses using baseline data only ($HR_{PA(1-2)\ vs\ (5-6)}$=1.32, 95% CI 0.71-2.45). The corresponding association in obese participants was $HR_{PA(1-2)\ vs\ (5-6)}$=3.08 (95% CI 1.76-5.39) ($p_{heterogeneity}$=0.05) (Table 3).

Using multiple imputation, we found that the estimates at all levels of adjustment and for all endpoints (overall endometrial cancer, type 1 endometrial cancer, and endometrioid carcinoma) were consistent with those obtained from the complete-case analyses (Table 4). ~~(Supplemental Table 1).~~ PAF calculations showed that if women with a PA level ≤4 increased to levels 5-10 in the scale~~that level to ≥ 8~~, 21.9~~31~~% (95% CI: 7.1~~6~~-34.3~~49~~) of endometrial cancers could be avoided (Table 5). PAF calculations based on the proportional hazards regression model including BMI yielded a lower proportion (17%, 95% CI: 2.3-29.5) (Table 5). The results did not differ substantially for subtypes of endometrial cancer (Supplemental table 1) ~~(more than 1 in 4) (Supplementary Figure 1).~~

Discussion

In this large Norwegian cohort we found an inverse dose-response association between PA and endometrial cancer overall, type 1 endometrial cancer, and endometrioid carcinoma. The results were consistent when using baseline data on PA and when using repeated PA measurements, as well as when multiple imputation was used. Our findings further suggest that the association between PA and endometrial cancer is independent of BMI, as risk estimates were attenuated, but still significant, when BMI was incorporated in the statistical models. Stratification by BMI category indicated that the risk of low PA on endometrial cancer was statistically significant among obese women only (although the test for interaction

was not statistically significant, p=0.49). Among women with PA levels ≤4, 21.931% of endometrial cancer could potentially be avoided if these women adopted a PA level between 5-10 in the scale~~≥8, which corresponds to approximately 150 minutes of moderate/vigorous PA per week~~.

Other cohort studies investigating the association between total PA levels – which include domains such as recreation, occupation, transportation, and household – and endometrial cancer are sparse; most studies measured recreational PA only and few studies use repeated measurements of PA. In contrast to our results, the European Prospective Investigation into nutrition and Cancer reported a non-significant trend (p-trend 0.36) for total PA (including the domains recreation, occupation, and household) when comparing active with inactive women (multivariable adjusted model including BMI: HR=0.88, 95% CI 0.61-1.27) [12]. This was similar for the Breast Cancer Detection Demonstration Project study, which measured the total intensity of PA and found no significant associations with endometrial cancer [31]. Findings from the Netherlands Cohort Study on Diet and Cancer showed that total baseline non-occupational PA was inversely associated with endometrial cancer, with a lower risk observed for a PA corresponding to >30 minutes per day [17, 32]. In a Swedish cohort the risk was decreased, although this decrease was not significant [16].

Several studies have reported on recreational PA and endometrial cancer. Nine prospective cohort studies on recreational PA were included in the WCRF/AICR CUP report up to 2012 [8], but due to different measures of PA, the meta-analysis of these studies only looked at the highest vs lowest PA level (RR=0.73, 95% CI 0.58-0.93), and these results were attenuated when the model was adjusted for BMI (RR=0.80, 95% CI 0.69-0.92). A limitation of this meta-analysis was the high heterogeneity (I^2=75.9%) of the individual studies [8]. Indeed, only three of these studies [33, 32, 34] found significant inverse associations, three found no significant association [35, 11, 36], and three [37, 12, 16] found an inverse, but

insignificant association between endometrial cancer and recreational PA. Since the publication of the WCRF/AICR CUP report from 2012 we have identified four additional prospective cohort studies on recreational PA and endometrial cancer [10, 13-15]. The Nurses' Health study investigated recreational PA in the past year and found no association between baseline recreational PA and endometrial cancer risk, however, brisk walking time ≥3 hours per week was inversely associated with endometrial cancer [15]. In the California Teachers Study cohort, moderate and vigorous recreational PA was associated with a 25% lower endometrial cancer risk [13]. The findings of Land et al [14] are in accordance with our findings, although they studied recreational PA and had a small number of cases in a population of women at high risk for breast cancer. A large pooled analysis of 12 cohorts was recently published and reported a HR of 0.79 (95% CI 0.68-0.92) in the association between recreational PA and endometrial cancer based on 5346 cases. However, the degree of heterogeneity between cohorts was high (I^2=69%)[10] .

Analysis of occupational PA measured twice during 1974 and 1981 in a Norwegian study showed a significant trend, with a reduced risk for women who were consistently moderately active; however, the association was attenuated in the multivariable model and the trend was no longer significant [36]. The WCRF/AICR CUP report [8] included four cohort studies [16, 38, 12, 39], none of which found a significant association between occupational PA and endometrial cancer. In a highest vs lowest occupational PA meta-analysis, the summary RR was 0.79 (95% CI 0.71-0.88), with a high degree of heterogeneity between studies (I^2= 75.9%) and concluded a probable inverse association between occupational PA and endometrial cancer [8].

Overweight and obesity are strong risk factors for endometrial cancer, and studies suggest that the association between PA and endometrial cancer is either mediated or confounded by body weight, which can affect hormone profiles. Therefore, it is important to model the

association both with and without adjustment for BMI [15]. In our study, adjustment for BMI in the multivariable analyses attenuated the associations. However, a modest inverse association remained, suggesting that PA is independently associated with endometrial cancer. Simultanously, the analyses of the different BMI categories showed that the association was more pronounced in obese than in normal-weight women. In our data, obesity may confound the association between PA and overall endometrial cancer. Our findings are in accordance with Friberg et al [16]. However, Moore et al adjusted for BMI in the association between recreational PA and endometrial cancer and showed an attenuation of the estimates from a significant towards a non-significant result compared to multivariable models unadjusted for BMI (HR=0.98, 95% CI 0.89-1.09 vs HR=0.79, 95% CI 0.68-0.92) . This was similar to several previous studies [14, 15, 33, 37]. Some studies have found a statistically significant increased endometrial cancer risk in both inactive and active overweight women [11], which correspond to our findings. Others have shown an effect modification, where the inverse relationship was only seen among overweight or obese women [10, 37]. As in our study, several other studies have reported no significant effect modification for BMI [33, 12, 16, 17, 31].

Heterogeneity in different study results may be explained by variations in the methods used to assess PA (self-adminstered questionnaires, interviews, or use of job titles); PA domains (recreation, occupation, transportation, household); frequency, duration, and intensity of PA; and time periods in life when PA was measured, as well as different statistical methods used in the data analysis [40]. Nevertheless, there is substantial biological evidence to support a potential protective role of PA on endometrial cancer. The mechanisms involved have been hypothesized as affecting endogenous sex hormone levels, insulin-mediated pathways, and maintenance of energy balance [41].

Physical inactivity is considered an important risk factor for different cancers [42-44]. The consistent associations between low PA levels and endometrial cancer risk in our study justify the estimation of PAFs. Our definition of low PA levels was based on self-reported PA using a validated 10-point scale [21]. Our PAF estimation represents the minimum move required from low to higher levels of PA to create a significant change in the incidence of endometrial cancer (21.931%, 95% CI: 7.1-34.3). However, the definite dose cannot be quantified and our results must be interpreted with caution. ~~, which corresponded to an increase in PA to 150 minutes of moderate/vigorous PA per week. This amount is in accordance with World Health Organization Global Recommendations on PA for Health .~~ In the UK, Parkin found a PAF for endometrial cancer of 3.8% attributable to exercising less than the minimum recommended amount [43]. The proportion related to inadequate PA in the UK in 2002 was 30% for endometrial cancer, however that compared the highest (≥60 minutes) and lowest (<30 minutes) PA levels, which gives a higher reference category than the recommendation of PA [45]. To quantify the PAF requires a realistic population distribution of the exposure of interest, which in our study is PA. We consider our cohort to be a nationally respresentative Norwegian cohort with a reliable population distribution of PA, and as such it should give a ~~more~~ robust estimate. Furthermore, it is valuable to evaluate the impact of different factors in cancer prevention, which is helpful in prioritizing cancer prevention and intervention strategies.

A major strength of our study is its prospective, population-based design, and the use of a high-quality, national~~ly representative~~ cancer registr~~yation system~~ to identify endometrial cancer cases [20]. The large sample size and representativeness of the Norwegian female population 30 to 70 years of age gives a unique opportunity to calculate robust PAF estimates. The PA scale has been validated [21] and correlated well with all-cause mortality rates [46]. Furthermore, PA level, BMI, and smoking were re-assessed at follow-up. Self-reported BMI

has been validated for the NOWAC study, indicating that there was a substantial agreement between self-reported and measured BMI values [47]. There was, however, a small but statistically significant under-reporting of weight, which would affect self-reported BMI; this tendency was largest among overweight and obese women [20, 47] . A survey of the PA levels in the adult population in Norway showed that 34% of women reached the national guidelines for PA [48]. This proportion is higher than in our study. The relatively large number of cases made it possible to investigate subtypes of endometrial cancer, however the proportion of type 2 endometrial cancer was too low to allow for separate analyses. Multiple imputation of missing data, in addition to complete-case analysis, confirmed our results. The PA assessment in our~~this~~ study comprised all areas of PA, not only recreational PA. However, the total self-reported measure of PA cannot differentiate intensity, duration, and frequency of PA, nor the type of PA in our study, and given the self report of PA, measurement errors cannot be ruled out. However, measurement errors would likely lead to a non-differential bias and a potential underestimation of the true effect. The PA assessment used in this study may not apply to women in other countries. Moreover, the potential for residual confounding, in particular by BMI, remains.

Conclusions

Overall, we found an inverse dose-response association between PA and endometrial cancer with similar findings for subtypes of endometrial cancer. This risk was higher in obese women. Also, 21.9~~31~~% of the endometrial cancer cases could be~~were~~ attributable to low levels of PA, and ~~more than 1 in 4 cases~~ could potentially be avoided if women attained a higher PA level~~ corresponding to 150 minutes per week or more.~~

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Table 1 Selected baseline characteristics of participants in the Norwegian Women and Cancer Study by physical activity level (n=82,759)

Characteristic	Physical activity level				
	1 to 4 N=21,953 (26.5%)		5 to 10 N=60,806 (73.5%)		
	1 to 2 N=3855 (4.7%)	3 to 4 N=18,098 (21.9%)	5 to 6 N=35,551 (43.0%)	7 to 8 N=20,991 (25.4%)	9 to 10 N=4264 (5.2%)
Age (mean, ±SE)	53.2 (.11)	52.1 (.05)	51.5 (.03)	51.3 (.04)	51.9 (.10)
Person-years at risk [1]	48 995	236 571	462 837	266 512	54 318
Overall endometrial cancer (total cases n=687)	56 (8.2%)	181 (26.3%)	283 (41.2%)	139 (20.2%)	28 (4.1%)
Endometrioid (total cases n=473	41 (8.7%)	134 (28.3%)	185 (39.1%)	100 (21.1%)	13 (2.7%)
Type 1 endometrial cancer[2] **(total cases n=576)**	47 (8.2%)	161 (28.0%)	226 (39.2%)	122 (21.2%)	20 (3.5%)
Other subtypes[3] **(total cases n=111)**	9 (8.1%)	20 (18%)	57 (51.4%)	17 (15.3%)	8 (7.2%)
BMI (mean, ±SE)	26.9 (.09)	25.8 (.03)	24.6 (.02)	23.8 (.02)	23.6 (.05)
Missing (%)	2.2	2.0	1.7	1.7	2.2
Age at menarche (mean, ±SE)	13.2 (.03)	13.3 (.01)	13.3 (.007)	13.7 (.01)	13.4 (.02)
Missing (%)	1.6	1.6	1.4	1.2	1.7
Parity (%)					
Nulliparity	10.4	9.2	8.2	8.0	8.2
1-2	51.6	52.7	53.2	53.0	50.4
≥3	38.0	38.1	38.5	39.0	41.4
Ever use of oral contraceptives (%)	49.6	53.9	53.8	54.8	50.4
Missing (%)	3.9	2.9	2.8	3.2	4.3
Menopausal status (%)					
Premenopausal	38.4	47.4	50.0	48.8	44.4
Perimenopause	7.0	5.9	5.9	6.5	6.1
Postmenopausal	49.0	41.9	39.0	39.4	44.4
Hormonal therapy use <53 years	3.0	2.8	2.8	3.1	3.3
Missing	2.6	2.0	2.3	2.3	1.8
Ever use of hormonal therapy (%)	36.9	35.5	32.5	31.4	29.6
Missing (%)	2.8	2.4	2.6	2.4	3.4
Years of education (mean, ±SE)	11.5 (.06)	12.2 (.03)	12.3 (.02)	12.6 (.02)	11.9 (.06)

Missing (%)	6.6	5.2	4.5	4.9	6.0
Smoking status (%)					
Never	29.6	36.1	37.3	37.4	35.2
Former	29.8	31.2	32.6	35.0	33.3
Current	39.1	31.4	28.9	26.3	30.0
Missing (%)	1.5	1.3	1.2	1.4	1.5
Alcohol consumption, mean ±SE (grams/day)	3.0 (.03)	3.4 (.03)	3.4 (.02)	3.5 (.03)	3.1 (.06)
Missing (%)	2.3	1.7	1.7	1.8	2.4
Diabetes mellitus (%)	4.4	2.1	1.6	1.3	1.6
Missing (%)	27.3	20.7	17.3	15.3	17.1

[1]Total person years=1,069,232; average follow-up time 12.92 years (SD=3.65)
[2]Type 1 includes adenocarcinoma, endometrioid, squamous types
[3]Other subtypes are cases not equal to Type 1

Table 2 Relative risk estimates of endometrial cancer (overall, type 1, and endometrioid) by physical activity (PA) level at baseline and follow-up in the Norwegian Women and Cancer Study (n=82 759)

	Endometrial cancer	Models[1, 2, 3, 4]	1 to 2	3 to 4	5 to 6	7 to 8	9 to 10	p_trend
Baseline	Overall endometrial cancer	Crude n=687	1.73 (1.30-2.31)	1.21 (1.00-1.46)	1.00	0.87 (0.71-1.07)	0.83 (0.56-1.22)	0.00
		PA + BMI n= 673	1.47 (1.09-1.97)	1.09 (0.9-1.32)	1.00	0.91 (0.74-1.11)	0.86 (0.58-1.27)	0.01
		Multivariable without BMI n=607	1.85 (1.36-2.53)	1.28 (1.05-1.56)	1.00	0.89 (0.72-1.11)	0.71 (0.45-1.12)	0.00
		Multivariable n=593	1.60 (1.16-2.20)	1.15 (0.94-1.41)	1.00	0.92 (0.74-1.15)	0.73 (0.45-1.16)	0.01
	Type 1 endometrial cancer	Crude n=576	1.83 (1.33-2.51)	1.35 (1.10-1.65)	1.00	0.96 (0.77-1.19)	0.74 (0.47-1.17)	0.00
		PA + BMI n=564	1.51 (1.10-2.09)	1.20 (0.97-1.47)	1.00	1.01 (0.81-1.26)	0.76 (0.48-1.22)	0.01
		Multivariable without BMI n=510	1.97 (1.4-2.78)	1.47 (1.19-1.82)	1.00	1.00 (0.79-1.26)	0.68 (0.4-1.15)	0.00
		Multivariable n=498	1.66 (1.17-2.36)	1.31 (1.05-1.63)	1.00	1.04 (0.82-1.32)	0.69 (0.40-1.18)	0.00
	Endometrioid subtype	Crude n=473	1.96 (1.39-2.75)	1.37 (1.10-1.72)	1.00	0.96 (0.75-1.22)	0.59 (0.33-1.03)	0.00
		PA + BMI n=463	1.59 (1.12-2.25)	1.20 (0.96-1.51)	1.00	1.00 (0.79-1.29)	0.59 (0.33-1.06)	0.004
		Multivariable without BMI n=428	2.25 (1.57-3.22)	1.51 (1.2-1.91)	1.00	1.01 (0.78-1.3)	0.61 (0.33-1.13)	0.00
		Multivariable n=418	1.83 (1.26-2.64)	1.32 (1.04-1.67)	1.00	1.06 (0.82-1.37)	0.60 (0.32-1.15)	0.001
Repeated measurements PA	Overall	Crude n= 450	1.78 (1.22-2.58)	1.31 (1.04-1.65)	1.00	0.86 (0.67-1.10)	0.87 (0.54-1.40)	0.00
		PA + BMI n=438	1.48 (1.01-2.17)	1.18 (0.93-1.49)		0.91 (0.71-1.17)	0.98 (0.61-1.57)	0.04
		Multivariable without BMI n=393	1.80 (1.19-2.72)	1.35 (1.06-1.73)	1.00	0.92 (0.71-1.2)	0.71 (0.4-1.26)	0.00
		Multivariable n=381	1.54 (1.01-2.35)	1.22 (0.95-1.58)	1.00	0.97 (0.74-1.26)	0.80 (0.45-1.41)	0.02
	Type 1	Crude n = 387	1.98 (1.34-2.91)	1.39 (1.09-1.78)	1.00	0.83 (0.63-1.09)	0.93 (0.56-1.53)	0.00
		PA + BMI n=377	1.60 (1.08-2.39)	1.25 (0.97-1.61)	1.00	0.88 (0.67-1.17)	1.06 (0.64-1.75)	0.01

		Multivariable without BMI n=337	2.10 (1.38-3.21)	1.46 (1.12-1.9)	1.00	0.94 (0.71-1.25)	0.8 (0.44-1.45)	0.00
		Multivariable n=327	1.75 (1.13-2.71)	1.33 (1.01-1.74)	1.00	0.99 (0.74-1.33)	0.91 (0.5-1.65)	0.01
	Endometrioid	Crude n = 321	1.90 (1.24-2.89)	1.30 (1.00-1.70)	1.00	0.72 (0.53-0.97)	0.61 (0.32-1.16)	0.00
		PA + BMI n=311	1.55 (1.00-2.39)	1.18 (0.9-1.55)	1.00	0.76 (0.55-1.03)	0.7 (0.37-1.34)	0.01
		Multivariable without BMI n=290	2.15 (1.38-3.34)	1.34 (1.01-1.79)	1.00	0.78 (0.57-1.07)	0.65 (0.33-1.28)	0.00
		Multivariable n=280	1.77 (1.12-2.81)	1.22 (0.91-1.63)	1.00	0.82 (0.60-1.14)	0.75 (0.38-1.49)	0.01

[1] Crude model with age as time-variable.
[2] Model with adjustment for BMI.
[3]Multivariable model adjusted for use of hormone therapy, oral contraceptive use, years of education, smoking, alcohol consumption (gram per day).
[4]Multivariable model same as above, but with adjustments for BMI included.
BMI: body mass index

Table 3 Relative risk estimates of overall endometrial cancer by physical activity (PA) level at baseline and follow-up according to body mass index (BMI) status at baseline in the Norwegian Women and Cancer study (n=82,759)

Complete case models	Model [1, 2]	BMI	1 to 2	3 to 4	5 to 6	7 to 10	p_trend
Baseline	Crude	Normal BMI n=318	1.28 (0.74-2.21)	1.06 (0.79-1.42)	1.00	0.83 (0.64-1.07)	0.10
		Overweight n=234	1.04 (0.60-1.83)	1.02 (0.75-1.39)	1.00	0.90 (0.64-1.26)	0.66
		Obese n=121	2.50 (1.49-4.20)	1.45 (0.92-2.29)	1.00	1.32 (0.74-2.36)	0.01
	Multivariable	Normal BMI n=281	1.32 (0.71-2.45)	1.19 (0.87-1.62)	1.00	0.86 (0.66-1.14)	0.07
		Overweight n=212	0.95 (0.51-1.77)	1.00 (0.73-1.39)	1.00	0.90 (0.63-1.28)	0.76
		Obese n=100	3.08 (1.76-5.39)	1.55 (0.93-2.56)	1.00	0.98 (0.48-1.99)	0.00
Repeated measurements PA	Crude	Normal BMI n=182	1.26 (0.58-2.73)	0.85 (0.56-1.30)	1.00	0.80 (0.58-1.12)	0.39
		Overweight n=169	1.44 (0.74-2.82)	1.39 (0.97-2.01)	1.00	1.16 (0.78-1.71)	0.61
		Obese n=87	1.78 (0.94-3.37)	1.39 (0.84-2.30)	1.00	0.73 (0.34-1.56)	0.01
	Multivariable	Normal BMI n=164	1.17 (0.47-2.91)	0.90 (0.58-1.41)	1.00	0.86 (0.61-1.21)	0.53
		Overweight n=147	1.15 (0.52-2.53)	1.35 (0.92-2.00)	1.00	1.17 (0.78-1.77)	0.81
		Obese n=70	2.45 (1.22-4.91)	1.63 (0.92-2.89)	1.00	0.56 (0.21-1.50)	0.00

[1] Crude model with age as time-variable.

[2] Multivariable model adjusted for use of hormone therapy, oral contraceptive use, years of education, smoking, alcohol consumption (gram/day).

Table 4: Relative risk estimates of endometrial cancer (overall, type 1 and endometrioid) by physical activity (PA) level at baseline and follow-up with imputation for missing variables in the Norwegian Women and Cancer study (n=82,759)

Imputation	Models [1,2,3,4]	1 to 2	3 to 4	5 to 6	7 to 8	9 to 10	p_trend
Overall	Crude n=687	1.76 (1.27-2.44)	1.34 (1.09-1.65)	1.00	0.80 (0.65-1.00)	0.73 (0.48-1.12)	0.00
	PA + BMI n= 687	1.47 (1.05-2.05)	1.22 (0.98-1.50)	1.00	0.85 (0.69-1.06)	0.80 (0.52-1.22)	0.001
	Multivariable without BMI n=687	1.87 (1.32-2.63)	1.40 (1.13-1.74)	1.00	0.85 (0.69-1.07)	0.71 (0.45-1.13)	0.02
	Multivariable n=687	1.58 (1.11-2.24)	1.28 (1.02-1.59)	1.00	0.90 (0.72-1.13)	0.78 (0.49-1.22)	0.02
Type 1	Crude n=576	1.87 (1.23-2.83)	1.30 (1.00-1.70)	1.00	0.71 (0.53-0.96)	0.60 (0.31-1.14)	0.00
	PA + BMI n= 576	1.51 (0.99-2.31)	1.16 (0.89-1.52)	1.00	0.77 (0.57-1.04)	0.67 (0.35-1.27)	0.001
	Multivariable without BMI n=576	2.05 (1.34-3.15)	1.34 (1.02-1.77)	1.00	0.77 (0.57-1.05)	0.66 (0.35-1.27)	0.00
	Multivariable n=576	1.66 (1.08-2.57)	1.19 (0.90-1.58)	1.00	0.83 (0.61-1.13)	0.74 (0.39-1.42)	0.002
Endometrioid	Crude n=473	1.89 (1.28-2.79)	1.45 (1.13-1.85)	1.00	0.76 (0.58-0.99)	0.48 (0.24-0.96)	0.00
	PA + BMI n= 473	1.51 (1.01-2.26)	1.28 (1.00-1.64)	1.00	0.82 (0.63-1.07)	0.54 (0.27-1.08)	0.01
	Multivariable without BMI n=473	2.11 (1.42-3.14)	1.53 (1.18-1.97)	1.00	0.83 (0.63-1.09)	0.54 (0.27-1.07)	0.00
	Multivariable n=473	1.70 (1.13-2.56)	1.35 (1.05-1.75)	1.00	0.89 (0.68-1.17)	0.60 (0.30-1.20)	0.00

[1] Crude model with age as time-variable.
[2] Model with adjustment for BMI.
[3]Multivariable model adjusted for use of hormone therapy, oral contraceptive use, years of education, smoking, alcohol consumption (gram per day).
[4]Multivariable model same as above, but with adjustment for BMI included.
BMI: body mass index

Table 5: **Population attributable fraction (PAF) for the proportion of endometrial cancer in the population that would be avoided if low physical activity (PA) level increased**

		Overall					
		Model 1[1] n= 673			Model 2[2] n= 593		
PA level	**Pe**	PAF	PAF 95% CI	RR= 95% CI	PAF	PAF 95% CI	RR= 95% CI
[1-4] to [5-10]	26.5 %	17%	[2.3-29.5]	1.21 [1.02-1.42]	21.9%	[7.1-34.3]	1.28 [1.08-1.52]

[1]Model 1: measured at baseline with age as time variable and adjusted for BMI.
[2]Model 2: Measured at baseline in a multivariable model adjusted for BMI, oral contraceptive use, hormone therapy use, years of education, smoking status, and alcohol consumption (grams per day).
Pe: proportion of low physical activity levels, RR: relative risk, CI: confidence interval