Physical activity and risk of endometrial cancer: The European prospective investigation into cancer and nutrition

Christine Friedenreich[1,2]*, Anne Cust[2,3,4], Petra H. Lahmann[5], Karen Steindorf[6], Marie-Christine Boutron-Ruault[7], Françoise Clavel-Chapelon[7], Sylvie Mesrine[7], Jakob Linseisen[8], Sabine Rohrmann[8], Tobias Pischon[5], Mandy Schulz[5], Anne Tjønneland[9], Nina Fons Johnsen[9], Kim Overvad[10], Michelle Mendez[11], M.V. Arguelles[12], Carmen Martinez Garcia[13], Nerea Larrañaga[14], María-Dolores Chirlaque[15], Eva Ardanaz[16], Sheila Bingham[17,18], Kay-Tee Khaw[18], Naomi Allen[19], Tim Key[19], Antonia Trichopoulou[20], Vardis Dilis[20], Dimitrios Trichopoulos[21], Valeria Pala[22], Domenico Palli[23], Rosario Tumino[24], Salvatore Panico[25], Paolo Vineis[26,27], H. Bas Bueno-de-Mesquita[28], Petra H.M. Peeters[29], Evelyn Monninkhof[29], Göran Berglund[30], Jonas Manjer[31], Nadia Slimani[2], Pietro Ferrari[2], Rudolf Kaaks[2,8] and Elio Riboli[27]

[1]*Division of Population Health and Information, Alberta Cancer Board, Calgary, Alberta, Canada*
[2]*Nutrition and Hormones Unit, International Agency for Research on Cancer, Lyon, France*
[3]*School of Public Health, University of Sydney, Sydney, Australia*
[4]*Centre for Research in Human Nutrition Rhône-Alpes, Université Lyon 1, France, Université Claude Bernard Lyon 1, Lyon, France*
[5]*Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany*
[6]*Unit of Environmental Epidemiology, German Cancer Research Centre, Heidelberg, Germany*
[7]*INSERM U ERI20, Institut Gustave Roussy, Villejuif, France*
[8]*Division of Clinical Epidemiology, German Cancer Research Centre, Heidelberg, Germany*
[9]*Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark*
[10]*Department of Clinical Epidemiology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark*
[11]*Department of Epidemiology, Catalan Institute of Oncology, IDIBELL, Barcelona, Spain*
[12]*Public Health and Health Planning Directorate, Principality of Asturias, Oviedo, Spain*
[13]*Andalusian School of Public Health, Granada, Spain*
[14]*Department of Public Health of Guipuzkoa, San Sebastian, Spain*
[15]*Department of Epidemiology, Health Council of Murcia, Spain*
[16]*Public Health Institute of Navarra, Pamplona, Spain*
[17]*MRC Dunn Human Nutrition Unit and MRC Centre for Nutritional Epidemiology in Cancer Prevention and Survival, University of Cambridge, United Kingdom*
[18]*Department of Public Health and Primary Care, School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom*
[19]*Cancer Research UK Epidemiology Unit, University of Oxford, Oxford, United Kingdom*
[20]*Department of Hygiene and Epidemiology, School of Medicine, University of Athens, Athens, Greece*
[21]*Hellenic Health Foundation, Athens, Greece*
[22]*Nutritional Epidemiology Unit, National Cancer Institute, Milan, Italy*
[23]*Molecular and Nutritional Epidemiology Unit, CSPO-Scientific Institute of Tuscany, Florence, Italy*
[24]*Cancer Registry, Azienda Ospedaliera "Civile-M.P.Arezzo," Ragusa, Italy*
[25]*Department of Clinical and Experimental Medicine, Frederico II University, Naples, Italy*
[26]*Department of Biomedical Sciences and Human Oncology, University of Torino, Italy*
[27]*Department of Epidemiology and Public Health, Imperial College, London, United Kingdom*
[28]*National Institute of Public Health and the Environment, Bilthoven, The Netherlands*
[29]*Julius Centre for Health Sciences and Primary Care, University Medical Centre, Utrecht, The Netherlands*
[30]*Department of Clinical Sciences, Malmö University Hospital, Lund University, Malmö, Sweden*
[31]*Department of Surgery, Malmö University Hospital, Lund University, Malmö, Sweden*

The etiologic role of physical activity in endometrial cancer risk remains unclear given the few epidemiologic studies that have been conducted. To investigate this relation more fully, an analysis was undertaken in the European prospective investigation into cancer and nutrition (EPIC). During an average 6.6 years of follow-up, 689 incident endometrial cancer cases were identified from an analytic cohort within EPIC of 253,023 women. Cox proportional hazards models were used to estimate the associations between type of activity (total, occupational, household, recreational) and endometrial cancer risk. For total activity, women in

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***Correspondence to:** Division of Population Health and Information, Alberta Cancer Board, Calgary, Alberta, Canada T2N 4N2. Fax: +403-270-8003. E-mail: chrisf@cancerboard.ab.ca

the highest compared with the lowest quartile of activity had a risk of 0.88 (95% confidence interval (95% CI = 0.61–1.27). No clear associations between each type of activity and endometrial cancer risk were found for the total study population combined. Associations were more evident in the stratified results, with premenopausal women who were active versus inactive experiencing a risk of 0.66 (95% CI = 0.38–1.14) overall. Among premenopausal women, for household and recreational activities the risk estimates in the highest as compared with the lowest quartiles were, respectively, 0.48 (95% CI = 0.23–0.99) and 0.78 (95% CI = 0.44–1.39). No effect modification by body mass index, hormone replacement therapy, oral contraceptive use or energy intake was found. This study provides no evidence of a protective effect of increased physical activity in endometrial cancer risk in all women but some support for a benefit among premenopausal women. The relative risk reductions are most apparent for household activities.

Key words: physical activity; endometrial cancer; etiology; biologic mechanisms

Endometrial cancer is the fourth leading cancer among women in developed countries and the most common gynaecologic cancer in terms of incidence.[1] Risk factors contributing to the aetiology of endometrial cancer include obesity,[2] diabetes mellitus,[3] exposure to estrogens insufficiently balanced by progestogens (estrogen-only hormone replacement therapy (HRT) increases risk and oral contraceptives (OC) generally decrease risk),[2,4,5] positive family history,[6] nulliparity, early age at menarche and late age at menopause.[7] Of these, the only readily modifiable lifestyle risk factors are those relating to obesity or energy balance, namely dietary intake and physical activity. Diet has not been shown to be strongly related to endometrial cancer risk,[8–10] but physical activity is emerging as a potentially important risk factor. Of the previous 19 studies[11–29] of physical activity and endometrial cancer risk, 15[13–21,23,25–29] have found risk reductions among the women who are the most physically active. Of the 19 studies, 8 were cohort studies[12–18,29] with varying levels of detail on physical activity performed. Only 2 cohort studies measured total activity[16,29] while most of the other studies were restricted to either occupational or recreational activity. Given the few cohort studies that have examined this association and the need for more clarity on the association, we undertook an analysis of physical activity and endometrial cancer risk in the European investigation into cancer and nutrition (EPIC), a large cohort study that combines epidemiologic and biologic data from over 500,000 European residents in 10 different countries for which over 250,000 women were available for this analysis. The heterogeneity of lifestyle patterns and habits in these countries make them an ideal group to examine the association of physical activity on endometrial cancer risk. Furthermore, analyses of subgroup effects within the cohort were feasible since standardized data on possible effect modifiers had been collected.

Methods

Study cohort

The EPIC study is an ongoing multicentre, prospective cohort study, designed primarily to investigate the associations between dietary and lifestyle factors and the risk of cancer. The design, study population and baseline data collection methods have been previously described in detail.[30,31] In brief, standardized questionnaire data on dietary and lifestyle factors were collected from ~370,000 women and 150,000 men, enrolled between 1992 and 2000 in 23 centres throughout 10 western European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, The Netherlands and United Kingdom).[30] Participants were mainly between 35 and 70 years of age at enrolment, and were recruited from the general population residing within defined geographic areas (*i.e.* town or province), with some exceptions: women who were members of a health insurance scheme for state school employees (France); women attending breast cancer screening (Utrecht, The Netherlands); blood donors (some centres in Italy and Spain) and a cohort of mainly vegetarians (Oxford 'health conscious' cohort). Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer and from all local recruiting institutions. All participants provided written informed consent.

For the present analysis, we excluded *a priori* the following women: 19,953 with prevalent cancer at enrolment, 1,293 with missing follow-up data, 35,444 with a hysterectomy at baseline, 6,091 participants who were in the top or bottom 1% of the distribution of the ratio of energy intake to estimated energy requirement[32] and 3,586 members with no dietary or lifestyle data. In addition, women with missing or nonstandardized physical activity questionnaire data were excluded, comprising all study subjects from Norway (n = 34,275) and Umeå, Sweden (n = 12,519), about 23% (n = 2,661) of the participants in Bilthoven, The Netherlands and less than 1% in other centres. A total of 253,023 women were included in this analysis.

Assessment of physical activity and other predictor variables

The assessment of physical activity has been previously described in detail.[33] The EPIC physical activity questionnaire was derived from a longer, modified version of the Baecke questionnaire,[34] and was administered at study entry predominantly by self-administration.[30,33] The stratification by study centre in this and other EPIC-analyses is considered to control for center effects related to different questionnaire design and follow-up procedures. In a study by Pols *et al.*,[35] the Spearman correlation coefficients for the estimated reproducibility of the EPIC questionnaire over 5–11 months ranged from 0.49 to 0.81 in women, and for the relative validity as assessed by 3-day activity diaries the correlation coefficients ranged from 0.28 to 0.72. They found the questionnaire to be satisfactory for the ranking of subjects although less suitable for the estimation of energy expenditure.

Data on current occupational activity included employment status and the level of physical activity done at work (nonworker, sedentary, standing, manual, heavy manual and unknown). Participants were also asked to report the frequency and duration of recreational and household activities, in summer and winter, during a typical week in the past year. Household activities included housework, home repair, gardening and stair climbing. Recreational activities included walking, cycling and sports activities. The overall level of recreational and household activity was calculated in MET-hours/week, by summing the metabolic equivalent intensity values (METs)[36] that were assigned to reported hours per week of recreational and household activities. The assigned MET values were 3.0 for walking, 6.0 for cycling, 4.0 for gardening, 6.0 for sports, 4.5 for home repair (do-it-yourself work), 3.0 for housework and 8.0 for stair climbing, obtained by estimating the average of all comparable activities in the compendium of physical activities.[36] In addition, the frequency and duration of vigorous nonoccupational activity, defined as activities causing sweating or faster heartbeat, was collected.

A physical activity index based on occupational activity, cycling and sports has been previously developed by Wareham *et al.*, and validated using heart rate monitoring and cardiorespiratory fitness tests.[37] However, low- and moderate- intensity activities such as walking and household activities are the most accessible and popular forms of physical activity,[38] and have been associated with lower rates of breast cancer[39] and other chronic diseases.[38,40] Therefore, to make the index more comprehensive, we derived an index of total physical activity (inactive, moderately inactive, moderately active, active), that was estimated by cross-tabulation of the level of occupational activity (nonworker, sedentary, standing, manual, heavy manual and unknown) with combined recreational and household activities (in quartiles of MET-hours/week) (Appendix Table AI). As a means of indirectly

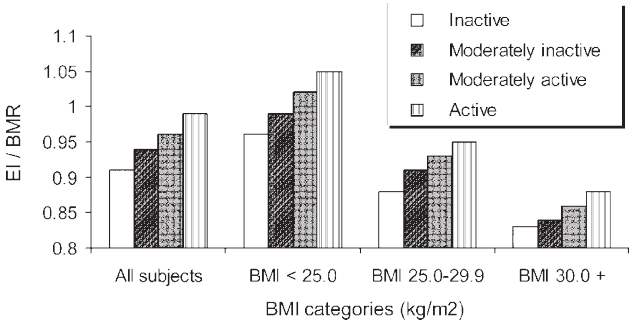

FIGURE 1 – Ratio of EI to predicted BMR, by categories of total physical activity level and body mass index (BMI). The mean ratio for each group is presented, adjusted by age and centre. $p_{\text{trend}} < 0.001$ for all groups.

assessing the validity of the total physical activity index, we compared the total physical activity index with estimates of the ratio of energy intake (EI), collected using EPIC dietary questionnaires, to predicted basal metabolic rate (BMR)[41] adjusted for age and centre and within different BMI categories. We found a positive relation between EI/BMR and total activity level, both overall and among women in different BMI subgroups, indicating that this index appropriately ranked the subjects according to their predicted energy requirements (Fig. 1).

Diet over the previous 12 months was assessed at the time of enrolment using country-specific, validated dietary assessment instruments.[30,42] Data on lifestyle, health and sociodemographic characteristics were collected *via* standardized questionnaires that included menstrual and reproductive history, use of OCs and HRT, medical history, lifetime history of tobacco smoking and alcohol consumption, brief occupational history and level of education. Height, weight and waist and hip circumferences were measured according to standardized protocols,[43] except for the majority of the French and UK Oxford "health conscious" cohorts, where height and weight were self-reported. Menopausal status at enrolment was defined as follows: women were "premenopausal" if they reported having had regular menses over the past 12 months; "postmenopausal" if they reported not having had any menses over the past 12 months, or if they had a bilateral ovariectomy; and "perimenopausal/unknown" if they reported irregular menses over the past 12 months (1–9 cycles) or if they indicated having had menses over the past 12 months but were no longer menstruating at the time of recruitment. Women with incomplete or missing questionnaire data, or who reported current use of exogenous hormones, were classified as premenopausal if they were less than 46 years of age, perimenopausal/unknown if they were between 46 and 55 years of age and postmenopausal if they were older than 55 years.

Follow-up for cancer incidence and vital status

Incident cases were identified through population-based cancer registries, except in France, Germany and Greece, where a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin was used. Data on vital status in most EPIC study centres were collected from mortality registries at the regional or national level, in combination with data collected by active follow-up (Greece). Vital status was known for 98.4% of all EPIC participants as at April 2004. Women were followed from the date of enrolment until endometrial cancer diagnosis, death, emigration or end of the follow-up period. The closure date for this study period for each EPIC centre was the date of the last complete follow-up for both cancer incidence and vital status, which varied between December 1999 and March 2004 between EPIC centres. A total of 689 incident cases of endometrial cancer were diagnosed during the follow-up period. The cancer diagnosis was confirmed by histology for 88% of cases, by clinical examination for 9% and the remaining 3% by either self-report, tomography scan, surgery, autopsy or by death certificate. Detailed morphology was specified for 226 (33%) cases, of which 207 (92%) were endometrioid, 8 (4%) serous, 5 (2%) mucinous, 4 (2%) clear cell and 2 (1%) undifferentiated.[44]

Statistical analyses

Descriptive statistics were calculated as age- and centre-adjusted means and standard deviations for continuous variables, or as percentages for categorical variables. All analyses were performed using SAS Statistical Software, version 9.1 (SAS Institute, Cary, NC), and all statistical tests were 2-sided.

We analyzed the association between physical activity and risk of endometrial cancer by estimating incidence rate ratios as estimates of relative risks (RR), using Cox proportional hazard models. Age was used as the underlying time variable, with entry and exit time defined as the subject's age at recruitment and age at endometrial cancer diagnosis or censoring (death, lost to follow-up, end of follow-up), respectively. Models were stratified by study centre to account for potential centre effects such as differing follow-up procedures and questionnaire design, and by age at recruitment (in 1-year categories), to be less sensitive to violations of the proportional hazards assumption. Continuous variables of physical activity (*e.g.* MET-hours/week of activity) and potential confounders were categorized into quartiles using cut-points based on the overall cohort for all centres combined. Trend tests were estimated on integer scores applied to the physical activity categories or quartiles, and entered as a continuous term in the regression models.

Two sets of models are presented: the "crude" model stratified by age and centre and mutually adjusted for other types of physical activity; and the fully adjusted multivariate model stratified by age and centre and adjusted for potential confounders: BMI (<25, 25–29.99, ≥30 kg/m^2), age at menarche (<12, 12, 13, 14, ≥15, missing), menopausal status (premenopausal, perimenopausal, postmenopausal), age at menopause (<43, 43–46, 47–49, 50–51, 52–53, ≥54, missing), number of full-term pregnancies (0, 1, 2, 3, ≥4, missing), age at birth of last child (<27, 27–29, 30–32, ≥33, missing), use of OCs (ever, never, missing), use of HRT (ever, never, missing), education (none, primary school completed, technical/professional school, secondary school, university degree, missing), smoking status (never, former, current, unknown), hypertension (yes, no, unknown), diabetes (yes, no, unknown), fruit and vegetable intake (grams/day in quartiles), fiber intake (grams/day in quartiles), carbohydrate intake (grams/day in quartiles), EI (grams/day in quartiles). All potential confounders were retained in the multivariate models, as the exclusion of single or multiple factors did not result in more precise estimates for the effects of physical activity, thus, there was no advantage in using more parsimonious models.[45] Since BMI is closely associated with physical activity, we also examined all the multivariate models with and without adjustment for BMI and found the results to be almost identical and include models fully adjusted for BMI.

We also examined associations of physical activity with endometrial cancer in subgroup analyses by separate stratification on menopausal status, BMI categories, ever HRT use, ever OC use, quartiles of EI and age groups by decade year. These factors were all identified as potential effect modifiers *a priori* based on the literature review and biologic plausibility. The possibility of effect modification was examined by adding subgroup interaction terms to the multivariate models. In the same way, we tested for heterogeneity of endometrial cancer risk estimates by country. The proportional hazards assumption was checked by adding interaction terms for the main physical activity variables and follow-up time (years) to the models.

TABLE I – SIZE OF THE EPIC COHORT FOR THE ANALYSES OF PHYSICAL ACTIVITY AND ENDOMETRIAL CANCER, BY COUNTRY

Country	Cohort size	Age at recruitment (mean, SD)	Number of years of follow-up (mean, SD)	Person-years	Number of endometrial cancer cases	MET-hours/week of combined household and recreational physical activity (mean, SD)
France	60,964	52.4 (6.6)	8.4 (0.9)	512,239	224	57.6 (30.7)
Italy	27,771	50.3 (8.1)	6.2 (1.5)	171,780	75	110.0 (56.3)
Spain	22,777	47.9 (8.4)	6.6 (1.0)	150,218	56	125.7 (47.5)
United Kingdom						
health conscious	32,245	41.9 (13.9)	5.4 (1.2)	173,202	22	92.1 (50.2)
general population	13,110	56.6 (9.40)	5.6 (1.4)	73,974	49	100.2 (51.0)
The Netherlands	20,179	50.6 (11.8)	6.4 (2.0)	129,570	50	118.0 (53.6)
Greece	13,748	52.8 (12.6)	3.7 (0.7)	51,213	11	116.5 (42.1)
Germany	23,718	48.1 (9.0)	5.9 (1.4)	138,788	33	100.3 (45.7)
Sweden	14,023	57.3 (7.9)	7.6 (1.7)	105,901	55	80.0 (38.1)
Denmark	24,488	56.7 (4.4)	6.7 (1.0)	165,232	114	67.0 (37.1)
Total	253,023	50.8 (10.3)	6.6 (1.8)	1,672,117	689	90.3 (50.5)

Results

There were 689 endometrial cancer cases diagnosed in this cohort of 253,023 women during an average 6.6 (SD 1.8) years and 1,672,117 person-years of follow-up (Table I). The mean age at recruitment was 50.8 (SD 10.3) years. The levels of combined household and recreational activity ranged considerably across the 10 separate cohorts included in the EPIC study with a low of 57.6 MET-hours/week in France and a high of 125.7 MET-hours/week in Spain.

The women who were diagnosed with endometrial cancer during follow-up were older at baseline, on average, than the women without endometrial cancer in this cohort and more likely to be postmenopausal, obese, to report hypertension and ever-use of HRT and less likely to have completed university or use OCs than the noncases (Table II). Incident cases and noncases were similar at baseline with respect to their reproductive and menstrual characteristics and their dietary intake. The total activity levels were comparable between the 2 groups however slight differences were noted for occupational activities.

The analysis of endometrial cancer risk by physical activity found no evidence for a trend of decreasing risk with increasing levels of total physical activity for the entire study population combined (Table III). All quartiles above the referent category of "inactive" observed risk reductions between 12 and 17% that were not statistically significant. When examining the risk by type of activity, we observed a somewhat greater risk reduction for manual and heavy manual workers than for standing, nonworkers or sedentary workers, however, this risk decrease was only 12% and not statistically significant, and few women were in this category of occupational activity. Similarly, there were no associations between endometrial cancer risk and household and recreational activity and no evidence for a dose-response effect for these 2 types of activity (Table III). There were no statistically significant associations with risk for individual nonoccupational physical activities except for stair climbing (multivariate RR for women in the highest versus lowest quartile = 0.77 (95% Confidence Interval (95% CI) = 0.60–0.99), p_{trend} = 0.009) (data not shown). The multivariate mutually adjusted RR, when comparing more than 2 hr of activity per week *vs.* no activity, was 0.95 (0.76–1.18) for cycling, 1.11 (0.92–1.34) for gardening, 1.07 (0.88–1.30) for sports, 1.11 (0.91–1.36) for home repair and 0.93 (0.74–1.16) for vigorous activity. The multivariate RR was 0.87 95% CI = 0.67–1.08 for walking and 0.84 (95% CI = 0.62–1.13) for housework for women in the highest versus lowest quartiles.

When examining the associations among subgroups of the study population, the risk estimates observed differed by menopausal status at baseline (Table IV) although the tests of interaction were not statistically significant for any of the physical activity measures. Women who were perimenopausal, or whose menopausal status was unknown at baseline, were excluded from this subgroup analysis. Among women who were postmenopausal at baseline, there were nonstatistically significant RR reductions of 15–17% for women whose total physical activity level was not classified as inactive, and manual workers had a multivariate risk of 0.69 (95% CI = 0.43–1.12) compared with sedentary workers. However no association was observed for household or recreational activity among postmenopausal women.

Among premenopausal women, those who were either active or moderately active compared with inactive had a multivariate RR estimate of 0.66 (95% CI = 0.38–1.14). There was little evidence for an association of occupational activity among premenopausal women; standing workers had a nonstatistically significant 24% RR reduction and manual workers experienced no decreased risk, although there were very few premenopausal manual workers. A statistically significant decreased risk of endometrial cancer was found among premenopausal women who were in the highest as compared with the lowest quartile of household activity. These women experienced a risk of 0.48 (95% CI = 0.23–0.99) and the test for a dose-response across the quartiles of household activity approached statistical significance (p_{trend} = 0.10). For recreational activity, there was a nonstatistically significant decrease in risk across the quartiles of activity for premenopausal women, with the highest quartile risk at 0.78 (95% CI = 0.44–1.39).

An analysis of effect modification by BMI, stratified into tertiles (<25, ≥25–<30, ≥30), for the association of physical activity and endometrial cancer risk was also conducted (data not shown). Of the analyses done for total physical activity and by type of activity, only 1 significant risk reduction was observed among normal weight women who were moderately inactive (multivariate RR = 0.68, 95% CI = 0.50–0.93). However, among moderately active or active normal weight women the risk reduction was only 12% and there was no evidence of a trend for any of the categories examined. There were also no clear differences by BMI categories for occupational, household or recreational activities and none of the interactions were statistically significant.

An additional analysis of effect modification by ever-use of HRT among postmenopausal women found that the risk estimates were generally lower among never HRT users than among ever HRT users for all types of physical activity examined except recreational activity (data not shown). However, none of the associations were statistically significant. We also examined the associations by current use of HRT and found somewhat stronger associations among noncurrent HRT users, however, the results were also not statistically significant and no dose-response trends were found.

A final analysis of effect modification by ever use of OCs among the premenopausal women did find some notable differences in the associations between the ever and never users (data not shown). Among the never OC users who were active or moderately active, the risk compared with inactive women was 0.52 (95% CI = 0.22–1.19). This reduction in risk appears to have been mainly attributable to the occupational and household activity that these women did. Among never OC users, women who

TABLE II – DEMOGRAPHIC AND LIFESTYLE CHARACTERISTICS OF THE INCIDENT ENDOMETRIAL CANCER CASES AND WOMEN WHO DID NOT DEVELOP ENDOMETRIAL CANCER IN THE EPIC COHORT

Characteristic	Endometrial cancer incident cases (n = 689)	Women without endometrial cancer (n = 252,334)
Age at recruitment (years) (mean, SD)	54.1 (8.9)	50.7 (10.8)
Education (%)		
None	4.3	4.9
Primary school completed	25.4	21.7
Technical/professional school	19.6	20.4
Secondary school	31.5	26.9
University degree	19.1	26.1
Menopausal status (%)		
Premenopausal	18.0	37.9
Perimenopausal	16.0	15.3
Postmenopausal	66.0	46.8
Reproductive and hormone factors (mean, SD)		
Age at menarche (years)	12.8 (1.5)	13.0 (1.8)
Age at menopause (years)	50.9 (4.4)	49.4 (5.7)
Age at first full-term pregnancy[1] (years)	24.8 (4.3)	25.1 (5.1)
Number of full-term pregnancies[1]	2.3 (1.0)	2.3 (1.2)
Age at birth of last child[1] (years)	29.3 (4.7)	29.9 (5.6)
Hormone replacement therapy (ever used; %)	34.9	22.5
Oral contraceptives (ever used; %)	42.1	59.0
Nulliparous	16.3	17.1
Dietary intake (mean, SD)		
Energy intake (kcal/day)	2040.3 (525.4)	2032.0 (636.9)
Fruits and vegetables (g/day)	530.1 (245.2)	510.6 (297.2)
Fibre (g/day)	23.2 (7.2)	22.5 (8.7)
Carbohydrate (g/day)	236.9 (69.6)	233.3 (84.4)
Smoking status (%)		
Never smoker	64.1	59.1
Exsmoker	21.0	22.5
Current smoker	14.9	18.4
Self-reported hypertension (%)	27.7	19.2
Self-reported diabetes (%)	3.7	2.3
Anthropometric factors (mean, SD)		
Body mass index (BMI; kg/m^2)	26.6 (4.1)	25.6 (4.9)
% Obese (BMI $\geq$30)	20.5	12.7
Total physical activity (%)		
Inactive	15.4	16.0
Moderately inactive	39.8	37.0
Moderately active	38.3	39.0
Active	6.6	8.1
Occupational activity (%)		
Nonworker	48.3	38.7
Sedentary	20.7	26.1
Standing	24.3	28.0
Manual/heavy manual	6.7	7.2
Household activity (MET-hours/week) (mean, SD)	69.4 (35.8)	70.3 (43.4)
Recreational activity (MET-hours/week) (mean, SD)	27.6 (22.6)	28.5 (27.4)

Abbreviations: SD, standard deviation; SE, standard error. Missing values were excluded from percentage calculations. Continuous variables are presented as means and standard deviations and are adjusted by age and centre, except age that is adjusted by centre only.
[1]Among parous women.

had standing occupations compared with women with sedentary jobs had a risk of 0.50 (95% CI = 0.24–1.05), and women in the highest versus the lowest quartile of household activity had a risk of 0.26 (95% CI = 0.09–0.79, p_{trend} = 0.02).

We also examined the association of total physical activity and endometrial cancer risk by country within the EPIC cohort study and found no statistically significant interaction ($p_{\text{heterogeneity}}$ = 0.91) suggesting that there was no heterogeneity of associations across the cohorts included in this analysis.

In sensitivity analyses, exclusion of 196 women who were diagnosed within the first 2 years of follow-up and 1,496 noncases who had less than 2-years follow-up slightly reduced the multivariate RR for active compared with inactive women to 0.82 (95% CI = 0.53–1.27, p_{trend} = 0.17). Exclusion of the French women (n = 224, 33% of analytic cohort), or the Spanish women (n = 56, differences in coding occupation for housewives) did not appreciably alter the risk estimates, suggesting that these groups of women did not bias the results.

Discussion

In this large, prospective cohort study of over 250,000 women from 9 European countries we found little association between physical activity and endometrial cancer risk. Although the overall risk reduction among active women, as measured by our total activity index, was modest at only 12% and did not achieve statistical significance, the risk decreases in the sub-group analyses stratified by menopausal status ranged up to a 52% risk decrease for premenopausal women in the highest category of household activity, although was also not statistically significant. Hence, this study provides some modest support for a protective effect of physical activity on endometrial cancer risk.

Before discussing the results, the limitations and strengths of the study should be considered. Although all types of activity were assessed in this study at recruitment, there was no information on the duration and frequency of occupational activity that precluded estimating a sum of all types of activity in MET-hours/week. Instead, we used an index of activity that was based on a

TABLE III – HAZARD RATIO ESTIMATES OF ENDOMETRIAL CANCER BY TYPE OF PHYSICAL ACTIVITY, EPIC COHORT

Type of activity	Number of cases	Number of person-years	Age- and centre- stratified hazard ratio and 95% CI	Multivariate[1] adjusted hazard ratio and 95% CI
Total Physical Activity[2]				
Inactive	103	261,857	1.00	1.00
Moderately inactive	267	643,979	0.84 (0.67–1.07)	0.83 (0.66–1.06)
Moderately active	257	597,784	0.83 (0.64–1.06)	0.83 (0.65–1.07)
Active	44	121,777	0.85 (0.59–1.23)	0.88 (0.61–1.27)
p_{trend}			0.25	0.36
Occupational activity[2,3]				
Sedentary	139	411,915	1.00	1.00
Standing	163	489,436	0.91 (0.72–1.15)	0.92 (0.73–1.17)
Manual/heavy manual	45	113,537	0.87 (0.61–1.22)	0.89 (0.63–1.26)
Nonworker	324	610,508	0.99 (0.78–1.25)	0.99 (0.78–1.25)
p_{trend}[4]			0.50	0.59
Household activity[3] (MET-hours/week)				
<25.12	194	454,799	1.00	1.00
≥25.12–<48.08	172	432,979	0.94 (0.76–1.16)	0.94 (0.76–1.16)
≥48.08–<85.10	173	406,650	0.99 (0.79–1.24)	1.00 (0.80–1.25)
≥85.10	150	377,689	0.91 (0.69–1.19)	0.93 (0.70–1.22)
p_{trend}			0.62	0.73
Recreational activity[3] (MET-hours/week)				
<12.01	192	438,560	1.00	1.00
≥12.01–<23.26	163	380,839	0.99 (0.80–1.22)	0.99 (0.80–1.23)
≥23.26–<41.26	176	434,829	0.93 (0.76–1.15)	0.94 (0.76–1.16)
≥41.26	158	417,888	0.92 (0.74–1.15)	0.94 (0.75–1.18)
p_{trend}			0.38	0.47

[1]Stratified by age and centre, and adjusted for BMI, age at menarche, menopausal status, age at menopause, number of full-term pregnancies, age at birth of last child, ever use of oral contraceptives, ever use of hormone replacement therapy, education, smoking status, hypertension, diabetes, fruit and vegetable intake, fibre intake, carbohydrate intake, energy intake.–[2]Totals exclude 18 cases and 6,439 noncases where the occupational activity is unknown.–[3]The models for occupational, household and recreational activity are mutually adjusted.–[4]The test for trend excludes nonworkers and unknown values.

TABLE IV – HAZARD RATIO ESTIMATES OF ENDOMETRIAL CANCER BY TYPE OF PHYSICAL ACTIVITY, ACCORDING TO BASELINE MENOPAUSAL STATUS[1]

Type of activity	Premenopausal women (n = 124 cases)			Postmenopausal women (n = 455 cases)		
	No. of cases	Age- and centre-stratified hazard ratios and 95% CI	Multivariate[2] hazard ratios and 95% CI	No. of cases	Age- and centre-stratified hazard ratios and 95% CI	Multivariate[2] hazard ratios and 95% CI
Total physical activity[3]						
Inactive	25	1.00	1.00	56	1.00	1.00
Moderately inactive	50	0.81 (0.50–1.33)	0.80 (0.49–1.32)	177	0.84 (0.61–1.14)	0.83 (0.60–1.14)
Moderately active/Active	47	0.63 (0.37–1.07)	0.66 (0.38–1.14)	211	0.82 (0.60–1.13)	0.85 (0.61–1.17)
p_{trend}		0.09	0.14		0.33	0.48
Occupational activity[3,4]						
Sedentary	36	1.00	1.00	75	1.00	1.00
Standing	46	0.79 (0.49–1.25)	0.76 (0.47–1.21)	84	1.03 (0.75–1.42)	1.07 (0.77–1.48)
Manual	8	1.10 (0.49–2.44)	1.15 (0.51–2.59)	23	0.67 (0.42–1.08)	0.69 (0.43–1.12)
Nonworker	32	1.10 (0.63–1.94)	1.17 (0.65–2.09)	262	0.93 (0.70–1.25)	0.93 (0.69–1.25)
p_{trend}[5]		0.70	0.82		0.24	0.26
Household activity (MET-hours/week) in quartiles[4]						
<25.12	38	1.00	1.00	119	1.00	1.00
≥25.12–<48.08	32	0.91 (0.56–1.48)	0.92 (0.56–1.50)	113	0.95 (0.73–1.24)	0.97 (0.75–1.27)
≥48.08–<85.10	27	0.77 (0.44–1.35)	0.76 (0.43–1.35)	119	1.01 (0.77–1.33)	1.04 (0.79–1.37)
≥85.10	27	0.48 (0.24–0.96)	0.48 (0.23–0.99)	104	1.02 (0.74–1.41)	1.07 (0.77–1.48)
p_{trend}		0.09	0.10		0.89	0.66
Recreational activity (MET-hours/week) in quartiles[4]						
<12.01	40	1.00	1.00	117	1.00	1.00
≥12.01–<23.26	40	1.13 (0.72–1.78)	1.19 (0.75–1.87)	105	1.04 (0.80–1.36)	1.05 (0.80–1.37)
≥23.26–<41.26	23	0.69 (0.41–1.18)	0.75 (0.44–1.28)	118	0.96 (0.74–1.26)	0.97 (0.74–1.27)
≥41.26	21	0.75 (0.43–1.31)	0.78 (0.44–1.39)	115	1.01 (0.77–1.33)	1.02 (0.77–1.35)
p_{trend}		0.14	0.22		0.86	0.94

[1]Excludes 110 cases and 38500 noncases who were perimenopausal or who had an unknown menopausal status at baseline.–[2]Stratified by age and centre, and adjusted for BMI, age at menarche, age at menopause (postmenopausal women), number of full-term pregnancies, age at birth of last child, ever use of oral contraceptives, ever use of hormone replacement therapy, education, smoking status, hypertension, diabetes, fruit and vegetable intake, fibre intake, carbohydrate intake, energy intake.–[3]Totals exclude 18 cases and 6,439 noncases where the occupational activity is unknown.–[4]The models for occupational, household and recreational activity are mutually adjusted.–[5]The test for trend excludes non-workers and unknown values.

cross-classification of occupational activity with the combination of household and recreational activity. We found an appropriate ranking of study participants according to their ratio of EI to BMR by categories of total physical activity level and BMI (Fig. 1). Furthermore, the relative validity and reproducibility of the EPIC physical activity questions has been conducted and a short version of the questionnaire,[35] that was used in EPIC, was found to rank study participants satisfactorily in terms of activity levels. It is recognized, nonetheless, that measurement error and misclassification exist in this physical activity assessment and that the results from

this study were likely attenuated. Our study also has several strengths including the large and heterogenous study sample, the standardized data collection methods for physical activity and confounding factors, and a comprehensive assessment of these factors that was undertaken.

Fourteen of nineteen previous studies[12–28] observed a risk decrease among the most physically active study participants. The risk reduction in these studies ranged from 20 to 90% with the average decrease at 30–40%. Evidence for a dose-response trend was noted as well in 8[14,15,17,18,20,25,26,28] of the 14 studies[11,14–18,20,23–29] that examined the trend in risk across categories of activity. Our study findings were not as strong or as consistent across different domains of activity as previously found since we observed a 12%, nonstatistically significant risk reduction for total physical activity and no associations overall by type of activity. Several effect modifiers have been considered in 12 previous studies[14,16–20,22,24,25,27–29] including age, weight, BMI, weight gain, HRT and OC use, menopausal status, parity, EI, education, income, history of hypertension and diabetes. No consistent effect modification has been found in these studies and only suggestive evidence for an interaction with menopausal status, BMI, caloric intake, OC use and smoking have been found in a few isolated studies.[16,18,19,25,28]

Three studies examined the interaction by menopausal status.[16,19,28] There was some evidence for a differential association of physical activity with endometrial cancer by menopausal status in the study by Matthews *et al.* only.[28] In that study, a stronger association of household and walking activities was found among premenopausal women compared with postmenopausal women but this difference in association was not observed when total physical activity done in adulthood was examined. These findings are in agreement with the results found in the EPIC study as we observed a stronger association of household activity in premenopausal women than in postmenopausal women although the interaction with menopausal status was not statistically significant. Household activity *per se* is a major contributor to women's overall daily activity[46] and has also been shown to confer large risk reductions for breast cancer.[39] One possibility for an apparent stronger association for household activity than for recreational activity is because the level of household activity was much higher and more variable than recreational activity. Given that only 2 studies have found some possible effect modification by menopausal status, there is insufficient evidence to conclude that physical activity has a more beneficial effect on pre- or postmenopausal endometrial cancer risk.

The potential for effect modification by BMI was examined in 6 studies with 3 suggesting a stronger association of physical activity among women with a BMI greater than 25,[17,19,20] 1 observing a potentially greater benefit among women with a BMI under 25[25] and 2 studies noting no significant multiplicative interactions by BMI.[28,29] In the EPIC cohort study, we also did not find any significant interactions with BMI and our risk estimates were fairly stable across the categories of BMI considered. Thus, the evidence for effect modification by BMI and physical activity risk remains inconsistent.

Finally, effect modification by estrogen or HRT use or OC use was observed in one[18] of the 4 studies[16,18,25,27] that examined these therapies. Overall, the never HRT users and never OC users had somewhat lower risks for endometrial cancer compared with ever-users for most types of physical activity examined. Again, this potential effect modification requires additional investigation in future studies.

Physical activity may influence endometrial cancer risk through several possible biologic mechanisms; the primary ones are an impact on endogenous sex hormone levels, body composition, and insulin levels. The endogenous balance of estrogen and progesterone is an important determinant of endometrial cancer risk. The "unopposed estrogen hypothesis"[2,47] is based on empirical epidemiologic evidence that endometrial cancer risk is increased when estrogen exposure is not adequately balanced by progesterone. Progesterone deficiency is the main risk factor for endometrial cancer among premenopausal women and estrogen excess is the main determinant among postmenopausal women.[2,47] It is unclear exactly how physical activity influences endometrial carcinogenesis but several hypotheses exist. One possibility is that activity acts by increasing the ratio of progesterone to estrogen before menopause and decreasing estrogens after menopause. However, physical activity has also been shown to decrease progesterone in premenopausal women for some vigorous activities or if EI is insufficient.[48,49] Physical activity is known to decrease endogenous estrogen production among physically active females during adolescence and early adulthood.[50] Amenorrhea, anovulation and delayed menarche are all consequences of high levels of activity that result in reduced ovarian estrogen and/or progesterone production and exposure.[48,51–53]

Obesity is a clearly established risk factor for endometrial cancer.[2] After menopause, when ovarian production of both estrogen and progesterone ceases, estrogens are mainly produced by conversion from androgens in the adipose tissue, hence, the level of adiposity is directly related to the amount of total and bioavailable estrogens.[2,47] In premenopausal women, obesity is associated with menstrual irregularities, early menarche and delayed menopause,[2,47,54] resulting in increased lifetime exposure to unopposed estrogens and decreased exposure to progesterone. Hence, physical activity could directly influence these pathways by decreasing total body fat levels which, particularly in postmenopausal women, reduce the total and bioavailable estrogen levels.

The related components of insulin resistance, hyperinsulinemia, hyperglycemia and impaired glucose regulation have been associated with an increased risk of endometrial cancer.[3,17,26,55–58] Specific mechanisms have been proposed to explain the association.[59–61] Insulin promotes carcinogenesis by inhibiting apoptosis and stimulating cell proliferation[59,60] and also results in increased exposure to bioavailable sex hormones and growth factors.[59] Lack of physical activity is a major cause of insulin resistance.[62] Changes in lifestyle such as weight loss, exercise and diet programs have been shown to improve insulin resistance and induce apoptosis in hormone-related cancers.[2,63–65]

In conclusion, this study has provided additional empirical evidence from a large, heterogeneous European population that physical activity may contribute to endometrial cancer risk reduction, particularly among premenopausal women. Household and recreational activity contributed to this overall association of physical activity among premenopausal women, with the largest benefit from 85 or more MET-hours/week of household activity. This level of household activity is equivalent to 28 hr per week of 3.0 MET activity (general housework) or 21 hr of 4.0 MET activity (gardening) which translates into 3–4 hr per day of household and/or recreational activity. This amount and type of activity is achievable by many of the at-risk population. Although the results from this study provide only modest support for a protective effect of physical activity on endometrial cancer risk, previous research is suggestive of a moderate beneficial effect and future research that examines more precisely the optimal dose, type and time periods in life when physical activity might have an impact is warranted.

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APPENDIX TABLE AI – CREATION OF TOTAL PHYSICAL ACTIVITY INDEX AS THE CROSS-CLASSIFICATION OF OCCUPATIONAL AND COMBINED RECREATIONAL AND HOUSEHOLD ACTIVITY

Occupational activity	Recreational and household activity (MET-hours/week in sex-specific quartiles)			
	Low	Medium	High	Very high
	Females: ≤51.11	>51.11–≤82.43	>82.43–≤123.02	>123.02
Sedentary	Inactive	Inactive	Moderately inactive	Moderately active
Standing	Moderately inactive	Moderately inactive	Moderately active	Active
Manual	Moderately active	Moderately active	Active	Active
Heavy manual	Moderately active	Moderately active	Active	Active
Nonworker	Moderately inactive	Moderately inactive	Moderately active	Moderately active