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Body Fatness, Physical Activity and the Risk of Cervical Cancer: Results From the Epic Cohort

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TITLE PAGE:

BODY FATNESS, PHYSICAL ACTIVITY AND THE RISK OF CERVICAL CANCER: RESULTS FROM THE EPIC COHORT

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Abstract

Background: Obesity is a recognized risk factor for several types of cancer, while being physically active is known to reduce cancer risk. However, evidence for both remains inconclusive for cervical cancer. We evaluated the associations between body fatness and physical activity and the risk of invasive cervical cancer (ICC) within the European Prospective Investigation into Cancer and Nutrition (EPIC) Study.

Methods: This analysis included 293,523 women who completed lifestyle questionnaires and provided serum samples at baseline. The anthropometric indicators assessed were Body Mass Index (BMI), "a body shape index" (ABSI), waist circumference and waist-to-hip ratio. Physical activity was evaluated using a combined index of total physical activity (occupational, household and recreational activities), an index of physical activity determined in a Cambridge validation study (occupational and recreational activities excluding walking), and a specific recreational activity variable (walking, cycling, sports). Over a median follow-up of 15 years, 369 incident ICC cases were reported. In a nested case-control study, serum from 171 cases and 342 matched controls were tested for L1 antibodies against Human Papillomavirus (HPV) types 11, 16, 18, 31, 33, 35, 45, 52, 58, *Chlamydia trachomatis* and *Human herpesvirus 2*. Multivariable Cox and conditional regression models adjusted for potential confounders were performed.

Results: Women with BMI over 30 kg/m^2 had a nonsignificant increased risk of ICC (Hazard Ratio (HR)=1.19, 95%CI: 0.87-1.65) compared to women with BMI between 18.5-24.9 kg/m^2. Women engaging occupational, household and recreational activities had a reduced risk of ICC (HR=0.74, 95%CI: 0.55-0.99) compared to being inactive. Sensitivity analysis incorporating HPV serology yielded similar results.

Conclusions: These findings support the potential protective effect of physical activity against ICC, though the evidence for anthropometric measures remains inconclusive.

Key words: cervical cancer; body fatness; physical activity; risk factors; prevention.

Article category: Research article – Cancer Epidemiology

Novelty and Impact

This study is the largest prospective investigation to jointly assess body fatness, physical activity, and cervical cancer risk. The detailed characterization of the study population, including HPV serology, provides an important framework for evaluating these associations. Our findings highlight the importance of promoting active lifestyles as a potential strategy to reduce cervical cancer risk in the general population.

Background

Over the last four decades, prevalence of body fatness has been increasing rapidly all over the world [1–3] . Previous epidemiological data have suggested that obesity is an established risk factor for several cancer sites [3,4]. In 2018, the World Cancer Research Fund (WCRF) summarized the evidence concluding that an excess of body fatness increases the risk of esophagus (adenocarcinoma), pancreas, liver, colorectum, breast (in postmenopausal women), endometrium and kidney cancers, and probably increases the risk of mouth, pharynx, larynx, stomach, gallbladder, ovary and prostate cancers [4]. The same year, the International Agency for Research on Cancer (IARC) reviewed the evidence for three additional cancers and concluded that greater body fatness is also associated with thyroid cancer, multiple myeloma and meningioma [1]. Concerning cervical cancer, the WCRF concluded that the evidence is limited although suggestive of an increased risk among women with excess body fatness [4]. Although most studies, mainly cohort studies, have shown a modest positive association between body fatness and cervical cancer risk [5–11], others did not find such association [5,12–14].

Previous research found beneficial effects of physical activity, a modifiable risk factor, on cancer risk [4]. The WCRF evaluated evidence that being physically active decreases the risk of cancers of the colon, breast (in postmenopausal women) and endometrium, and that undertaking physical activity of vigorous intensity decreases the risk of pre and postmenopausal breast cancer[4]. Related to cervical cancer, only three case-control studies, to the best of our knowledge, have evaluated the relationship with physical activity, finding a somewhat protective effect [15–17]. The evidence was considered too limited to conclude that physical activity directly modifies the risk of this cancer.

Infection of Human Papillomavirus (HPV) is the necessary cause of cervical cancer [18], thus it is essential to adjust for HPV status to perform high-quality studies. However, only few previous studies evaluating body fatness and cervical cancer risk have adjusted for HPV in their analyses or stratified by HPV infection [15,19,20].

Globally, the literature is inconclusive and scarce about the relationship between cervical cancer, body fatness and physical activity, and most studies did not consider HPV infection. Therefore, the objective of our study was to determine whether body fatness and physical activity were associated with the risk of cervical cancer and precancer in the large European Prospective Investigation into Cancer and Nutrition (EPIC) study, including a subgroup of women with serological markers of HPV infection.

Methods

The EPIC cohort study

EPIC is an ongoing multicenter prospective cohort study investigating associations between nutrition and cancer. The methods have been previously reported in detail [21]. Approval of this study was obtained from the Ethical Review Boards of the IARC and from local institutions in each center. In brief, the cohort includes more than half a million people recruited in 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom (UK)). The recruitment was conducted between 1992 and 2000, and most participants were aged 35 to 70 years. All participants provided written informed consent and completed questionnaires on their diet, medical and lifestyle history [21,22], and were invited to a center to provide a blood sample.

Study population

For the present study and from the initial EPIC cohort of 343,985 women, we excluded *a priori* the following women: 35,683 with a hysterectomy, 527 without lifestyle questionnaire at enrolment and 14,252 women from Greece currently out of the EPIC study. The final study sample included 293,523 women for our analyses.

Assessment of physical activity and anthropometric measurements

Physical activity and anthropometric measurements are explained in detail in a supplementary file (Additional file 1: Supplementary Methods 1). Briefly, baseline physical activity was assessed using standardized questionnaires capturing occupational, household, and recreational activities. MET (Metabolic Equivalent) values were assigned to each activity, and MET-hours/week were calculated. Two composite indices were derived: the Cambridge index (occupational and recreational activities) and the total physical activity index (including household activities). Differences across centers were harmonized, and validation studies confirmed adequate reproducibility. Regarding anthropometric measurements, height, weight, waist, and hip circumferences were measured using standardized protocols or, in some centers, self-reported data previously validated. BMI (Body Mass Index) reflected general adiposity, while WHR (Waist-to-hip ratio), WHtR (Waist-to-height ratio), and ABSI ("A Body Shape Index") captured central obesity.

Follow-up procedures and assessment of outcomes

Incident cervical cancer cases were identified through a linkage with population-based cancer registries (Denmark, Italy, The Netherlands, Norway, Spain, Sweden, and the UK), or an active follow-up of study participants, including health insurance records, cancer and pathology registries and direct contact to participants or next of kin (France and Germany). Mortality data was also obtained from cancer and mortality registries at regional and national level. Women were followed from date of enrolment until first cervical cancer or precancer diagnosis or until death, loss or end of follow-up. The closure date varied between June 2008 (France) and December 2013 (Malmö, Sweden) depending on the center. The median follow-up time in this cohort was around 15 years, contributing a total of 4,146,574 person-years. A total of 369 invasive cervical cancer (ICC) cases (defined according to International Classification of Diseases, 10th revision, code

C53) were identified within the EPIC cohort. Detailed histology was specified for 92.7% of cases, of which 254 (68.8%) were squamous cell carcinoma, 88 (23.8%) were adenocarcinoma and the rest were others (27 cases).

Nested case-control study

Using this database, a nested case-control study within the EPIC cohort was conducted to further adjust by serological markers of HPV and other sexually transmitted infections (STIs) [23]. In brief, for each case of ICC with available blood sample, two matched control subjects were chosen at random among cancer-free cohort women. Matching criteria were study center, age at recruitment (5-year intervals), menopausal status (pre-, peri- and postmenopausal), follow-up time, date, time and fasting status at blood collection, and, among premenopausal women, phase of the menstrual cycle [24]. In this paper, we conducted sensitivity analyses including 171 ICC cases and 342 matched controls to confirm the associations found in the cohort study.

Serological testing

HPV serology testing was performed at the German Cancer Research Centre in Heidelberg, Germany. Assay procedures have been explained in detail previously [25]. Briefly, antibodies to the capsid protein L1 of high-risk mucosal HPV types 16, 18, 31, 33, 35, 45, 52, and 58, and of low-risk mucosal HPV type 11 were tested by Glutathione S-transferase capture and fluorescent bead-based multiplex serology [26–28]. Serum antibodies against *Chlamydia trachomatis* (CT) and *Human herpesvirus 2* (HHV-2) were tested at the Hospital of Santa Creu i Sant Pau in Barcelona, Spain. We used the commercial assay Chlamydia MIF IgG (Focus Diagnostics, Cypress, CA, USA) for the detection of CT IgG serum antibodies performed by microimmunofluorescence, and the commercial kit HerpeSelect® 2 ELISA IgG (Focus Diagnostics, Cypress, CA, USA) for the detection of antibodies against HHV-2 evaluated by an enzyme immunoassay. The positive

213 results of HHV-2 were confirmed by a membrane-based immunoassay with the biokitHSV-2
214 Rapid Test (Biokit USA, Lexington, MA, USA). Details have been described previously [23].

215 All serological assays were performed blinded to case-control status.

216

217 *Statistical analysis*

218 We estimated multivariable hazard ratios (HR) and 95% confidence intervals (CI) to evaluate the
219 risk of ICC in relation to anthropometric measurements and physical activity collected at
220 recruitment using Cox proportional hazard regression models. Age was used as the underlying
221 time variable, and models were stratified by age at recruitment (in one-year categories) and study
222 center. The proportional hazards assumption was evaluated for all models fitted using tests based
223 on weighted residuals. Tests for linear trend were performed using continuous variables.

224 Physical activity levels evaluated in these analyses were: total physical activity index adjusted by
225 sex (inactive, all non-inactive including moderately inactive, moderately active and active, and
226 unknown), Cambridge physical activity index (inactive, all non-inactive including moderately
227 inactive, moderately active, active, and unknown), and recreational physical activity (categorized
228 using the validated quartiles within InterAct in the study PANACEA, in MET-hours/week: ≤19.5
229 as inactive, >19.5 as all non-inactive including >19.5 to ≤33.75 as moderately inactive, >33.75 to
230 ≤54.75 as moderately active, >54.75 as active, and unknown [29]). Three different measures of
231 physical activity were evaluated: two indices attempting to capture overall physical activity
232 (combined total physical activity and Cambridge physical activity index), and one variable
233 specifically focused on recreational activity. The anthropometric measurements analysed
234 included: weight (continuous and categorized in quintiles, in kg), BMI (continuous and
235 categorized into underweight, normal, overweight, obesity, and unknown), ABSI (continuous and
236 categorized in quintiles), hip circumference (categorized in quintiles, in cm), waist circumference
237 (categorized in quintiles, in cm, and using a WHO categorization: ≤88 cm, >88 cm, and
238 unknown[28]), WHR (categorized in quintiles, and using a WHO categorization: <85, ≥85, and

239 unknown [29]), and WHtR (categorized in quintiles, and using a NICE guidelines: <0.5, ≥0.5, and
240 unknown [30,31]). For the ABSI measurement as continuous variable, we computed study-specific
241 z-scores as value minus mean divided by standard deviation. To explore non-linearity, we derived
242 study-specific quintile categories [30].

243 We used Cox regression models to assess potential confounding by other variables such as:
244 marital status (single, married/cohabiting, divorced/separated, widowed, and unknown),
245 education level (none, primary school, technical/professional school, secondary school, university
246 degree, and unknown), smoking habits (never, former and duration <15 years, former and
247 duration ≥15 years, current and intensity <10 cig/day, current and intensity ≥10 cig/day, and
248 unknown), number of full-term pregnancies (0, 1, 2, 3, ≥4, and unknown), and oral contraceptive
249 (OC) use and duration (never, past for <10 years, past for ≥10 years, current for <10 years, current
250 for ≥10 years, and unknown). BMI (underweight (<18.5), normal (18.5-25), overweight (25-30),
251 obesity (≥30), and unknown) and physical activity (inactive, moderately inactive, moderately
252 active, active, and unknown, using the Cambridge physical activity index) were also used as
253 adjusting variables when appropriate (adjustment by BMI when physical activity levels were
254 evaluated, adjustment by physical activity when anthropometric measurements were evaluated)[32].

255 In the nested case-control analysis, multivariable odds ratios (OR) and 95% CI were estimated
256 using conditional logistic regression models. Models were adjusted for HPV L1 serology, CT
257 serology, HHV-2 serology, and other potential confounding factors (marital status, education
258 level, smoking habits, number of full-term pregnancies, OC use and duration, and BMI and
259 physical activity when appropriate).

260 Stratified analyses by physical activity, BMI, and menopausal status were evaluated in both the
261 cohort and the nested case-control studies. Tests for interaction were also calculated and based on
262 the likelihood ratio test comparing the models with and without the interaction terms. We
263 evaluated the goodness of fit of these models by performing an influence analysis following the
264 approach described by Hosmer and Lemeshow [33]. Specifically, we computed leverage and other

influence statistics such as changes in deviance, changes in regression coefficients and Cook's distance to identify highly influential observations, which were excluded to improve model stability. Analyses by histological type (SCC, adenocarcinoma) were also performed. In addition, sensitivity analyses were conducted. To address potential measurement error, we excluded participants with self-reported body size measures to assess potential changes in risk estimates.

When applicable, variables included a missing or unknown category to avoid the exclusion of participants in the regression models. However, when variables included only missing information for a whole center, we decided to exclude the center from the pertinent analysis. All statistical tests were 2-tailed, and p-values below 0.05 were considered statistically significant. Statistical analyses were performed using the R programming language (R Development Core Team, 2005, http://www.R-project.org).

Results

Baseline characteristics of the study population are described elsewhere [34]. A supplementary table (Additional file 1: Supplementary Table 1) shows EPIC study's characteristics by country. France and the UK had the largest cohort size of 61,951 (21,1%) and 49,209 (16,8%) women respectively. Denmark had the highest mean age at recruitment (56.7 years) compared with other countries.

Table 1 shows BMI distribution patterns. Most women had normal weight (58.8%), while few were underweight (2.2%). About 27.5% of data were self-reported, mainly from France and Norway. Women with normal weight were more often married (66.5%) than those with obesity (50.8%), whereas single status was more common among underweight women (20.5%). Nearly half had secondary or technical education, except women with obesity, who more frequently had none or primary education (49.1%). Non-smoking was prevalent (53.5–59.9%), and pregnancy rates increased with BMI (69.6% underweight to 87.8% obesity). Physical activity was generally low, especially among women with obesity.

Table 2 shows the distribution by physical activity levels. Over half of women were inactive or moderately inactive (55.3%). Married or cohabiting women were more frequent in moderately active groups (63.7–69.0%) than among inactive (56.2%) or active (57.5%) women. Inactive women mostly had none or primary education (42.2%), while secondary or technical education predominated among active women (50.8%). Over half were non-smokers and were pregnant across all activity levels. Lower physical activity was associated with higher overweight and obesity prevalence, whereas normal weight exceeded 50% among more active women.

HRs and 95% CIs of ICC according to anthropometric measures and physical activity levels are shown in Table 3 and Table 4 respectively. No significant associations were found with anthropometrics measurements, although women with higher BMI (≥30 kg/m^2), ABSI (Q3, Q4), waist circumference or waist-to-hip ratio showed estimates above 1, still nonsignificant, compared to women with lower values. Women with a BMI lower than 18.5 kg/m^2 had a nonsignificant increased risk of ICC, although very few cases are categorized as underweight. Regarding physical activity levels, small or no effects were statistically significant. Women in moderately inactive, moderately active and active categories, had lower risk of developing ICC compared to inactive women (HR of 0.74 95% CI: 0.55, 0.99). Notably, all HRs were below 1 for both the total physical activity (adjusted by age) and the Cambridge physical activity index. Higher recreational activity per week showed a null association with ICC risk.

Additional analyses from the nested case–control study yielded broadly similar results, showing no significant associations for anthropometric measures and some variability according to the physical activity metric used. These results are provided in a supplementary table (Additional file 1: Supplementary Table 2).

By histological type, anthropometric measurements showed a clearer positive association with adenocarcinoma than with SCC, however we accounted for a small number of cases (Additional file 1: Supplementary Table 3). Comparing women with obesity's risk estimates for both

316 outcomes, a higher risk with adenocarcinoma (HR=1.80 95% CI: 0.94, 3.44) compared with SCC
317 (HR=1.09, 95% CI: 0.74, 1.60) was observed.

318 Women with premenopausal status showed higher hazard estimates for a waist circumference
319 higher than 88 cm (HR=1.40, 95% CI: 0.77, 2.52) than women with postmenopausal status
320 (HR=0.99, 95% CI: 0.66, 1.47). Furthermore, despite borderline statistical significance, the
321 estimates for recreational household activity varied by menopausal status: among premenopausal
322 women, all hazard ratios were below 1 (non-inactive vs. inactive women: HR=0.66, 95% CI: 0.44,
323 1.00), whereas among postmenopausal women hazard ratios were above 1 (non-inactive vs.
324 inactive women: HR=1.38, 95% CI: 0.97, 1.99).

325 Sensitivity analyses were conducted to address potential sources of bias, including measurement
326 error. Importantly, excluding self-reported BMI from France, Norway, and Oxford (United
327 Kingdom), resulted in a decrease on the risk of ICC of moderately active women (HR of 0.67,
328 95% CI: 0.43, 1.02) for the Cambridge physical activity index. In addition, an algorithm was
329 developed to check the goodness of fit of the general conditional logistic regression. This analysis
330 suggested the exclusion of some observations (n=131,886) because of their high leverage [35]. Most
331 of the excluded observations coincided with women with a self-reported BMI. Removing these
332 observations did not alter the results from overall analyses, although slight changes in the decrease
333 of ICC risk and some categories of the Cambridge physical activity index were observed (data
334 not shown). The effects observed for the other variables were consistent with the overall findings,
335 although they suggest that the magnitude of some associations may be greater than reported.

336

337 **Discussion**

338 In the present study, we report suggestive but not conclusive evidence indicating a slight increase
339 in ICC among women with obesity, and a lower risk of cervical cancer among those with active
340 or moderately active physical activity levels compared to inactive women. Considering HPV
341 serological status, these findings were consistent for most indicators.

No significant associations were found between ICC and BMI although a nonsignificant higher risk was observed among women with obesity. Previous studies are in line with our study: some studies, including three cohort studies, one case-control study and one meta-analysis, have shown obesity as a potential risk factor for cervical cancer, showing significant estimates from 1.22 to 1.70 [6–10], and others found the direction of the association but did not find the statistically significance, displaying estimates above 1[11–14]. Hence, more evidence is still needed to conclude that an excess of body fatness increases the risk of ICC. The association between obesity and cervical cancer risk might be explained by hormonal patterns, including alterations in the metabolism of endogenous hormones, production of cytokines and other factors that promote growth of cancer cells, adiposity related to inflammatory reactions, and genetic factors [36].

The nonsignificant higher risk of ICC found in our study among women with low BMI was also observed in some previous studies [15,37], but not in all [9,11,14]. However, some studies combined women with underweight and normal weight because of the few numbers of women with underweight, making it impossible to directly compare results [5,9]. In our study, we decided to maintain both categories although few women were classified as underweight, and thus no conclusions can be drawn for this group. A prospective cohort study of more than 5.2 million adults from the UK found that women having underweight seemed to be a risk factor of several cancers (oral cavity, esophageal, stomach, and lung cancers) [7]. Impaired immune function due to undernutrition could partially explain the increased risk of cervical cancer observed among women with underweight although the underlying mechanisms remain unclear [37].

A previous study conducted by Lacey et al in 2003 hypothesized that obesity may be a potential risk factor for cervical adenocarcinomas but not for SCC [5]. Our study, although including small numbers of adenocarcinomas, has also evaluated the risk of cervical adenocarcinoma and SCC in women with obesity, observing a higher risk of adenocarcinoma than SCC, although estimates were not statistically significant (HR of 1.80, 95% CI: 0.94, 3.44 for adenocarcinoma, and HR of 1.09, 95% CI: 0.74, 1.60 for SCC). These results are in line with Lacey et al, hypothesizing that cervical adenocarcinoma risk factors are similar to endometrial ones, including changes in

hormonal patterns [3,4]. Obesity may be associated with an increase of sex hormone levels, through conversion of androgen to estrogen by the enzyme aromatase located in adipose tissue [38,39]. This would be especially relevant in postmenopausal women. However, in our study results were not statistically different when analyzing the risk of ICC in women with obesity stratifying by menopausal status (p of interaction = 0.99) and the associations were not statistically significant (HR of 1.17, 95% CI: 0.65, 2.10 for premenopausal women, and HR of 1.16, 95% CI: 0.74, 1.82 for postmenopausal women).

Although the two physical activity indices used in this study differ in scope (Spearman correlation coefficient (rho) = 0.37), both capture overall activity levels and showed associations in the same protective direction with respect to ICC risk. The association was stronger and reached statistical significance only for the index that includes household activities in addition to occupational and recreational ones. In contrast, associations for recreational activity alone were null, suggesting that the lower effect seen for overall physical activity may be driven by other physical activities or by the combined effect of total activity. Few studies have reported associations between physical activity and cervical cancer risk, finding a somewhat protective effect, in accordance with our results [6,40,41]. Lee et al found a decreased risk of cervical cancer about 0.61 (95% CI: 0.38, 0.98) among women with high leisure-time physical activity, measured in MET-hours/week, with a significant linear trend (p=0.003) [6]. Similar estimates were observed in Xing et al (OR of 0.45, 95% CI: 0.28, 0.73) among women with an average daily walking time of >140 minutes compared to ≤60 minutes, measured on their smartphone movements, and an OR of 0.53 (95% CI: 0.32, 0.86) among women with an average physical activity distance over 8 km compared to ≤3 km [40]. Szender et al found that women reporting on average no moderate or vigorous recreational physical activity, classified as inactive, had a greater risk of cervical cancer compared to active women (OR of 2.14, 95% CI: 1.32, 3.47) [41]. However, these studies exhibit certain limitations – such as study design, limited sample sizes, or insufficient data – which vary across studies. Our study, with a prospective design including a large number of participants and a comprehensive assessment of different domains of physical activity, enforces the idea that

physical activity is a protective factor for cervical cancer, but more evidence is needed to conclude the role of physical activity in preventing cervical cancer. Biological mechanisms may help explain these findings. Increased physical activity has been associated with a reduction in inflammatory cytokines, testosterone, and circulating estradiol levels, whereas physical inactivity may promote the production of estrogens and androgens [42–45].

One of the most important strengths of our study is the large sample size of the cohort and wide number of anthropometric and physical activity variables, as well as the multicentric and long-term prospective design. This is especially important for physical activity levels compared to other studies that have had difficulty collecting this information or dealing with missing data. The collection of the anthropometric data was by measurements by trained personnel in most of the EPIC countries, and not self-reported as in previous studies, producing more reliable findings in most cases. A comprehensive analysis of various anthropometric measures represents an additional strength of the study, enhancing the reliability of our findings. Moreover, adjustment for serological markers of exposure to HPV L1, CT and HHV-2 is particularly relevant, as these markers may serve as proxies for sexual behavior, an important risk factor for cervical cancer that was not otherwise available in our study. These variables are not consistently evaluated in previous studies and may act as potential confounders since they might vary according to BMI. Thus, it is important to assess associations with anthropometrical measurements and physical activity after adjusting for sexual behavior [43]. After the adjustment for those serological markers, the effects obtained in the cohort study were consistent with those found in the nested case-control study for most of the key outcomes, even considering the difficulty on comparing hazard ratios and odds ratios [46].

This prospective study has several limitations. First, its design did not account for changes and events occurring between recruitment and diagnosis or end of follow-up, such as modifications in the habits of physical activity, BMI composition, or incident HPV infections. Second, the relatively small sample size of the nested case-control study (513 women) compared with the overall EPIC cohort (approximately 300,000 women) limited statistical power and robustness of

the analyses, resulting in wide 95%CI and unstable effect estimates for key exposures. Finally, the inclusion criteria for the nested case–control study, partly based on the availability of biological samples, may have introduced selection bias, potentially affecting the internal validity of the results.

Conclusions

In summary, our findings do not support a definitive association between anthropometric measurements and the development of invasive cervical cancer. Nonetheless, improving cervical cancer screening, particularly among women with obesity, remains crucial to detect precancerous lesions and prevent progression to invasive disease. Importantly, our results reinforce the potential protective role of physical activity on invasive cervical cancer. Overall, the consistent and robust beneficial effects of engaging in moderate to high levels of physical activity and maintaining a healthy BMI support a clear public health message: promoting physical activity and a healthy lifestyle may contribute to reducing the risk of cervical cancer.

List of abbreviations:

ABSI: “A Body Shape Index”

BMI: Body Mass Index

CI: Confidence Intervals

CT: *Chlamydia trachomatis*

EPIC: European Prospective Investigation into Cancer and Nutrition

HHV-2: *Human herpesvirus 2*

HPV: Human Papillomavirus

HR: Hazard Ratio

IARC: International Agency for Research on Cancer

ICC: Invasive Cervical Cancer

MET: Metabolic Equivalent

SCC: Squamous Cell Carcinoma

STI: Sexually Transmitted Infection

UK: the United Kingdom

WCRF: World Cancer Research Fund

WHR: Waist-to-hip ratio

WHtR: Waist-to-height ratio

Declarations

- **Ethics approval and consent to participate**

Informed consent was obtained from all participants involved in the study during recruitment. The study was conducted in accordance with the Declaration of Helsinki and all relevant guidelines and regulations. The EPIC study was approved by the *IARC Ethics Committee* (reference number 20-02) of the International Agency for Research on Cancer (IARC), in Lyon, France, as well as the local ethics committee of each study center.

- **Consent for publication**

Not Applicable.

- **Availability of data and materials**

The data presented in this study is preserved by the EPIC centers. Data are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC centers. The primary responsibility for accessing the data belongs to IARC and the EPIC centers. Access to materials from the EPIC study can be requested by contacting epic@iarc.fr.

- **Competing interests**

The authors declare that they have no competing interests.

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- **Authors' contributions**

ER, LB, MCB contributes to Conceptualization. ER, JAP, CB, NT, MCB contributes to Methodology. ER, JAP contributes to Software. ER, JAP contributes to Data curation. ER, JAP contributes to Formal analysis. ER, JAP, MCB contributes to Investigation. ER contributes to Funding acquisition. ER, JAP, CB, NT, AKLC, CCD, CK, AT, XR, SN, MK, RTF, MBS, GM, VP, SS, RT, LD, EM, MWL, KBB, MJS, CS, OMC, JMH, NA, DA, RK, LB, MCB contributes to Validation. ER, JAP contributes to Visualization. ER, JAP contributes to Writing – original draft. CB, NT, MCB contributes to Writing – review & editing. MCB contributes to Supervision.

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- **Authors' information (optional)**

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Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

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Figure, tables and additional files

Tables

Table 1 – Characteristics of study participants in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort by BMI categories.

	Categories of BMI (kg/m^2)			
Characteristics	**<18.5**	**18.5-<25**	**25-<30**	**≥30**
BMI, kg/m^2				
N (row %)	6,509 (2.2)	172,681 (58.8)	81,639 (27.8)	32,694 (11.1)
Mean (SD)	17.7 (0.8)	22.2 (1.7)	27.0 (1.4)	33.6 (3.6)
Range	10.2-18.4	18.5-24.9	25.0-29.9	30.0-77.9
Mean (SD) age, years	46.8 (11.7)	48.9 (9.9)	52.2 (9.3)	52.7 (8.9)
Mean (SD) weight, kg	47.5 (4.3)	59.3 (6.2)	70.8 (6.6)	86.1 (11.4)
Mean (SD) waist circumference, cm	64.7 (4.6)	72.9 (6.1)	83.7 (7.0)	97.2 (10.0)
Mean (SD) hip circumference, cm	87.4 (4.6)	95.4 (5.2)	103.6 (5.3)	115.0 (8.8)
Mean (SD) waist-to-hip ratio	0.74 (0.1)	0.76 (0.1)	0.81 (0.1)	0.85 (0.1)
Mean (SD) waist-to-height ratio	0.39 (0.03)	0.45 (0.04)	0.52 (0.1)	0.61 (0.1)
Mean (SD) ABSI, (m/kg$^{2/3}$*m$^{5/6}$ * 1,000)	74.5 (5.3)	72.2 (4.9)	73.2 (5.4)	74.0 (5.9)
Cambridge physical activity Index [1], N (%)				
Inactive	1,225 (18.8)	27,054 (15.7)	19,816 (24.3)	11,290 (34.6)
Moderately inactive	2,267 (34.8)	58,650 (34.0)	27,992 (34.3)	10,929 (33.4)
Moderately active	1,933 (29.7)	54,115 (31.3)	20,267 (24.8)	6,151 (18.8)
Active	994 (15.3)	29,628 (17.1)	11,687 (14.3)	3,701 (11.3)
Missing	90 (1.4)	3,234 (1.9)	1,877 (2.3)	623 (1.9)
Marital status, N (%)				
Single	1,334 (20.5)	19,593 (11.3)	5,306 (6.5)	1,900 (5.8)
Married or living together	4,143 (63.6)	114,732 (66.5)	48,441 (59.3)	16,613 (50.8)
Divorced or separated	292 (4.5)	8,569 (5.0)	3,916 (4.8)	1,487 (4.5)
Widowed	137 (2.1)	4,045 (2.3)	3,280 (4.0)	1,444 (4.5)
Missing	603 (9.3)	25,742 (14.9)	20,696 (25.4)	11,250 (34.4)
Educational level, N (%)				

None or Primary education	762 (11.7)	31,134 (18.0)	29,105 (35.7)	16,068 (49.1)
Secondary or Technical education	3,078 (47.3)	85,104 (49.3)	35,513 (43.5)	11,704 (35.8)
University	2,388 (36.7)	49,876 (28.9)	13,701 (16.8)	3,643 (11.1)
Missing	281 (4.3)	6,567 (3.8)	3,320 (4.0)	1,279 (4.0)
Smoking status, N (%)				
Never smokers	3,592 (55.2)	92,292 (53.5)	44,622 (54.7)	19,584 (59.9)
Former smokers	1,136 (17.4)	40,128 (23.2)	19,505 (23.9)	7,256 (22.2)
Current smokers	1,619 (24.9)	35,745 (20.7)	15,711 (19.2)	5,317 (16.3)
Missing	162 (2.5)	4,516 (2.6)	1,801 (2.2)	537 (1.6)
Full-term pregnancies, N (%)				
No	1,661 (25.5)	25,520 (14.8)	8,385 (10.3)	3,084 (9.4)
Yes	4,527 (69.6)	140,010 (81.1)	70,481 (86.3)	28,694 (87.8)
Missing	321 (4.9)	7,151 (4.1)	2,773 (3.4)	916 (2.8)
OC use, N (%)				
Never	2,176 (33.4)	55,103 (31.9)	34,920 (42.8)	16,364 (50.0)
Ever	4,092 (63.9)	112,317 (65.0)	44,312 (54.3)	15,462 (47.3)
Missing	241 (3.7)	5,261 (3.1)	2,407 (2.9)	868 (2.7)
Menopausal status, N (%)				
Premenopausal	3,101 (47.6)	72,889 (42.2)	25,438 (31.2)	9,691 (29.6)
Perimenopausal	1,063 (16.3)	33,113 (19.2)	14,061 (17.2)	5,210 (15.9)
Postmenopausal	2,327 (35.8)	66,250 (38.4)	41,885 (51.3)	17,644 (54.0)
Surgical postmenopausal	18 (0.3)	429 (0.2)	255 (0.3)	149 (0.5)

Abbreviations: SD: standard deviation; BMI: body mass index; ABSI: a body shape index; OC: oral contraceptives.
[1] The Cambridge Index of physical activity combines occupational and recreational activities (cycling and sports), excluding walking.

Table 2 – Characteristics of study participants in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort by physical activity categories.

Characteristics	Categories of Cambridge physical activity Index [1]			
	Inactive	**Moderately inactive**	**Moderately active**	**Active**
Physical activity				
N (row %)	59,385 (20.6)	99,838 (34.7)	82,466 (28.7)	46,010 (16.0)
Mean (SD) age, years	53.2 (10.3)	50.6 (9.8)	48.7 (8.7)	48.6 (10.0)
Mean (SD) weight, kg	66.7 (12.6)	65.0 (11.7)	64.4 (10.9)	65.0 (10.9)
Mean (SD) waist circumference, cm	82.8 (12.0)	79.0 (10.9)	77.4 (10.3)	77.6 (10.3)
Mean (SD) hip circumference, cm	102.6 (10.0)	100.2 (8.9)	99.2 (8.5)	99.2 (8.4)
Mean (SD) waist-to-hip ratio	0.81 (0.1)	0.79 (0.1)	0.78 (0.1)	0.78 (0.1)
Mean (SD) waist-to-height ratio	0.52 (0.1)	0.49 (0.1)	0.48 (0.1)	0.47 (0.1)
BMI, N (%)				
<18.5 kg/m^2	1,225 (2.1)	2,267 (2.3)	1,933 (2.3)	994 (2.2)
18.5 - < 25 kg/m^2	27,054 (45.6)	58,650 (58.7)	54,115 (65.6)	29,628 (64.4)
25 - < 30 kg/m^2	19,816 (33.4)	27,992 (28.0)	20,267 (24.6)	11,687 (25.4)
≥30 kg/m^2	11,290 (19.0)	10,929 (10.9)	6,151 (7.5)	3,701 (8.0)
Mean (SD) ABSI (m/$kg^{2/3}$*$m^{5/6}$ * 1,000)	74.0 (5.5)	72.7 (5.2)	72.2 (5.0)	72.1 (5.0)
Marital status, N (%)				
Single	5,029 (8.5)	9,797 (9.8)	7,551 (9.2)	5,315 (11.6)
Married or living together	33,401 (56.2)	63,640 (63.7)	56,914 (69.0)	26,444 (57.5)
Divorced or separated	2,973 (5.0)	4,871 (4.9)	3,418 (4.1)	2,826 (6.1)
Widowed	3,106 (5.2)	2,969 (3.0)	1,541 (1.9)	1,181 (2.6)
Missing	14,876 (25.1)	18,561 (18.6)	13,042 (15.8)	10,244 (22.2)
Educational level, N (%)				
None or Primary education	25,089 (42.2)	24,965 (25.0)	15,639 (19.0)	10,075 (21.9)
Secondary or Technical education	21,096 (35.5)	45,681 (45.8)	42,531 (51.6)	23,360 (50.8)
University	9,907 (16.7)	25,579 (25.6)	22,123 (26.8)	11,337 (24.6)

Missing	3,293 (5.6)	3,613 (3.6)	2,173 (2.6)	1,238 (2.7)
Smoking status, N (%)				
Never smokers	35,352 (59.5)	56,681 (56.8)	42,960 (52.1)	23,320 (50.7)
Former smokers	11,186 (18.8)	22,593 (22.6)	20,843 (25.3)	12,213 (26.5)
Current smokers	11,985 (20.2)	18,696 (18.7)	16,410 (19.9)	9,796 (21.3)
Missing	862 (1.5)	1,868 (1.9)	2,253 (2.7)	681 (1.5)
Full-term pregnancies, N (%)				
No	7,203 (12.1)	13,462 (13.5)	10,082 (12.2)	7,043 (15.3)
Yes	50,104 (84.4)	82,861 (83.0)	69,497 (84.3)	37,382 (81.2)
Missing	2,078 (3.5)	3,515 (3.5)	2,887 (3.5)	1,585 (3.5)
OC use, N (%)				
Never	30,700 (51.7)	37,159 (37.2)	25,789 (31.3)	13,433 (29.2)
Ever	27,090 (45.6)	60,216 (60.3)	54,558 (66.1)	31,091 (67.6)
Missing	1,595 (2.7)	2,463 (2.5)	2,119 (2.6)	1,486 (3.2)
Menopausal status, N (%)				
Premenopausal	18,318 (30.8)	37,183 (37.2)	34,067 (41.3)	19,047 (41.4)
Perimenopausal	8,057 (13.6)	17,198 (17.2)	18,575 (22.5)	8,290 (18.0)
Postmenopausal	32,805 (55.2)	45,185 (45.2)	29,620 (35.9)	18,525 (40.3)
Surgical postmenopausal	205 (0.4)	272 (0.4)	204 (0.3)	148 (0.3)

Abbreviations: SD: standard deviation; BMI: body mass index; ABSI: a body shape index; OC: oral contraceptives.
[1] The Cambridge Index of physical activity combines occupational and recreational activities (cycling and sports), excluding walking.

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) of invasive cervical cancer (ICC) according to anthropometric measures in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study.

	ICC	
Risk factor	**Non-cases / Cases**	**HR (95% CI) [1]**
BMI (kg/m^2)		
<18.5	6,499 / 10	1.33 (0.70, 2.52)
18.5 - < 25	172,475 / 206	1
25 - < 30	81,545 / 94	0.85 (0.66, 1.10)
≥30	32,635 / 59	1.19 (0.87, 1.65)
Per 5 kg/m^2		1.03 (0.91, 1.17)
ABSI (m/kg$^{2/3}$*m$^{5/6}$) [2]		
ABSI - Q1	40,892 / 50	1
ABSI - Q2	40,896 / 50	0.98 (0.66, 1.47)
ABSI - Q3	40,883 / 55	1.04 (0.70, 1.56)
ABSI - Q4	40,880 / 61	1.13 (0.75, 1.69)
ABSI - Q5	40,886 / 57	0.90 (0.59, 1.38)
Per 1 SD		0.96 (0.84, 1.09)
Waist circumference (cm) [2]		
≤88	165,343 / 205	1
>88	39,094 / 68	1.14 (0.84, 1.55)
Per 1 cm		1.00 (0.99, 1.01)
Waist-to-hip ratio [2]		
<0.85	166,857 / 210	1
≥0.85	37,570 / 63	1.07 (0.79, 1.45)

Abbreviations: HR: hazard ratio; CI: Confidence Interval; ICC: invasive cervical cancer; BMI: body mass index; ABSI: a body shape index; Q1-Q5: quintile 1 – quintile 5; SD: standard deviation.
[1] Cox regressions models stratified by age and center, and adjusted by marital status, level education, smoking habits, number of full-term pregnancies, oral contraceptive use and duration, BMI (for physical activity variables), and Cambridge physical activity index (for anthropometric variables). ABSI was added as an adjustment variable for the specific Cox regression model of BMI and vice versa. [2] Excludes Norway and Sweden (Umeå) because information was not collected for this variable.
The number of cases does not add up the total number of cases because of missing values of the exposure variable.
Bold font signifies a statistically significant effect ($p<0.05$).

Table 4. Hazard ratios (HRs) and 95% confidence intervals (CIs) of invasive cervical cancer (ICC) according to physical activity levels in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study.

	ICC	
Risk factor	**Non-cases / Cases**	**HR (95% CI) [1]**
Combined total physical activity [2,3]		
Inactive	42,968 / 67	1
All non-inactive	232,576 / 279	**0.74 (0.55, 0.99)**
Moderately inactive	101,176 / 112	0.77 (0.56, 1.06)
Moderately active	109,316 / 139	**0.70 (0.51, 0.98)**
Active	22,084 / 28	0.74 (0.47, 1.17)
Cambridge physical activity Index [4]		
Inactive	59,296 / 89	1
All non-inactive	228,040 / 274	0.83 (0.63, 1.09)
Moderately inactive	99,715 / 123	0.89 (0.66, 1.19)
Moderately active	82,375 / 91	0.76 (0.54, 1.06)
Active	45,950 / 60	0.77 (0.54, 1.12)
Recreational activity (MET*hr/week) [5,6]		
Inactive	97,220 / 107	1
All non-inactive	147,525 / 189	1.10 (0.85, 1.42)
Moderately inactive	62,545 / 77	1.09 (0.81, 1.48)
Moderately active	50,165 / 56	0.96 (0.69, 1.35)
Active	34,542 / 56	1.35 (0.95, 1.92)

Abbreviations: HR: hazard ratio; CI: Confidence Interval; ICC: invasive cervical cancer; MET*hr/week: metabolic equivalent value-hour per week.
[1] Cox regressions models stratified by age and center, and adjusted by marital status, level education, smoking habits, number of full-term pregnancies, oral contraceptive use and duration, BMI (for physical activity variables), and Cambridge physical activity index (for anthropometric variables). ABSI was added as an adjustment variable for the specific Cox regression model of BMI and vice versa. [2] Excludes Sweden (Umeå) because information was not collected for this variable. [3] Combined total physical activity includes occupational, household and recreational activities. [4] The Cambridge Index of physical activity combines occupational and recreational activities (cycling and sports), excluding walking. [5] Excludes Norway and Sweden (Umeå) because information was not collected for this variable. [6] The recreational activity, in MET-hours/week, includes walking, cycling and sports.
The number of cases does not add up the total number of cases because of missing values of the exposure variable.
Bold font signifies a statistically significant effect ($p<0.05$).

Supplementary Files

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