DR OXANA GAVRILYUK (Orcid ID : 0000-0003-3939-6420)

PROFESSOR ELISABETE WEIDERPASS (Orcid ID : 0000-0003-2237-0128)

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Lifetime number of years of menstruation as a risk index for postmenopausal endometrial cancer in the Norwegian Women and Cancer Study

Running headline: Menstruations and endometrial cancer

Oxana Gavrilyuk[1], Tonje Braaten[1], Elisabete Weiderpass[1, 2, 3, 4], Idlir Licaj[1,#] & Eiliv Lund[1,3,#]

[#]Authors contributed equally

[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 Institute, Stockholm, Sweden,

[3]Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway,

[4]Genetic Epidemiology Group, Folkhälsan Research Center, and Faculty of Medicine, University of Helsinki, Helsinki, Finland

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Corresponding author:

Oxana Gavrilyuk

Institutt for samfunnsmedisin, Det helsevitenskapelige fakultet, UiT Norges Arktiske Universitet, 9037 Tromso, Norway

E-mail: oxana.gavrilyuk@uit.no

Conflict of interest

The authors declare that they have no conflict of interest.

Abstract

Introduction. Lifetime number of years of menstruation (LNYM) reflects a woman's cumulative exposure to endogenous estrogen and can be used as a measure of the combined effect of reproductive factors related to endometrial cancer (EC) risk.

Material and methods. We aimed to study the association between LNYM and EC risk among postmenopausal women and calculate the population attributable fraction of EC for different LNYM categories. Our study sample consisted of 117 589 women from the Norwegian Women and Cancer (NOWAC) Study. All women were aged 30-70 years at enrollment and completed a baseline questionnaire between 1991 and 2006. Women were followed up for EC through December 2014 via linkages to national registries. We used Cox proportional hazards models to estimate hazard ratios with 95% confidence intervals (CIs), adjusted for potential confounders.

Results. Altogether, 720 women developed EC. We found a statistically significant, positive dose-response relationship between LNYM and EC, with a 9.1% higher risk for each additional year of LNYM (p for trend <0.001). Using the LNYM category ≥40 as a reference, the hazard ratios for LNYM <25, 25-29, 30-34, 35-39 were 0.17 (95% CI 0.22-0.27), 0.25

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(95% CI 0.17-0.36), 0.43 (95% CI 0.32-0.58), and 0.68 (95% CI 0.51-0.92), respectively. The association between LNYM and EC was independent of incomplete pregnancies, menopausal hormone therapy, diabetes and body mass index. When considering population attributable fraction, 67% of EC was estimated to be attributable to LNYM ≥25.

Conclusions. Our study supports that increasing LNYM is an important and independent predictor of EC risk.

Keywords

endometrial cancer; number of menstruations; reproductive factors; prospective study; menopause

Abbreviations

BMI body mass index;

CI confidence interval;

EC endometrial cancer;

HR hazard ratio;

LNYM lifetime number of years of menstruation;

MHT menopausal hormone therapy;

NOWAC Study Norwegian Women and Cancer Study

PA physical activity

PAF population attributable fraction

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Key Message

Higher number of years of menstruation is significantly associated with increased risk of endometrial cancer in Norwegian women.

Introduction

Endometrial cancer (EC) is the sixth most common cancer among women worldwide and the most common gynecological cancer in the Western World (1). In Norway, EC incidence rates have increased markedly in the last decades (2), with age-standardized rates of 19.7 per 100 000 person-years reported in the period 1982-1986 and 27.6 per 100 000 person-years in the period 2012-2016 (3). Further, EC incidence rates in Norway are predicted to increase by 57% in 2025, compared with the rates observed in 2005 (4).

Among women, menstrual and reproductive factors, such as earlier age at menarche (5-9), later age at menopause (5-8, 10, 11), nulliparity, and/or nulligravidity (5-9, 12-17), contribute to hormonal changes, the effects of which play an important role in the development of hormone-related cancers. Indeed, these factors might be linked to prolonged, excessive exposure of endometrial cells to estrogen, leading to an increased EC risk. Conversely, full-term pregnancies (9, 14), later age at last birth (5, 16, 17), and breastfeeding (5, 9, 12, 13) play a protective role in EC risk due to prolonged exposure to progesterone. Studies investigated relationship between incomplete pregnancies and EC risk provided controversial results, showing no association (5, 12, 18-21), inverse association (9, 16, 22) or even increased risk (8). Lifetime number of years of menstruation (LNYM) can be used as a composite variable to summarize the effect of the above-mentioned factors and indirectly measure cumulative exposure to endogenous hormones during a woman's reproductive years.

Several epidemiological studies have prospectively investigated the combined impact of menstrual and reproductive factors on EC risk. The most cited reports investigated the effect of number of years of ovulation or total menstrual lifespan (5, 8, 9). However, studies based

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on postmenopausal populations from the USA (IOWA population) (8) and China (9) were limited by a small number of cancer cases, and they presented age-adjusted analyses only, failing to control for potential risk factors. The study by Dossus et al. (5) included both pre- and postmenopausal women with heterogeneous information on breastfeeding and number of full-term pregnancies from different European countries. That study presented risk estimates per year of menstruation, but did not show any association between increasing LNYM and EC.

When strong associations are observed between an outcome and a risk factor, population attributable fraction (PAF) is often used to measure the impact of that risk factor on a population level (23). Although recent studies have investigated the PAF of EC in relation to physical activity (PA), obesity, menopausal hormone therapy (MHT) use, parity, and breastfeeding (14, 24, 25), to our knowledge, there are no published cohort studies that have calculated PAF in regard to composite variable like LNYM, which covers cumulative menstrual and reproductive risk factors. Using a population-based cohort of Norwegian women, we aimed to study the association between LNYM and EC risk among postmenopausal women and calculate the PAF of EC for different LNYM categories.

Material and methods

The Norwegian Women and Cancer Study

The Norwegian Women and Cancer (NOWAC) Study is an ongoing, nationally-representative, prospective cohort study, which includes Norwegian women aged 30-70 years who were randomly selected from the Central Population Register of Norway (26). Selected women received a comprehensive, eight-page, self-administered questionnaire, which included questions on diet, medical history, and lifestyle; and an informed consent form. Women were recruited during two waves of data collection (1991/97 and 2003/06), with an overall response rate of 57% and 48.4% respectively. In total, more than 172,478 women completed the enrollment questionnaire. Follow-up questionnaires were sent at intervals of 6-

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8 years. The external validity of the NOWAC Study is reported to be acceptable (27). Further details on the NOWAC Study and its design have been described in detail elsewhere (28).

Study sample

Women who reported that their periods stopped spontaneously (*Do you still have regular/irregular menstruation? Did menstruation stop? yes/no*) in either their baseline or follow-up questionnaire were categorized as postmenopausal and were eligible for inclusion (n = 159 246). We then excluded participants with prevalent cancer (*n* = 7246), those who reported hysterectomy or oophorectomy at baseline or follow-up (*n* = 12 221), and those who emigrated or died before the start of follow-up (*n* = 7). We further excluded women with missing information on years of menstruation (*n* = 11 113), which included missing information in age at menarche (*n* = 2274) and ever use of oral contraceptive and duration (*n* = 8839). Women with missing information on the selected confounders: height or weight (*n* = 2666) (24), smoking status (*n* = 557), and PA (*n* = 7847) were also excluded. Thus, the final study cohort included 117 589 postmenopausal women.

Assessment of covariates and calculation of lifetime number of years of menstruation

Information on the covariates age at menarche, age at menopause, number of full-term pregnancies, duration of breastfeeding, pregnancies shorter than 6 months of duration, height, weight, oral contraceptive use, smoking status, MHT use, diabetes and smoking status was taken from NOWAC questionnaires. Self-reported height and weight (29) were used to calculate body mass index (BMI) in kg/m^2. Parity and breastfeeding variables are generally reported to have good validity in the NOWAC Study (27). Missing information on age at menopause was treated according to smoking status, as women who smoke have been shown to have earlier menopause (30). Mean age at menopause for current and former smokers in our study (49 and 50 years, respectively) was used to complete missing data for participants who were current or former smokers. For non-smokers, missing data on age at menopause was set at 53 years, which has been used in the NOWAC Study before (31) and represents approximately 80% of women in our study population. Assessment of PA level was performed as in previous NOWAC reports (32, 33).

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LNYM represented the cumulative duration of menstrual cycles in a woman's lifetime. However, we used a definition that was slightly different from that used in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study (34). Instead, we defined LNYM as the number of years between age at menarche and age at menopause, minus the cumulative duration of full-term pregnancies (calculated as the number of full-term pregnancies, including live and stillbirths, times 0.75 years), duration of breastfeeding (calculated as the cumulative number of months of breastfeeding in all pregnancies), and duration of oral contraceptive use. LNYM was then divided into 5 categories: <25, 25-29, 30-34, 35-39, ≥40. All the aforementioned variables were added on a continuous scale in years.

MHT is an established risk factor for EC (35) and is also associated with menstrual characteristics (36). However, we decided not to include MHT in the multivariable models, since this variable is included in the calculation of LNYM through age at menopause.

Identification of endometrial cancer

Women with EC were identified through linkage to the Cancer Registry of Norway via the unique identification number assigned to each resident of Norway. The registry provides detailed information on all cancer sites and histology, and covers the whole population of Norway (3). To identify topography, we used the International Classification of Diseases (ICD), Revision 7 and 10 (code 172 for corpus uteri cancer in ICD-7 or corresponding code C54 in ICD-10 version). Morphological codes were further classified according to the International Classification of Diseases for Oncology, Revision 2 and 3. Ninety-nine percent of identified EC cases were type 1 and 0.4% were type 2 (37, 38), with the following distribution of histological subtypes: 670 (93%) endometrioid adenocarcinoma, 38 (5.3%) adenocarcinoma with squamous metaplasia, and <1% other types, including five (0.7%) irregular plate epithelium, two (0.28%) adenocarcinoma UNS, one (0.14%) undifferentiated carcinoma, one (0.14%) combined small cell carcinoma, one (0.14%) papillary adenocarcinoma, one (0.14%) serous papillary adenocarcinoma, and one (0.14%) stromal sarcoma respectively.

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Statistical analyses

As we studied postmenopausal women, age at inclusion into the present study was set as the age at menopause. Therefore, we calculated person-years from age at menopause to the date of any incident cancer diagnosis (except basal cell carcinoma), emigration, death, or the end of the study (31 December 2014), whichever came first.

We used Cox proportional hazards regression (39), with age as the underlying time scale, to estimate age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between EC and LNYM. Multivariable-adjusted models included BMI (normal weight: <25, overweight: 25–29.9, obese: ≥30 kg/m^2), smoking status (never, former, current), and PA level (PA <5, PA ≥5). The proportional hazards assumption was checked by Schoenfeld residuals, and there was no evidence of deviation from proportionality. We further used Royston-Parmar flexible parametric proportional hazard models (40) to estimate the baseline HRs according to different LNYM categories (Figure 1). Cubic splines were used to show the dose-response associations between LNYM and EC risk. Adjusted HRs and 95% CIs (dashed lines) were constructed with four knots based on Harrell's default percentiles (41) (Supporting Information Figure S1). We then used a Wald-type test to check for any non-linear relationship between LNYM and EC risk.

We performed sensitivity analyses estimating the association between LNYM and EC risk in each BMI category (<25, 25–29.9, ≥30 kg/m^2) and in each PA category (PA <5, PA ≥5). We also estimated Cox regression with additional adjustment for diabetes and MHT separately and combined. Other sensitivity analyses were undertaken, which included information on incomplete pregnancies (abortion, yes/no; extra-uterine pregnancy, yes/no). There were 52 796 (48%) women with information on abortions (without separating into induced or spontaneous, defined as "abortion variable" in our analysis), 29 250 (27%) with information available on extra-uterine pregnancies (defined as "exu-variable" in our analysis), and 33 450 with information on both these variables. Therefore we constructed models with two new LNYM values, which were calculated in the same manner as LNYM above, but also subtracted 12 weeks for each incomplete pregnancy. The value LNYM_1 included both the abortion and exu-variables (n = 33 450), and LNYM_2 included just the

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abortion variable (n = 65 548). Using Cox regression, we then estimated the association between LNYM_1 and EC risk, and between LNYM_2 and EC risk (data not shown). A final sensitivity analysis was restricted to women who never used oral contraceptives.

We calculated the PAF to estimate the proportion of EC that could have been prevented in the population if women had a lower LNYM, using the formula: PAF=Pe*(RRe-1)/[Pe*RR+(1-Pe)], where Pe is the proportion of LNYM in the study population, and RRe is the RR in the final baseline multivariable proportional hazards regression model, including all aforementioned confounders and BMI. We calculated two-sided 95% CIs for the PAFs using the PUNAF Stata module (42).

We constructed cumulative incidence rate (CIR) plots for EC in the NOWAC Study and compared them with those of the cumulative incidence rate in the general Norwegian female population (Supporting Information Figure S2).

All the analyses were done in 214 STATA version 14.0 (Stata Corp, College Station, TX, USA).

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. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. All the participants were informed about the study objectives and provided informed consent.

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Results

Of the 117 589 included postmenopausal women, 720 developed EC during the study period. Age at EC diagnosis among our NOWAC participants ranged between 31 and 70 years, with a mean age of 62 (standard deviation [SD] 6.5) years. On average, participants reported age at menarche of 13 (SD 1.4) years and age at menopause of around 50 (SD 3.6) years (Table 1). With increasing LNYM, we observed the following linear change in baseline characteristics: decrease in age at menarche, increase in age at menopause, increase in nulliparity, decrease in duration of breastfeeding, younger age at last birth, increased number of incomplete pregnancies, increase in mean BMI and obesity (BMI ≥30), decrease in smoking, decrease in MHT and oral contraceptive use among ever users, and an increase in the number of women with diabetes (Table 1).

Our participants breastfed for on average around 7 months (SD 1.0), had a mean BMI of 24.3 (SD 3.9) kg/m^2, and almost half had at least two children and were ever users of oral contraceptives (n = 47 287) (Table 1). Interestingly, women who developed EC had a mean BMI of 26.5 (SD 5.2) kg/m^2, 306 women (42.5%) had two children, only 31 (4.3%) had diabetes, 197 (27.4%) had ever used oral contraceptives, and 159 (22.1%) were ever MHT users (data not shown).

We observed a significant dose-response association between LNYM and EC risk (p trend <0.0001). Compared to women with a LNYM >40 (reference group), the multivariable HR for those with LNYM <24, 25-29, 30-34, and 35-39 were 0.17 (95% CI 0.22-0.27), 0.25 (95% CI 0.17-0.36), 0.43 (95% CI 0.32-0.58) and 0.68 (95% CI 0.51-0.92), respectively. For every additional LNYM, women experienced a 9.1% higher EC risk. Using the lowest LNYM category (LNYM <25) as a reference, as was done in previous analogue reports, rendered a HR of 5.0 (95% CI 3.10-8.03) (Table 2).

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Although the test for interaction between BMI and LNYM was not statistically significant ($p = 0.78$), we decided to look at the association between EC risk and BMI in 2 categories ≤24.9 and ≥25 (Table 3). When we did this, both age-adjusted and multivariable analysis showed a significant ($p = 0.0001$) increased EC risk with increasing LNYM.

Figure 1 illustrates age-specific HRs for EC by LNYM. All lines showed a sharp increase in hazards in the perimenopausal period and a peak in postmenopause (60-65 years), before levelling off after age 70. Cubic splines illustrating dose-response associations between LNYM and EC risk showed nonlinearity tests of $p = 0.001$, and the restricted cubic splines model showed a consistent increase in EC risk for each additional LNYM (Figure S1).

Sensitivity analyses restricted to never users of oral contraception, as well as models using the values LNYM_1 (that included both the abortion and exu-variables) and LNYM_2 (that included just the abortion variable), were of similar magnitude and in line with the main dose-response trend. Additional stratification for PA, MHT, and diabetes did not attenuate these results. Tests for interaction between PA (PA <5, PA ≥5) and BMI (BMI ≤24.9 and BMI ≥25) were not significant (Table 3).

PAF calculations showed that if women with LNYM ≥35 could decrease their LNYM <35 years, 48% of EC could be avoided. The proportion of avoided cases increased to 64% and 67%, if LNYM was decreased to 20 and 25 years, respectively (Supporting Information Table S1).

Discussion

To our knowledge, this is the first large, nationally-representative cohort study that estimated the fraction of EC in postmenopausal women attributable to LNYM. We observed a significant increase in EC risk with each additional LNYM. EC risk was more pronounced in women in aged 50-65 years, but this was no longer significant after approximately 70 years

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of age, confirming the limited effect of reproductive factors in EC risk. Stratification for BMI, MHT use, and diabetes did not attenuate the association between LNYM and EC risk.

The PAF was interpreted as the proportion of overall ECs that would not occur in the average population if women with a LNYM ≥35 had a LNYM <35 (Table S1), assuming that the distribution of the adjustment variables remained unchanged. Our PAF estimates are consistent with other studies (14), showing that reproductive factors explain almost half of EC incidence.

Several studies have investigated the association between cumulative lifetime hormonal exposure and EC risk by merging the effects of several hormone-related factors (43-49). In 1986, Pettersson et al. were the first to present a clear, dose-response association and a 4-fold increased EC risk with a longer menstruation span (50). Thereafter, other studies looked at this association using a prospective design (5, 8, 9). All analogue cohort and case-control studies have substantial methodological heterogeneity in their construction of LNYM and in the number of potential confounders available for adjustment (46). In addition, and in contrast to other studies, we used the highest LNYM category (LNYM ≥40 years) as the reference category, as there were fewer EC in the lowest category of LNYM, and our intention was to show the distribution of risk estimates in 5-year intervals. When we ran analyses using our lowest LNYM category (LNYM <25) as a reference, women with >40 LNYM showed a five-fold increased EC risk (HR=5.0, 95% CI 3.10-8.03). Nevertheless, this methodological difference did not alter the significant dose-response association found in our study, which is in line with other earlier reports.

Despite the limited number of reports that directly investigated the association between EC risk and LNYM, there are numerous studies that indirectly confirmed this association by showing the effect of each individual component of LNYM. A woman's natural menstrual lifespan starts at menarche, is interrupted by pregnancies and breastfeeding periods, and ends with menopause (50). All these factors contribute to changes in lifetime exposure to natural

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estrogen and progesterone and may, therefore, contribute to endometrial carcinogenesis. However, the possible long-term consequences of each reproductive factor differ substantially and vary across individuals (51).

In order to minimize the possible influence of lifestyle risk factors on the association between LNYM and EC risk, we took into account the effect of BMI, MHT use, and diabetes. Obesity and overweight are reported to contribute to about 40% of EC cases, and according to several reports, they confer a 4- to 6-fold increase in risk (52). However, when we adjusted for or stratified by BMI, the results and dose-response trend were lightly attenuated but remained significant, suggesting that LNYM and BMI have an independent effect on EC risk. These findings are in line with another recently published study, showing that, in comparison to genetic determinants, reproductive factors are less dependent on obesity and overweight in regard to EC risk (45). We did not observe any changes in the main association when we stratified by diabetes and MHT. The possible effect of MHT use in our study was also ruled out by including this variable in multivariable-adjustment analysis and in the calculation of LNYM.

The relationship between LNYM and EC risk is clearly biologically plausible. In terms of EC development, there are two possible key mechanisms. The first one relates to the widely proposed “estrogen window hypothesis”, which is based on incessant ovulation causing prolonged exposure to unopposed estrogen (53). The second mechanism supports the theory that the increased number of periods and, therefore, cycles, creates incessant repeated disruption of the uterine lining and increases the probability of genetic alterations (8). Previous studies reported a low incidence of breast and other estrogen-dependent malignancies among indigenous women. It has been shown that these women historically had fewer periods and ovulatory cycles during their life, due to multiple pregnancies and long periods of breastfeeding (54).

The main strength of our study is the population-based prospective design, as the NOWAC Study is representative of Norwegian middle-aged women. A good illustration of this are the cumulative incidence rate plots for EC constructed for both NORDCAN

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(Norway) (2) and NOWAC, which are matched by age group (Figure S2). Another important strength of our study is the large sample size, which gave sufficient statistical power to investigate the association between LNYM and EC risk, as well as the effect of important confounding factors. Being population-based, our study is of particular interest in showing the independent association between reproductive factors and EC risk, which can likely be extrapolated to similar populations. We observed normal or slightly increased BMI and few cases of diabetes among our participants, allowing us to propose that other factors might also contribute to the continuous increase in EC in Norway. Along with other Scandinavian countries, and in contrast to several other countries in Europe, Norwegian women had earlier access to oral contraceptives, which were widely used in this study population (55). This allowed us to perform additional analyses among ever users and never users of oral contraceptives and conclude that the dose-response relationship we observed between LNYM and EC risk is independent of oral contraceptive use. Moreover, 99% of the EC cases in our study were type 1, which is believed to be more associated with reproductive factors (38), thus strengthening the plausibility of our findings. The results of sensitivity analyses also confirmed the validity of our LNYM variable, showing unchanged HRs regardless of which risk factors were included.

Our study also had several methodological limitations. First, we used information about past events in women's life, thus misclassification of exposures may have occurred. However, given the prospective nature of our design, if recall errors exist, we would expect them to be non-differential. Second, although we were able to include information on incomplete pregnancies for some women, a substantial proportion of women had missing data on these variables. However, several studies with higher statistical power showed no biological evidence that incomplete pregnancies produce the equivalent long-term decrease in estrogen levels that full-term pregnancies do in regard to hormone-dependent cancers (56). Third, due to lack information on menstrual regularity, bleeding volume, anovulation, and cycle length, we cannot rule out the possibility of residual confounding (57). Moreover, ovulatory cycles and LNYM might be independent risk factors (58), and we could not address the potential effect of other bleeding problems, like secondary amenorrhea, that some women might experience during their reproductive life. Finally, due to a limited number of premenopausal EC in NOWAC, our analysis was restricted to postmenopausal women, which, on the other hand, allowed us to look at the effect of the entire menstrual span.

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In summary, the results indicate that a higher LNYM increases EC risk among postmenopausal women. Our results support the hypothesis that LNYM is an important tool that represents the cumulative effect of several risk factors and can be used to predict EC risk at a population level, which is, in our opinion, a better indicator of risk than each individual component.

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Supporting Information legends

Table S1. Population attributable fraction (PAF): proportion of endometrial cancer in the population that would be avoided if lifetime number of years of menstruation (LNYM) category decreased.

Figure S1. Spline regression models for lifetime number of years of menstruation in relation to endometrial cancer risk. Four knots determined by Harrell's default percentiles of lifetime number of years of menstruation. Solid lines – hazard ratios, dashed lines - 95% confidence intervals.

Figure S2. Cumulative incidence rate (CIR) for endometrial cancer in Norwegian Women and Cancer (NOWAC) Study and Cancer statistics for the Nordic countries (NORDCAN). PY – person-years.

Figure and Table legends

Table 1. Selected baseline characteristics of participants in the Norwegian Women and Cancer Study by lifetime number of years of menstruation (LNYM) (n=117 589). BMI, body mass index.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CI) for endometrial cancer by lifetime number of years of menstruation (LNYM) in the Norwegian Women and Cancer Study (n=117 589).

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Table 3. Sensitivity analyses. Hazard ratios (HRs) and 95% confidence intervals (CI) for endometrial cancer by lifetime number of years of menstruation (LNYM) according to body mass index (BMI), physical activity (PA), diabetes and menopausal hormone therapy (MHT) use, abortions, extra-uterine pregnancies, and never oral contraceptive (OC) use in the Norwegian Women and Cancer Study.

Figure 1. Smoothed baseline hazard rate of endometrial cancer by lifetime number of years of menstruation category estimated with stpm2 models.

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Table 1. Selected baseline characteristics of participants in the Norwegian Women and Cancer Study by LNYM (n=117 589)

Characteristics	LNYM				
	<25	**25-29**	**30-34**	**35-39**	**≥40**
Person-years at risk[a]	21 779	288 258	684 430	452 787	41 874
N of endometrial cancer cases	27	60	270	314	49
Age at menarche (mean, ±SD)[b]	13.6 (1.4)	13.6 (1.5)	13.5 (1.3)	12.8 (1.2)	12.0 (1.2)
Age at menopause (mean, ±SD)[c]	46.9 (5.5)	48.3 (3.5)	49.9 (2.2)	52.1 (2.5)	54.4 (2.1)
Age at first birth (mean, ± SD)	24.3 (4.9)	24.2 (4.5)	23.9 (4.3)	24.5 (4.6)	25.4 (5.1)
Age at last birth (mean, ±SD)	30.1 (5.6)	30.7 (5.2)	29.9 (5.1)	29.2 (5.1)	28.8 (5.2)
Number of full-term pregnancies (among parous women) (%)					
0	8.3	5.8	4.8	13.6	43.9
1	11.8	9.2	9.0	15.7	20.3
2	42.5	37.9	42.4	45.5	25.8
3	25.8	30.9	31.4	18.9	7.1
≥4	11.6	16.2	12.5	6.2	2.9
Cumulative duration of breastfeeding (%)					
0	50.3	43.9	48.9	66.9	89.8
≤1	29.4	30.7	31.9	25.3	9.0
1-3 years	16.4	20.4	17.5	7.7	1.2
>3 years	3.9	4.9	1.7	0.2	0.0
Cumulative duration of breastfeeding (years) (mean, ±SD)	0.96 (1.39)	1.08 (1.29)	0.82 (0.98)	0.49 (0.71)	0.21 (0.47)
Number of ectopic pregnancies (%)[d]					
Ever	1.2	1.3	1.3	1.2	0.8
Never	98.8	98.7	98.7	98.8	99.2
Number of abortions (%)[e]					
0	71.5	69.3	65.9	68.8	75.2
1	18.7	20.4	22.7	21.2	16.0
≥2	9.7	10.3	11.4	10.0	8.8

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BMI[f] (%)					
<20	6.9	6.2	5.6	4.9	4.3
20-24.9	54.8	53.7	53.6	50.2	41.6
25-29.9	29.9	31.2	31.9	33.6	36.2
≥30	8.4	8.9	8.9	11.4	17.9
BMI (mean, ±SD)	24.2 (3.8)	24.3 (3.8)	24.1 (3.8)	24.4 (4.1)	25.5 (4.7)
Oral contraceptive use (%)					
Never	13.2	31.8	64.9	82.3	89.9
Ever	86.9	68.2	35.1	17.7	10.2
Smoking status (%)					
Never	25.1	27.2	25.9	52.9	73.0
Former	38.9	39.5	38.7	28.9	18.6
Current	36.1	33.4	35.3	18.5	8.4
Menopausal hormone therapy use (%)[g]					
Never	53.9	56.3	62.3	66.1	71.5
Former	17.8	17.3	14.6	13.3	10.2
Current	18.9	17.8	17.1	16.2	14.4
Diabetes (%)[h]					
Yes	1.6	1.7	1.7	2.1	3.4

[a] Total person-years=1,685,143; average follow-up time 14.3 years (sd 7.1)

[b] SD-standard deviation

[c] Age at menopause is the start-age of follow-up in the present study

[d] Information available in limited number of questionnaires (n= 35,540)

[e] Without separating into spontaneous or induced. Information available in limited number of questionnaires (n= 65,548)

[f] BMI: Body mass index. Measured at baseline

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[g] Number of total missing 22,147(19%)

[h] Number of total missing 7,336 (6.2%)

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CI) for endometrial cancer by lifetime number of years of menstruation (LNYM) in the Norwegian Women and Cancer Study (n=117 589)

LNYM	N of cases	Age-adjusted analyses HR (95% CI)	Multivariable analyses[a] HR (95% CI)
0-24	27	0.17 (0.22-0.27)	0.20 (0.12-0.32)
25-29	60	0.25 (0.17-0.36)	0.29 (0.19-0.42)
30-34	270	0.43 (0.32-0.58)	0.49 (0.36-0.68)
35-39	314	0.68 (0.51-0.92)	0.75 (0.55-1.01)
≥40	49	1.00	1.00
P for trend		0.00	0.00
Risk per year of menstruation		1.09 (1.08-1.11)	1.09 (1.07-1.11)

[a] Multivariable model adjusted for smoking, body mass index, and physical activity.

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Table 3. Sensitivity analyses. Hazard ratios (HRs) and 95% confidence intervals (CI) for endometrial cancer by lifetime number of years of menstruation (LNYM) according to body mass index (BMI), physical activity (PA), diabetes and menopausal hormone therapy (MHT) use, abortions, extra-uterine pregnancies, and never oral contraceptive (OC) use in the Norwegian Women and Cancer Study

LNYM	Multivariable-adjusted analyses, HR (95% CI)						
	BMI[a] (N = 68 158)		Physical activity (PA)[b] (N = 28 847)		Diabetes+MHT[c] (N = 117 589)	Abortions[d] + extra-uterine pregnancy[e] (N = 33 540)	Never OC users[f] (N = 28 847)
	BMI <25	BMI ≥25	PA <5	PA ≥5			
≤24	0.25 (0.11-0.56), *n* = 13	0.17 (0.09-0.32), *n* = 14	0.22 (0.10-0.45), *n* = 11	0.19 (0.10-0.36), *n* = 16	0.20 (0.13-0.33), *n* = 27	0.07 (0.01-0.53), *n* = 1	0.12 (0.04-0.38), *n* = 3
25-29	0.34 (0.16-0.69), *n* = 26	0.26 (0.16-0.42), *n* = 34	0.29 (0.16-0.54), *n* = 23	0.28 (0.17-0.47), *n* = 37	0.29 (0.19-0.43), *n* = 60	0.26 (0.10-0.68), *n* = 9	0.29 (0.18-0.49), *n* = 26
30-34	0.56 (0.31-1.06), *n* = 110	0.46 (0.32-0.66), *n* = 160	0.43 (0.69-1.26), *n* = 86	0.55 (0.36-0.88), *n* = 184	0.49 (0.37-0.68), *n* = 270	0.46 (0.23-0.91), *n* = 78	0.51 (0.36-0.72), *n* = 186
35-39	0.98 (0.53-1.83), *n* = 126	0.65 (0.46-0.92), *n* = 188	0.65 (1.06-2.03), *n* = 106	0.83 (0.55-1.23), *n* = 208	0.75 (0.56-1.02), *n* = 314	0.81 (0.42-1.55), *n* = 121	0.81 (0.58-1.12), *n* = 267
≥40	1.00, *n* = 11	1.00, *n* = 38	1.00, *n* = 22	1.00, *n* = 27	1.00, *n* = 49	1.00, *n* = 10	1.00, *n* = 41
P for trend	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Risk per year of menstruation	1.09 (1.06-1.12)	1.10 (1.07-1.12)	1.09 (1.06-1.13)	1.09 (1.07-1.12)	1.09 (1.07-1.11)	1.12 (1.07-1.17)	1.10 (1.07-1.13)

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[a] Stratification analysis according to BMI. Multivariable model adjusted for smoking, physical activity.

[b] Stratification according to PA. Multivariable analysis adjusted for smoking and BMI.

[c] Multivariable model adjusted for smoking, BMI, physical activity, diabetes, and MHT use.

[d,e] Model with new LNYM_1, which includes information on both abortions ("abortion variable" in the text)[4] and information on extra-uterine pregnancy ("exu-variable" in the text)[5]. Multivariable analysis adjusted for smoking, BMI and physical activity.

[f] Model for never users of OC. Multivariate analysis adjusted for physical activity, smoking and BMI.

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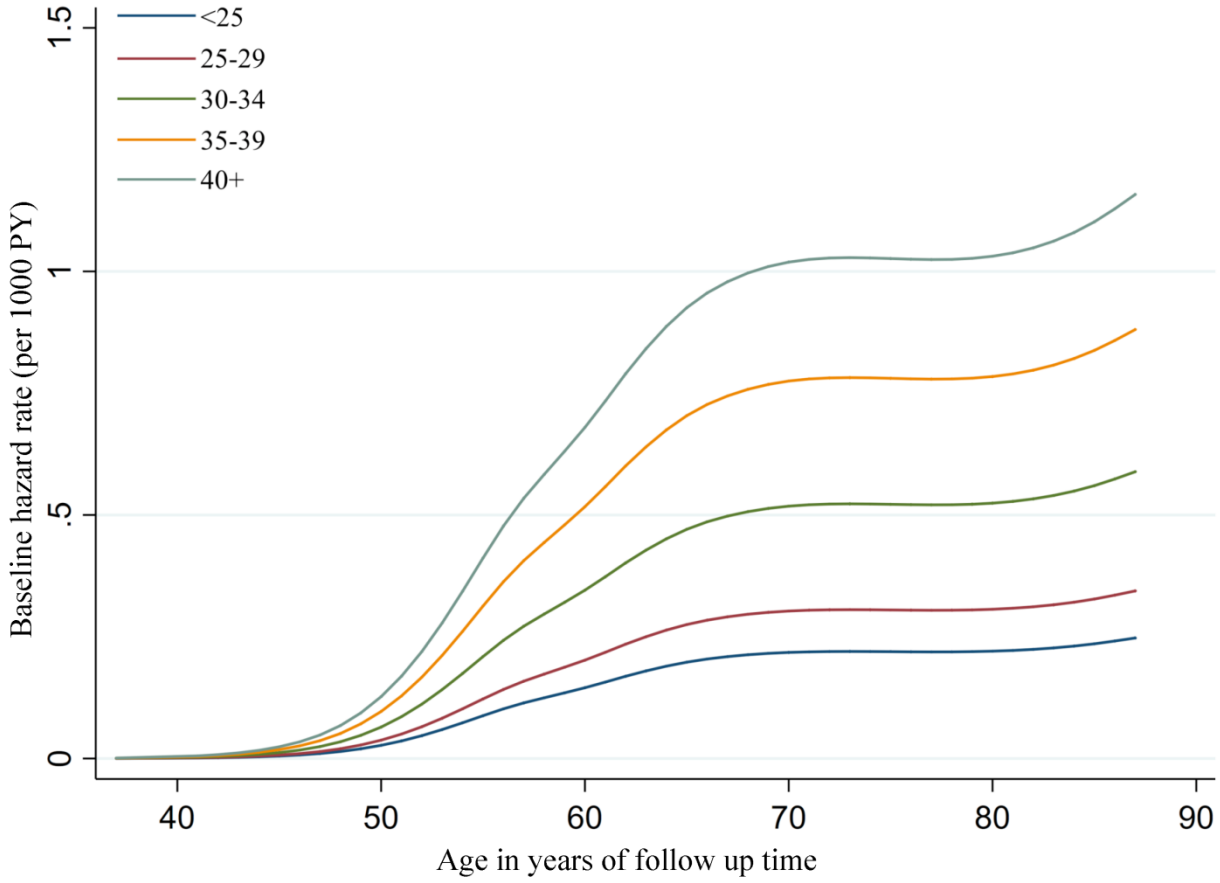

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