The etiology of uterine sarcomas: a pooled analysis of the epidemiology of endometrial cancer consortium

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Background: Uterine sarcomas are characterised by early age at diagnosis, poor prognosis, and higher incidence among Black compared with White women, but their aetiology is poorly understood. Therefore, we performed a pooled analysis of data collected in the Epidemiology of Endometrial Cancer Consortium. We also examined risk factor associations for malignant mixed mullerian tumours (MMMTs) and endometrioid endometrial carcinomas (EECs) for comparison purposes.

Methods: We pooled data on 229 uterine sarcomas, 244 MMMTs, 7623 EEC cases, and 28 829 controls. Odds ratios (ORs) and 95% confidence intervals (CIs) for risk factors associated with uterine sarcoma, MMMT, and EEC were estimated with polytomous logistic regression. We also examined associations between epidemiological factors and histological subtypes of uterine sarcoma.

Results: Significant risk factors for uterine sarcoma included obesity (body mass index (BMI) ≥ 30 vs BMI < 25 kg m⁻²) (OR: 1.73, 95% CI: 1.22–2.46), P-trend = 0.008 and history of diabetes (OR: 2.33, 95% CI: 1.41–3.83). Older age at menarche was inversely associated with uterine sarcoma risk (≥ 15 years vs < 11 years (OR: 0.70, 95% CI: 0.34–1.44), P-trend: 0.04). BMI was significantly, but less strongly related to uterine sarcomas compared with EECs (OR: 3.03, 95% CI: 2.82–3.26) or MMMTs (OR: 2.25, 95% CI: 1.60–3.15, P-heterogeneity = 0.01).

Conclusion: In the largest aetiological study of uterine sarcomas, associations between menstrual, hormonal, and anthropometric risk factors and uterine sarcoma were similar to those identified for EEC. Further exploration of factors that might explain patterns of age- and race-specific incidence rates for uterine sarcoma are needed.
Uterine sarcoma is a rare form of uterine cancer that arises from the myometrium or connective tissue of the uterus and accounts for 3–7% of all uterine cancer diagnoses in the United States (D’Angelo and Prat, 2010). Unlike the common uterine cancer histological type, endometrioid endometrial carcinoma (EEC), uterine sarcomas are highly aggressive, with 5-year overall survival rates ranging between 17 and 55% (Prat, 2009). The peak incidence of uterine sarcoma occurs at a younger age than EEC and several studies reported higher incidence rates of uterine sarcoma among Black compared with White women (Harlow et al., 1986; Schwartz et al., 1996; Brooks et al., 2004), the opposite of overall endometrial carcinoma trends (Sherman and Devesa, 2003).

Owing to the low incidence of this disease, the aetiology of uterine sarcomas has been investigated in only a few small case–control studies (Kvale et al., 1988; Schwartz and Thomas, 1989; Schwartz and Weiss, 1990; Schwartz et al., 1991, 1996; Lavie et al., 2008; Jaakkola et al., 2011). Obesity, menopausal use of oestrogen plus progesterin, oral contraceptives (OC), and tamoxifen use are associated with increased risks of uterine sarcoma, whereas cigarette smoking and parity are associated with a reduced risk. Recently, there was an important change in the classification of uterine sarcoma; malignant mixed Mullerian tumours (MMMTs), which previously accounted for 40% of all uterine sarcomas, are now classified as metastatic endometrial carcinomas given their similarities in aetiology and metastatic patterns (McCluggage, 2002; Prat, 2009). Consequently, previous risk factor associations may have been affected by the inclusion of the MMMT subtype. Here, we examine relationships between epidemiological risk factors and uterine sarcoma, overall and by histological subtype, in a large pooled analysis using the updated histological classification for uterine sarcoma. Furthermore, we examine risk factor associations for MMMTs and EECs to evaluate potential aetiological heterogeneity across a spectrum of uterine cancer diagnoses.

### MATERIALS AND METHODS

**Study population.** The Epidemiology of Endometrial Cancer Consortium (E2C2), sponsored in part by the National Cancer Institute, was designed to combine data from cohort and case–control studies to elucidate the aetiology of uterine cancer (Olson et al., 2009). Any study that included at least one uterine sarcoma case was eligible for the current analysis. The 10 cohort and five case–control studies that contributed data to this analysis are summarised in Table 1. For the cohort studies that contributed data to E2C2 (other than the California Teachers Study (CTS)), a nested case–control study design was employed, with inclusion of up to four controls (women with an intact uterus and no uterine cancer diagnosis) randomly selected from the risk set and matched to the corresponding uterine cancer case on year of birth, date of entry (within 6 months), and any additional matching criteria as appropriate in the individual study. For the CTS, data came from a previous nested case–control study in which two controls per case were identified and matching was based on 5-year age group, race/ethnicity, and broad geographic area within California. Cases in the cohort studies were identified through annual linkage to state or national cancer registries (Multiethnic Cohort Study, NIH-AARP Diet and Health Study (NIH-AARP), Iowa Women’s Health Study (IWHS), Netherlands Cohort Study (NLCS), Canadian National Breast Screening Study (NBSS), and CTS) or by self-report on follow-up questionnaires and confirmed through medical record review, linkage to cancer registries, or the National Death Index (Cancer Prevention Study II Nutrition Cohort, Breast Cancer Detection Demonstration Project (BCDDP), Nurses’ Health Study (NHS), and Black Women’s Health Study (BWHS)).

In the case–control studies, population-based controls were frequency-matched to cases except in the US Case–Control Study (US) where individual 1:1 matching was employed. Eligible controls were those women with an intact uterus and no history of uterine cancer. Methods to select controls within each source population included random digit dialling (US, Bay Area Womens Health Study (BAWHS), Endometrial Cancer and Physical Activity Study (ECPA)) and random selection from data registrars of all citizens (Polish Endometrial Cancer Study (PECS) and Shanghai Endometrial Cancer Study (SEC)). All studies were approved by the institutional review boards (IRBs) of their parent institutions, and written informed consent was obtained from all participants. In addition, Memorial Sloan–Kettering Cancer Centre has IRB approval as the data co-ordinating centre for E2C2.

**Data collection.** De-identified data from the participating studies were centrally collected and harmonised at Memorial Sloan–Kettering Cancer Centre. We made an effort to collect a core set of standardized variables, but not all variables were collected by each study. Some studies did not provide information on menopausal oestrogen plus progesterin use (NBSS, ECPA, NLCS, IWHS, BCDDP), menopausal oestrogen-alone use (NBSS, ECPA, IWHS), diabetes (BAWHS and NBSS), parity (NLCS), or smoking status (BAWHS). As the number of live births was not reported by the NLCS, we used the number of pregnancies lasting $\geq 7$ months as a surrogate for parity among NLCS cases and controls.

**Case definitions.** Women with an incident, histologically confirmed diagnosis of uterine sarcoma, MMMT, or EEC were included as case patients in the current study. Although the emphasis of this study is on uterine sarcomas, women with MMMTs or EECs were included for comparison purposes. Uterine sarcoma cases with the following International Classification of Diseases for Oncology (ICD)-O-3 morphology codes were included: sarcoma, not otherwise specified (NOS) 8800–8806, fibromatous neoplasms 8810–8815, myomatous neoplasms 8890–8896 (includes leiomyosarcoma), rhabdomyosarcoma 8900–8902, embryonal rhabdomyosarcoma 8910–8912, and endometrial stromal sarcoma 8930–8934. Four studies (PECS, SECS, BWHS, and NHS) did not have ICD-O-3 codes and instead supplied a summary histology variable for each case (i.e., sarcoma, EEC, MMMT, etc). The ICD-O-3 codes 8950–8982 or summary variable ‘MMMT’ were used to define MMMT, while ICD-O-3 codes 8380–8383 and summary variable ‘endometrioid’ identified EECs. EEC cases from the NHS could not be distinguished from adenosarcoma, NOS cases and were excluded from analysis.

**Statistical methods.** Categories for exposure variables were created including age ($\leq 54$, $55–59$, $60–64$, $65–69$, $\geq 70$ years), race (White, Black, Asian, other), BMI ($<25$, $25–30$, $\geq 30 \text{ kg m}^{-2}$), age at menarche ($\leq 11$, $11–12$, $13–14$, $\geq 15$ years), menopausal status (premenopausal, peri-menopausal, postmenopausal), parity (no live births, 1 or more live births), number of live births among parous women (1, 2, 3–4, $\geq 5$ live births), smoking status (never, former, current), menopausal hormone use (never, ever), menopausal oestrogen use (never, ever), menopausal oestrogen plus progesterin use (never, ever), OC use (never, ever), and history of diabetes (no, yes). Given the importance of these variables in the aetiology of common endometrial carcinoma subtypes, we included all exposure variables simultaneously in an unconditional polytomous logistic regression model to estimate the magnitude of association (odds ratios (ORs) and 95% confidence intervals (CIs)) between risk factors and case groups. Polytomous logistic regression was used when the outcome variable is nominal with more than two levels (Hosmer, 2000). When a study did not report values for a particular variable, that study was excluded from the specific risk factor analysis. Missing values were coded as a separate category for each variable; when excluding subjects with missing values the results did not appreciably change.
All models were adjusted for age and race; however, we do not present effect estimates for these variables given their use as matching criteria in all studies. Tests for linear trend were performed for BMI, age at menarche, and number of live births among parous women by including the ordinal form of each variable in the model. We also examined risk factors for endometrial stromal sarcoma and leiomyosarcoma, the two main histological subtypes of uterine sarcoma, compared with controls. Differences in ORs between case groups were quantified using case-only logistic regression models. A $P$-heterogeneity of effect estimates was examined by creating a multiplicative interaction term between study site (fixed effect covariate) and each risk factor and performing a likelihood ratio test comparing models with and without the risk factor-study site interaction terms.

Using the distribution of risk factors in our sample, a binary outcome (control vs uterine sarcoma), power of 80% and a two-sided $z$ of 0.05, we calculated minimum detectable ORs for each risk factor, which ranged from 1.45–1.89 for factors associated with increased risk and 0.35–0.67 for protective factors. All tests of statistical significance were two-sided. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

### Table 1. Description of the 15 observational studies included in the pooled analysis of uterine sarcoma risk factors, E2C2

| Study                        | Uterine sarcoma ($n = 229$) | Malignant mixed mullerian tumour ($n = 244$) | Endometrioid endometrial carcinoma ($n = 7623$) | Controls ($n = 28 829$) | Recruitment period | Matching factors                        |
|------------------------------|------------------------------|---------------------------------------------|-----------------------------------------------|-------------------------|-------------------|----------------------------------------|
| **Cohort***                  |                              |                                             |                                               |                         |                   |                                        |
| Multiethnic Cohort Study (MEC) | 35                           | 34                                         | 515                                           | 2623                    | 1993–1996         | Birth year, cohort entry, race, area   |
| Cancer Prevention Study II Nutrition Cohort (CPS-II) | 11                           | 20                                         | 573                                           | 2664                    | 1992–1993         | Birth year, cohort entry, race, area   |
| NIH-AARP Diet and Health Study (NIH-AARP) | 49                           | 71                                         | 1508                                          | 7400                    | 1995–1996         | Birth year, cohort entry, race, area   |
| Breast Cancer Detection Demonstration Project (BCDDP) | 5                            | 7                                          | 424                                           | 2418                    | 1979–1980         | Birth year, cohort entry, clinic       |
| Nurses’ Health Study (NHS)*   | 15                           | 6                                          | —                                             | 1641                    | 1976              | Birth year, cohort entry, race, area   |
| Iowa Women’s Health Study (IWHS) | 10                           | 22                                         | 466                                           | 2212                    | 1986              | Birth year, cohort entry, race, area   |
| Black Women’s Health Study (BWHR5)* | 7                            | 6                                          | —                                             | 52                      | 1995              | Birth year, cohort entry, race, area   |
| Netherlands Cohort Study (NLCS) | 6                            | 10                                         | 402                                           | 896                     | 1986              | Birth year, cohort entry               |
| Canadian National Breast Screening Study (NBSS) | 29                           | 11                                         | 643                                           | 3072                    | 1980–1985         | Birth year, cohort entry, race, area   |
| California Teachers Study (CTS)* | 3                            | 6                                          | 351                                           | 686                     | 1996–2004         | Five-year age categories, race/ethnicity, area |
| **Case–control***            |                              |                                             |                                               |                         |                   |                                        |
| US Case–Control Study (US)    | 23                           | 22                                         | 332                                           | 526                     | 1987–1990         | Age (± 5 years), race, telephone area code |
| Bay Area Women’s Health Study (BAWHS) | 12                           | 12                                         | 429                                           | 470                     | 1996–1999         | Five-year age categories, race/ethnicity |
| Polish Endometrial Cancer Study (PECS) | 8                            | 0                                          | 435                                           | 1925                    | 2000–2003         | Age (± 5 years), site                  |
| Shanghai Endometrial Cancer Study (SECS) | 15                           | 0                                          | 1071                                          | 1212                    | 1997–2004         | Age (± 5 years)                        |
| Endometrial Cancer and Physical Activity Study (ECPA) | 1                            | 17                                         | 474                                           | 1032                    | 2002–2006         | Age (± 5 years)                        |

Abbreviation: E2C2 = Epidemiology of Endometrial Cancer Consortium (E2C2).

*The NHS combined endometrioid endometrial carcinoma and adenocarcinoma cases in one group.

**The BWHS only submitted patients with uterine sarcoma, malignant mixed mullerian tumours and matched controls to the Epidemiology of Endometrial Cancer Consortium (E2C2).

†The CTS data include only participants in a nested case–control study of endometrial cancer.

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A total of 229 uterine sarcomas, 244 MMMTs, 7623 EECs, and 28829 controls were available for this pooled analysis. Black race was more prevalent among MMMTs compared with uterine sarcoma and EEC cases (17.2%, 11.3%, and 2.6%, respectively, data not tabulated), and median age at diagnosis was oldest among MMMT cases compared with uterine sarcoma and EEC cases (67.0, 61.4, and 64.3 years, respectively, data not tabulated). Distributions of risk factors, ORs, and 95% CIs are shown in Table 2. Significantly increased risk of uterine sarcoma was observed for obese compared to normal BMI (OR: 1.73, 95% CI: 1.22–2.46) and a history of diabetes compared with no diabetes (OR: 2.33, 95% CI: 1.41–3.83), whereas older age at menarche (age at menarche $\geq$ 15 compared with age at menarche <11 years OR: 0.70, 95% CI: 0.34–1.44, p-trend = 0.04) was associated with a lower risk of uterine sarcoma. Any live births, postmenopausal status, OC use, and current or former smoking were inversely but not statistically significantly associated with uterine sarcoma risk. BMI was significantly, but less strongly related to uterine sarcoma than to EECs (OR: 3.03, 95% CI: 2.82–3.26) or MMMTs (OR: 2.25, 95% CI: 1.60–3.15) for the heaviest compared with the leanest women (P-heterogeneity = 0.01).

In exploratory analyses, we examined risks associated with the most prevalent histological subtypes of uterine sarcoma: endometrial stromal sarcoma (n = 98) and leiomyosarcoma (n = 82) (Table 3). Black race was more prevalent among leiomyosarcoma compared with endometrial stromal sarcoma cases (20.7% vs 6.1%, data not tabulated), whereas median age at diagnosis was similar (61.8 and 63.6 years, respectively, data not tabulated). The direction of most associations for the histological subtypes was similar to patterns observed for uterine sarcoma overall. Obesity (OR: 1.74, 95% CI: 1.03–2.93) and a history of diabetes (OR: 2.28, 95% CI: 1.02–5.12) were associated with significantly higher risks of endometrial stromal sarcoma, whereas reduced risk of leiomyosarcoma was observed for postmenopausal compared with premenopausal women (OR: 0.35, 95% CI: 0.16–0.75). Compared with the overall associations, less consistency in histological subtype associations was noted for age at menarche and former or current smoking. However, no significant heterogeneity of effects between these two histological subtypes was observed (P-heterogeneity > 0.10).

In contrast to prior reports, we observed statistically non-significant inverse associations between OC use and uterine sarcoma risk overall, as well as risk of both histological subtypes, whereas Schwartz et al. (1996) reported positive, albeit, statistically non-significant associations. Given the absence of statistical significance and information on the formulation and duration of OC use in ours and the previous study, these findings should be interpreted cautiously. Furthermore, we did not observe an association between menopausal oestrogen plus progestin use and uterine sarcoma risk, which has been observed previously. In a recent Finnish cohort study, menopausal estradiol and progestin treatment was associated with increased risks of leiomyosarcoma and endometrial stromal sarcoma, especially among women with longer exposures (Jaakkola et al., 2011). Finally, the relationship between a history of diabetes and uterine sarcoma risk has been explored in one previous study (Brinton et al., 2005). Of 137 uterine sarcoma cases, only 2 had a history of diabetes resulting in a null association. We noted strong risks associated with a history of diabetes for uterine sarcoma overall and both histological subtypes, which is consistent with aetiological studies of endometrial carcinoma (Weiderpass et al., 2000; Rosato et al., 2011). Obesity and diabetes are associated with metabolic disturbances and our finding of a stronger association with diabetes for uterine sarcoma compared with EEC raises questions about the possibility of a more central role of insulin in their aetiology.

Similarities in risk factor associations for uterine sarcoma and EECs suggest overlap in the biological mechanisms associated with development of these tumours. Commonly described mechanisms relating menstrual, reproductive, and anthropometric factors to EEC risk include imbalances in multiple pathways, including sex hormones (oestrogen and progesterone), insulin and insulin-like growth factors (IGFs), and inflammatory markers such as interleukins. Higher expression of oestrogen, IGFs, and interleukins is associated with increased risk of EECs (Calle and Kaaks, 2004; Oh et al, 2004; Dossus et al, 2010; Audet-Walsh et al, 2011; Wang et al, 2011). Key cytogenetic and molecular events observed in endometrial stromal sarcomas include chromosomal rearrangements, loss of heterozygosity of tumour suppressor genes, and
| Characteristics | Controls | n = 28,829 | n (%) | OR (95% CI) | P-heterogeneity | P-trend |
|----------------|----------|------------|-------|-------------|----------------|---------|
| Age at menarche | <11 | 1,252 | 43 | 13 | 5 | 0.01 | 0.44 |
|                | 11–12 | 10,408 | 246 | 4.3 | 37 | 5.3 | 0.01 | 0.80 |
|                | 13–14 | 12,808 | 384 | 6.2 | 33 | 5.1 | 0.01 | 0.79 |
|                | >15 | 4,932 | 88 | 1.8 | 0.5 | 0.01 | 0.98 |
| Body mass index | <25 kg/m² | 1,449 | 244 | 17.1 | 60 | 26.2 | 2.25 (1.20, 4.24) | 0.001 |
|                | 25–30 kg/m² | 9,044 | 2,408 | 34.4 | 84 | 2.17 (1.17, 3.99) | 0.001 |
|                | >30 kg/m² | 9,944 | 2,408 | 34.4 | 84 | 2.17 (1.17, 3.99) | 0.001 |
| Number of live births (among parous women) | 1 | 2,346 | 12 | 14.0 | 1.00 | 0.43 | 0.001 |
|                | 2 | 5,040 | 180 | 36.0 | 1.00 | 0.43 | 0.001 |
|                | 3–4 | 10,040 | 180 | 36.0 | 1.00 | 0.43 | 0.001 |
|                | 5 | 3,446 | 180 | 36.0 | 1.00 | 0.43 | 0.001 |
| Menopausal status | Premenopausal | 15,194 | 14,922 | 81 | 1.00 | 0.43 | 0.001 |
|                | Perimenopausal | 5,040 | 180 | 36.0 | 1.00 | 0.43 | 0.001 |
|                | Postmenopausal | 4,944 | 180 | 36.0 | 1.00 | 0.43 | 0.001 |
| Menopausal hormone use | Never | 15,019 | 14,922 | 81 | 1.00 | 0.43 | 0.001 |
|                | Ever | 3,935 | 180 | 36.0 | 1.00 | 0.43 | 0.001 |
| Menopausal oestrogen use | Never | 15,019 | 14,922 | 81 | 1.00 | 0.43 | 0.001 |
|                | Ever | 3,935 | 180 | 36.0 | 1.00 | 0.43 | 0.001 |

Table 2. Adjusted ORs and 95% CIs of risk factors for uterine sarcomas and endometrioid endometrial carcinomas, based on a pooled analysis of 15 observational studies in the E2C2.
Table 2. (Continued)

| Characteristicsa | Controls \( n = 28829 \) | Uterine sarcoma \( n = 229 \) | Malignant mixed mullerian tumour \( n = 244 \) | Endometrioid endometrial carcinoma \( n = 7623 \) |
|------------------|---------------------------|-----------------|-----------------|-----------------|
|                  | \( n \) | %   | \( n \) | %   | OR (95% CI)b | \( n \) | %   | OR (95% CI)b | \( n \) | %   | OR (95% CI)b | \( P \)-heterogeneityc |
| Menopausal oestrogen plus progestin\( g \) | 11 390 | 69.7 | 70 | 55.1 | 1.00 | 115 | 71.9 | 1.00 | 2975 | 70.1 | 1.00 |
| Never            | 3424  | 20.9 | 40 | 31.5 | 1.07 (0.52, 2.20) | 28 | 17.5 | 0.85 (0.38, 1.90) | 852 | 20.1 | 0.84 (0.70, 1.00) |
| Ever             |       |      |    |      |       |      |      |       |      |      |       | 0.40       |
| Oral contraceptive use | 17 894 | 62.1 | 127 | 55.5 | 1.00 | 85 | 34.8 | 1.00 | 5201 | 71.6 | 1.00 |
| Never            | 10 670 | 37.0 | 94 | 41.0 | 0.85 (0.63, 1.16) | 153 | 62.7 | 0.95 (0.70, 1.28) | 2357 | 32.5 | 0.74 (0.70, 0.79) |
| Ever             |       |      |    |      |       |      |      |       |      |      |       | 0.37       |
| Smoking statusb\( h \) | 14 926 | 52.6 | 122 | 56.2 | 1.00 | 128 | 55.2 | 1.00 | 4599 | 63.4 | 1.00 |
| Never            | 8504  | 30.0 | 58 | 26.7 | 0.84 (0.60, 1.16) | 75 | 32.3 | 0.92 (0.69, 1.24) | 1915 | 26.6 | 0.89 (0.84, 0.95) |
| Former           | 4133  | 14.6 | 30 | 13.8 | 0.88 (0.58, 1.33) | 20 | 8.6 | 0.63 (0.39, 1.03) | 618 | 8.6 | 0.62 (0.56, 0.68) |
| Current          |       |      |    |      |       |      |      |       |      |      |       | 0.50       |
| History of diabetesi\( i \) | 15 889 | 62.8 | 108 | 57.4 | 1.00 | 128 | 57.9 | 1.00 | 4288 | 65.5 | 1.00 |
| No               | 1583  | 6.3  | 22 | 11.7 | 2.33 (1.41, 3.83) | 29 | 13.1 | 1.38 (0.84, 2.26) | 747 | 11.4 | 1.50 (1.34, 1.67) |
| Yes              |       |      |    |      |       |      |      |       |      |      |       | 0.09       |

Abbreviations: CI = confidence interval; ECC2 = Epidemiology of Endometrial Cancer Consortium; OR = odds ratio.

a Missing values were excluded from presentation, but included as a separate category in logistic regression analysis.
b Polytomous logistic regression models adjusted for age, race, BMI, age at menarche, parity, menopausal status, menopausal oestrogen plus progestin, menopausal oestrogen use, oral contraceptive use, smoking status, history of diabetes, and site.
c \( P \)-values for tumour heterogeneity are based on case-only multivariable-adjusted logistic regression models using endometrioid endometrial carcinoma cases as the ‘controls’.
d \( P \)-values for trend calculated with the variable modelled ordinally.
e Among postmenopausal women.
f Among postmenopausal women in 12 studies with menopausal oestrogen use data.
g Among postmenopausal women in 10 studies with menopausal oestrogen plus progestin use data.
h Among 14 studies with smoking data.
i Among 13 studies with diabetes data.
Table 3. Adjusted ORs and 95% CIs of risk factors for histological subtypes of uterine sarcoma, based on a pooled analysis of 15 observational studies in the E2C2

| Characteristics | Controls | Endometrial stromal sarcoma | Leiomyosarcoma | P-heterogeneity |
|-----------------|----------|-----------------------------|----------------|-----------------|
|                 | n = 28829 | n = 98                      | n = 82         |                 |
| **Body mass index** |          |                             |                |                 |
| Normal weight (<25 kg·m⁻²) | 14244    | 49.4 42 42.9 1.00 | 33 40.2 1.00 | 0.39           |
| Overweight (25–30 kg·m⁻²) | 9044     | 31.4 26 26.5 1.02 (0.62, 1.68) | 20 24.4 0.90 (0.51, 1.60) | 0.26           |
| Obese (>30 kg·m⁻²) | 4932     | 17.1 27 27.6 1.74 (1.03, 2.93) | 23 28.0 1.56 (0.88, 2.77) |                |
| **Age at menarche** |          |                             |                |                 |
| <11             | 1252     | 4.3 7 7.1 1.00 | 6 7.3 1.00 | 0.10           |
| 11–12           | 10408    | 36.1 39 39.8 0.88 (0.39, 2.01) | 38 46.3 1.10 (0.44, 2.73) |                |
| 13–14           | 12808    | 44.4 42 42.9 0.88 (0.38, 2.01) | 27 32.9 0.75 (0.29, 1.91) |                |
| >15             | 4103     | 14.2 8 8.2 0.60 (0.21, 1.71) | 9 11.0 1.01 (0.34, 2.98) |                |
| **Parity**      |          |                             |                |                 |
| Nulliparous     | 3234     | 11.2 11 11.2 1.00 | 12 14.6 1.00 | 0.40           |
| Parous          | 24912    | 86.4 81 82.6 0.97 (0.51, 1.83) | 65 79.3 0.76 (0.40, 1.44) |                |
| **Number of live births (among parous women)** |          |                             |                | 0.17           |
| 1               | 3621     | 14.5 8 9.9 1.00 | 13 20.0 1.00 |                |
| 2               | 7805     | 31.3 26 32.1 1.59 (0.71, 3.56) | 19 29.2 0.71 (0.35, 1.46) |                |
| 3–4             | 10040    | 40.3 38 46.9 2.02 (0.91, 4.45) | 28 43.1 0.78 (0.39, 1.54) |                |
| ≥5              | 3446     | 13.8 9 11.1 1.36 (0.50, 3.67) | 5 7.7 0.35 (0.12, 1.03) |                |
| **Menopausal status** |        |                             |                | 0.22           |
| Premenopausal   | 4015     | 13.9 23 23.5 1.00 | 25 30.5 1.00 |                |
| Peri-menopausal | 281      | 1.0 0 0.0 NE | 2 2.4 0.73 (0.12, 4.41) |                |
| Postmenopausal  | 23826    | 82.6 70 71.4 0.85 (0.42, 1.72) | 50 61.0 0.35 (0.16, 0.75) |                |
| **Menopausal hormone use** | |                             |                | 0.98           |
| Never           | 13412    | 58.5 26 40.6 1.00 | 27 54.0 1.00 |                |
| Ever            | 9287     | 40.5 37 57.8 1.53 (0.54, 4.31) | 23 46.0 0.80 (0.22, 2.98) |                |
| **Menopausal oestrogen-alone use** | |                             |                | 0.97           |
| Never           | 15019    | 76.9 40 63.5 1.00 | 32 78.0 1.00 |                |
| Ever            | 2878     | 14.7 12 19.0 1.02 (0.29, 3.61) | 6 14.6 1.43 (0.18, 14.95) |                |
| **Menopausal oestrogen plus progestin use** | |                             |                | 0.72           |
| Never           | 11390    | 69.7 26 47.3 1.00 | 21 55.3 1.00 |                |
| Ever            | 3424     | 20.9 17 30.9 1.43 (0.35, 5.76) | 13 34.2 0.79 (0.08, 7.90) |                |
| **Oral contraceptive use** | |                             |                | 0.54           |
| Never           | 17894    | 62.1 52 53.1 1.00 | 44 53.7 1.00 |                |
| Ever            | 10670    | 37.0 44 56.4 0.85 (0.53, 1.34) | 36 43.9 0.72 (0.44, 1.19) |                |
| **Smoking status** |        |                             |                | 0.22           |
| Never           | 14926    | 52.6 50 56.2 1.00 | 41 50.6 1.00 |                |
| Former          | 8504     | 30.0 21 23.6 0.66 (0.39, 1.11) | 28 34.6 1.15 (0.70, 1.90) |                |
| Current         | 4133     | 14.6 16 18.0 1.09 (0.61, 1.94) | 9 11.1 0.75 (0.36, 1.56) |                |
| **History of diabetes** | |                             |                | 0.65           |
| No              | 15889    | 62.8 47 64.4 1.00 | 33 48.5 1.00 |                |
| Yes             | 1583     | 3.6 11 15.1 2.28 (1.02, 5.12) | 10 14.7 1.91 (0.77, 4.77) |                |

Abbreviations: CI = confidence interval; E2C2 = Epidemiology of Endometrial Cancer Consortium; NE = not estimable (due to zero cells); OR = odds ratio.

*Missing values were excluded from presentation, but included as a separate category in logistic regression analysis.

**Polytomous logistic regression models adjusted for age, race, BMI, age at menarche, menopausal status, menopausal oestrogen plus progestin, menopausal oestrogen use, oral contraceptive use, smoking status, history of diabetes, and site.

***P-values for tumour heterogeneity are based on case-only multivariable-adjusted logistic regression models using endometrial stromal sarcoma cases as the ‘controls’.

****P-values for trend calculated with the variable modelled ordinally.

*****Among postmenopausal women.

******Among postmenopausal women in 12 studies with menopausal oestrogen use data.

*******Among postmenopausal women in 10 studies with menopausal oestrogen plus progestin use data.

********Among 14 studies with smoking data.

*********Among 13 studies with diabetes data.
deregulation of the Wnt signalling pathway (Chiang and Oliva, 2011), while leiomyosarcomas are characterised by chromosome 1 deletion. The relationship between aetiologic risk factors and these molecular data is lacking, but this information would allow for a better understanding of uterine sarcoma tumour biology.

Our pooled analysis has several strengths, including the largest sample size of uterine sarcomas examined in the literature to date and availability of data on important risk factors and confounders. Several limitations of the current analysis should be noted. Although our sample size was large relative to previous studies, the histological subtype analyses were affected by small numbers as evidenced by large CIs. The ascertainment of exposure variables differed across studies, potentially introducing misclassification bias. Because of these differences, some variables were classified using crude categories to harmonise across studies. Importantly, we did not observe between-study statistical heterogeneity for any variable under consideration. We had insufficient data from the studies in the pooled analysis on other risk factors of interest, including infertility history, tamoxifen use, history of uterine fibroids, and previous cancer diagnoses. Other novel risk factors, including occupational exposures (Koivisto-Korander et al, 2012) and in vitro fertilisation (Venn et al, 2001), have been examined infrequently and should be studied in appropriate epidemiological settings. Disease misclassification is another possible bias given the potential for differential diagnosis of uterine cancer across diagnosis years, regions, and countries represented by the individual studies. Although MMMTs have recently been excluded from the uterine sarcoma classification, we expect a small proportion of these tumours to be misclassified as primary uterine sarcomas. Finally, this pooled analysis included cases and controls from diverse geographic regions, potentially introducing clinical heterogeneity in our study design. In conclusion, we provide evidence of common aetiologic pathways for EEC and uterine sarcoma. Further exploration of factors that might explain patterns of age- and race-specific incidence rates for uterine sarcoma are needed.

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